HIV EXAMINER

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Treating AIDS in the 21st Century

Research into the human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS), has made remarkable progress since it began in the early 1980s. Preventive efforts have reduced the number of new cases of the disease, and for people already living with HIV/AIDS, the survival rate is increasing because of advances in drug therapy. But the majority of those affected by the disease live in developing nations, which, like many minority communities of the United States, are unable to afford the latest drug therapies and are still seriously threatened by the disease, according to this article from the September 1998 Encarta Yearbook.

By Joan Stephenson

“I'm one of the lucky ones,” said Mark Harrington in June 1998, describing his body's response to a potent combination of three anti-AIDS drugs before thousands of delegates in Geneva, Switzerland, at the 12th World AIDS Conference. Harrington, an American AIDS activist, became infected in 1985 with the human immunodeficiency virus (HIV) that causes acquired immune deficiency syndrome (AIDS). He began taking the drugs in 1996. “There can be little question that my immune system is much better, and my health stronger, than it was in 1996,” he told the assembled delegates.

Harrington's story illustrates the enormous progress made in treating people living with HIV and the infection's late stage, AIDS. But Harrington is lucky: The vast majority of HIV-infected people across the globe live in developing countries, where access to sophisticated medical care and costly medications is far beyond the reach of nearly all of those infected.

Another conference delegate, Rubarima Ruranga, a major in the Ugandan army and an AIDS activist who has lived with HIV for 13 years, painted a starkly contrasting picture. In Uganda nearly 2 million of the country's 20 million people are infected with HIV. Despite a public health budget of only about $8 per person, Uganda has one of Africa's most effective AIDS prevention programs. But even if pharmaceutical firms substantially lower the cost of their anti-AIDS drugs, as some have agreed to do, the country's meager resources could not be stretched to provide these medications for all of its HIV-infected citizens, Ruranga said.

AIDS Around the World: Global Gaps

The theme of the Geneva conference, which was held in late June and early July, was "Bridging the Gap." The theme underscored grave concerns about a growing "AIDS gap" between wealthy and poor nations. Although the spread of the disease is leveling off or even declining in most industrialized countries and a few developing nations, the epidemic is spreading dramatically in most poor countries, reflecting a gap in prevention efforts. AIDS-related death rates are also plummeting in industrialized countries but rising alarmingly in developing nations, underlining an enormous gap between rich and poor societies in their ability to provide life-prolonging treatment.

More than 30 million people throughout the world are currently living with HIV and AIDS. Some 16,000 people are newly infected by the virus each day, according to estimates by the Joint United Nations Program on HIV/AIDS (UNAIDS). The growing AIDS gap in different regions of the world came into sharp focus in a recent report prepared by UNAIDS and the World Health Organization (WHO). The report was released in June 1998, on the eve of the Geneva conference.

The report provides the most comprehensive country-by-country analysis of the pandemic to date, and it paints a grim picture of AIDS in the developing world. The area most devastated by the disease is sub-Saharan Africa, where nearly 21 million people are living with HIV infection. In 13 countries in this region, at least 10 percent of all adults

are infected. In Botswana and Zimbabwe, 25 percent of adults were infected by the end of 1997—the highest prevalence rate ever recorded.

The UNAIDS report also noted that infection rates are soaring in much of Asia and Eastern Europe, with many countries tripling their AIDS rates between 1994 and 1997. "HIV was a latecomer to Asia, but its spread has been swift," the report stated. Overall, about 6.4 million people in Asia and the Pacific island nations are thought to be living with HIV—more than one in five of the world's total HIV cases. The figure is expected to grow to one in four by 2000.

In India the HIV infection rate is less than 1 percent of the total adult population, but that translates to an estimated four million people living with HIV, making India the country with the largest number of HIV-infected people. Figures from the UNAIDS report and from studies presented at the Geneva conference indicate that tens of millions of people could soon become infected if efforts are not made to slow the spread of the virus. In China the nationwide infection rate is low, but the number of cases in the country doubled from 200,000 to 400,000 between the end of 1996 and the beginning of 1998.

An April 1998 UNAIDS report indicated a sixfold increase in HIV infections since the beginning of 1995 in countries of the former Union of Soviet Socialist Republics (USSR). UNAIDS officials warned that this dramatic increase portends a potential explosion of the disease in Eastern Europe and Central Asia. The virus has spread primarily among people who inject drugs, but there are signs that a sexually transmitted HIV epidemic may be emerging. Testing of blood donors and pregnant women indicates that the virus is becoming more prevalent in the general population. Sharp increases in other sexually transmitted diseases (STDs) may reflect the rapid spread of unsafe sex practices, a breakdown in health services for treating STDs, or both.

In contrast, prevention efforts have helped slow the rate of new HIV infections in the United States, Western Europe, and Australia. The availability of a screening test to detect HIV in donated blood has nearly eliminated blood transfusions as a possible source of infection. Anti-HIV drugs given to pregnant women and the promotion of safe alternatives to breast-feeding have dramatically reduced the rate of mother-to-child

transmission in these regions. Other preventive efforts include education about safer sex practices, such as consistent condom use, and avoidance of needle sharing among people who inject drugs. Some countries have programs that make clean needles available to drug users, helping curtail the spread of AIDS.

Preventive measures have actually led to a decrease in HIV infection rates in Western Europe. In the United States new HIV diagnoses have leveled off at about 40,000 cases per year, according to a 1998 report by the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. But prevention efforts have been more successful in some groups than in others. The majority of new infections in 1997 occurred among minority populations, notably African Americans and Hispanic Americans.

Medical Advances: Anti-AIDS Drug Cocktails

Although preventive efforts have helped slow the spread of AIDS in industrialized countries, an important treatment advance—the development of effective "drug cocktails" that combine three or more anti-AIDS drugs—has allowed HIV-infected people to live longer and stay healthier. These new combination regimens, called highly active antiretroviral therapy, or HAART, were introduced in 1995. They have become widely available to HIV-infected people in industrialized countries, a handful of Latin American nations, and Thailand. But few people have access to the new treatments in the areas of the world where most infected people live.

A HAART regimen typically combines a protease inhibitor—a powerful new anti-HIV agent that interferes with the last stage of HIV's reproductive cycle—with two older anti-AIDS drugs that attack a different reproductive stage. Studies have shown that, in patients who respond to HAART, the treatment suppresses HIV levels in the body, slows the virus's damage to the immune system, and even allows at least partial recovery of immunity.

For many patients, triple-drug therapy staves off their HIV infections' progression to AIDS. This more advanced stage of HIV infection is characterized by high levels of virus

in the body, low levels of the immune cell that HIV infects, and the appearance of infections and certain types of cancers. For patients whose immune systems are already ravaged by HIV, the new therapies have dramatically reduced the onslaught of these illnesses, reducing AIDS-related death rates as well.

Drug Regimens: Limitations and Drawbacks

Although HAART has transformed the treatment landscape, it is not without limitations. The costly drugs can exceed $1000 per month. HAART's combination treatments require the patient to take as many as 20 pills each day according to a complicated dosing regimen, and various dietary restrictions are necessary. For example, some drugs must be taken twice a day, and others require three daily doses, all at precise intervals. Some must be taken on an empty stomach; others must be taken with meals. One commonly prescribed protease inhibitor requires refrigeration, while another requires patients to drink large quantities of water.

Many patients have difficulty following the dosing instructions to the letter. CDC researchers reported in Geneva that only 65 percent of 1247 HIV-infected patients said they always took their medications as directed. The longer the patients were taking the drug combinations, the more likely they were to make mistakes. The reasons the patients gave for these lapses included forgetfulness, difficulty fitting the pill-taking into their schedules, and side effects from the drugs, including nausea, diarrhea, pain, headache, and other problems.

Physicians and patients are also concerned about the possible long-term effects of the treatments. A number of studies published in 1998 linked the use of anti-HIV drugs, notably protease inhibitors, with disruptions in metabolism, including increased levels of cholesterol in the blood, wasting of the face and limbs, and unsightly deposits of body fat around the abdomen or elsewhere.

Although HAART has greatly benefited many people infected with HIV, for others the drug combinations have failed to keep the virus under control. Researchers have found,

for example, that people in advanced stages of the disease are less likely to respond to HAART than patients whose immune systems are less damaged. There are many reasons patients fail to respond to certain drugs, but perhaps the most important is drug resistance, which occurs when a patient is infected with a strain of HIV that is impervious to the medication. In some cases, the virus is susceptible to the drugs when the patient first begins taking them, but later develops resistance.

Resistance is more likely to occur when a patient fails to take the drugs as prescribed. It may also develop when physicians prescribe drug regimens that are considered inadequate by current treatment guidelines. In either case, physicians may be able to prescribe a different combination of anti-HIV drugs against which the virus has no defenses. But some patients run out of options when the currently available drugs fail to arrest their infection.

AIDS experts are particularly concerned about a new report aired at the Geneva conference involving a gay man who had been extensively treated with a variety of anti-HIV drugs. The man infected a sexual partner with an HIV strain that was already resistant to all four available protease inhibitors as well as most other anti-HIV drugs. This development, the experts said, is a warning that prevention is vitally important to thwart the spread of multiple-drug resistant HIV strains to uninfected people, who would find themselves with few or no treatment options.

Promising Research

New medications on the horizon and others in more preliminary stages of research may provide much-needed alternatives for people who are not helped by currently available agents. Results from a number of human trials suggest that two new drugs, efavirenz and abacavir, could extend the benefits of HAART to more patients. These new agents are taken less frequently and have less stringent dietary requirements than protease inhibitors, so patients may be less likely to skip doses. Efavirenz, for example, which received approval from the U.S. Food and Drug Administration (FDA) in September 1998, is

taken just once a day, in three capsules. Researchers are currently developing another form of efavirenz that will require ingestion of only one tablet a day.

Scientists continue to study HIV's structure, looking for clues that will help them design new drugs. For example, protruding from the outer surface of HIV are two proteins that allow the virus to attach and fuse to human cells. In June 1998 U.S. researchers determined the three-dimensional shape of one of these proteins, called gp120. When the investigators analyzed the protein's structure, they found potentially vulnerable regions, such as cavities in gp120's surface. Researchers believe that detailed knowledge of the protein's architecture will allow them to design drugs that target these critical regions and disrupt HIV's ability to infect cells.

A variety of other possible approaches for anti-AIDS drugs are also being pursued, including a genetically engineered protein called T-20. This compound, currently being tested, foils HIV's ability to fuse with a human cell, an important step in the infection process. Another promising strategy involves attempts to block certain *cell receptors* (structures on a cell's surface that allow it to admit outside substances). HIV uses cell receptors as molecular doorways to gain entry into cells.

Although the development of new and better anti-AIDS drugs is an active area of research, experts are concerned that the usefulness of medications may be limited by problems such as possible long-term side effects and the development of drug-resistant strains of HIV. As a result, researchers are seeking ways to either eradicate the virus from the body or boost the immune system's ability to rein it in.

Some scientists, most prominently David Ho of the Aaron Diamond AIDS Research Center in New York City, have proposed that banishing the virus from the body may be possible. Ho and his colleagues suggested in 1995 that if HAART could prevent the virus from making new copies of itself, HIV eventually would be eliminated from the body as infected cells died off within a few years. But researchers have since learned that reservoirs of HIV may linger for many years in certain long-lived white blood cells and that current treatments fail to halt viral replication completely, allowing this reservoir to be replenished.

Investigators in the United States and Europe are now exploring the possibility of flushing HIV out of these long-lived cells and into the blood, where the virus is vulnerable to the anti-AIDS drug cocktails. There is promising preliminary evidence that such a strategy may work for some patients. However, the only way to be certain that all HIV has been purged from the body—or that the body is able to keep lingering traces of HIV in check—is to stop all treatment and see if the virus rebounds and begins to multiply.

Research teams in the United States and Switzerland plan to do just that with small numbers of patients who were treated with HAART within days to weeks after they became infected. These patients have nearly undetectable amounts of virus in their bodies. The investigators will offer them the opportunity to stop taking their medications to see if their immune systems can keep the remaining traces of virus permanently under wraps. (Study participants will be carefully monitored and will immediately resume treatment if the virus appears to rebound.) The hope is that patients who received early treatment will be able keep any lingering virus under permanent control.

Even if these patients are able to suppress the virus indefinitely, the vast majority of people infected with HIV are not identified and treated so soon after becoming infected. There is evidence that aggressive treatment with anti-AIDS cocktails can bring levels of HIV down to nearly undetectable levels and allow the immune system to partially recover, even late in the disease. But some gaps in immunity may remain, so researchers are searching for ways to enhance the immune system's ability to contain very low levels of HIV.

One immunity-boosting strategy under investigation involves giving patients an experimental “therapeutic vaccine.” Unlike conventional preventive vaccines, which are used to protect healthy people against diseases such as measles or polio, therapeutic vaccines would be administered to people already infected with HIV. Researchers hope that such a vaccine will help people by boosting their immune system's ability to suppress the virus. Efforts to develop a preventive vaccine for AIDS are still underway.

The Rich-Poor AIDS Gap

Although these strategies offer hope to many HIV-infected patients in industrialized countries, it seems unlikely that such expensive and complicated treatments will become available to most of the millions of HIV-infected people in developing countries. The costly drugs are beyond the reach of most African countries, which have an average of less than $10 to spend on health care per person each year.

Even in wealthy industrialized countries, not all patients with HIV infection have access to combination-drug therapy. One U.S. study published in 1998 found that people who obtained their anti-HIV drugs from publicly funded clinics were less likely to receive the latest drug cocktails than patients with private insurance. During a June 1998 briefing before the U.S. Congress, researchers from Johns Hopkins University in Baltimore, Maryland, noted that people with HIV who relied on federal and state drug-assistance programs for treatment sometimes received substandard care. The researchers reported that these patients were sometimes denied coverage for protease inhibitors, and that others were turned away because of insufficient funding.

There are many reasons why AIDS has exploded in impoverished and marginalized populations. In Eastern Europe, with the dissolution of the former USSR and the social and economic disruptions that followed, a growing infection rate among people who inject drugs has fueled the epidemic. Other factors, including the spread of HIV from infected drug users to their sexual partners and skyrocketing increases in STDs, may encourage the expansion of HIV into the general population.

HIV has swept into South and Southeast Asia because of “ignorance and denial in some countries, political instability in others, [and] a relative lack of funds in still others,” director of the Malaysian AIDS Council Marina Mahathir told delegates at the Geneva meeting. According to many observers, factors contributing to the spread of infection also include reluctance in many cultures to talk frankly about sex; lack of educational and prevention services, including counseling and testing for HIV; and the inability of women

in many cultures to protect themselves by insisting on condom use by their male sex partners.

Similarly, a combination of factors has contributed to the disproportionate spread of HIV among African Americans and Hispanic Americans in the United States, who together account for more than half of all the nation's AIDS cases. According to a 1998 CDC report, one key element fueling the spread of HIV in communities of color is the nation's inability to successfully deal with substance abuse. Another important factor is that AIDS awareness, prevention, and treatment programs have failed to reach minority communities. Some public health experts believe that ignorance about HIV infection and prevention, stigma surrounding the disease and its link with drug abuse and risky sexual behaviors, and a persistent myth that only gay men are at risk have also contributed to a reluctance within minority communities to discuss the problem.

The social costs of the HIV pandemic are considerable, particularly among impoverished populations. As the United Nations' 1997 Human Development Report notes, poverty "offers a fertile breeding ground for the epidemic's spread, and infection sets off a cascade of economic and social disintegration and impoverishment." One manifestation of social disintegration is AIDS's enormous legacy of orphans, which is both a tragedy for families and a strain on national social systems that often must assume the care of the children. In 1997 alone, 1.6 million children—90 percent of whom live in sub-Saharan Africa—were orphaned when their parents died of the disease.

HIV is also reversing a decades-long trend toward greater life expectancy in African countries. In a study published in 1997, researchers estimated that in a rural Ugandan community where 8 percent of adults were infected—a relatively moderate rate for sub-Saharan Africa—the presence of HIV slashed 16 years from the average life expectancy.

The Search for a Preventive Vaccine

Experts agree that a preventive vaccine is needed to rein in the runaway AIDS pandemic. Neal Nathanson is director of the U.S. National Institutes of Health (NIH) Office of

AIDS Research (OAR), which determines general research priorities for the NIH's $1.7 billion AIDS research budget. Nathanson said revitalizing the U.S. vaccine effort is his top priority. In addition to substantially increasing funding for vaccine research to nearly $180 million for 1999, a 79 percent increase from four years earlier, OAR is calling for a coordinated approach to systematically test candidate vaccines in monkeys and move the most promising ones into human trials.

The challenge of developing a safe and effective AIDS vaccine is formidable. Researchers have tested at least two dozen experimental vaccines in small numbers of volunteers over the last decade or so, but only one vaccine candidate has entered the process of wide-scale testing, in the United States and Thailand. Many researchers are skeptical about the vaccine's potential effectiveness, because it stimulates only one of two components of an immune response: the production of antibodies to “neutralize” HIV in the blood. It does not, however, stimulate the second component of immunity, the mobilization of killer T cells, which are capable of recognizing and destroying HIV-infected cells.

Some investigators believe that another approach currently under development is more likely to offer some protection against HIV. This approach uses a combination of vaccines, one to elicit antibodies and another to activate killer T cells. Wide-scale trials of this approach are unlikely to begin before 1999, and finding out whether it actually protects against HIV will take several years.

Another more controversial strategy involves the use of a weakened strain of live HIV to stimulate the immune system. Many scientists believe that such an approach offers the best hope for an effective vaccine. However, recently reported study results have dealt this strategy a potentially fatal setback. Tests in monkeys revealed that the weakened virus can mutate into a form that can cause the disease rather than protect against it.

What Should Be Done?

With no safe and effective vaccine on the immediate horizon, there is a growing sense in the global AIDS community that more needs to be done to prevent and alleviate suffering today. Many public health experts, policy makers, and AIDS advocacy groups are calling for increased efforts to use today's tools, including anti-HIV drugs and prevention programs, to help those who are currently infected and to curb the further spread of HIV.

A UNAIDS-initiated effort, announced at the Geneva meeting, seeks to make anti-HIV drugs more accessible to people in developing countries. Through negotiations with pharmaceutical firms, UNAIDS has convinced several companies to offer their AIDS drugs at a substantial discount.

Public health experts hope one arm of this initiative will help prevent the virus from being passed to babies during birth. About 1600 cases of mother-to-child transmission occur daily, almost exclusively in developing countries. Researchers recently demonstrated that this risk is cut in half when about $50 worth of a drug called zidovudine, or AZT, is administered during delivery. UNAIDS announced at the Geneva meeting that it would launch a pilot program to provide AZT to 30,000 women in poor countries in Africa, Asia, and South America.

Extending the benefits of combination-drug therapy to people in developing countries is a more daunting challenge. Currently, providing HAART to the more than 30 million HIV-infected people around the globe would cost at least $35 billion annually. Even if such a program made anti-HIV drugs available for substantial discounts, the cost of treatment might not be low enough for many impoverished countries, which also lack sufficient medical facilities and trained professionals to administer the drugs properly.

AIDS experts and advocates also cite the need to channel more resources into prevention programs. In one large U.S. study of more than 3700 inner-city clinic patients—mostly African Americans and Hispanic Americans at high risk for HIV infection—those who attended small-group AIDS education and counseling sessions were likely to use condoms more frequently and have unprotected sex less often.

Studies show that HIV infection rates have slowed in countries with strong prevention programs that stress consistent condom use and sexual abstinence for young people.

Uganda cut HIV prevalence by more than a quarter, from nearly 13 percent in 1994 to 9.5 percent in 1997. In Thailand prevention efforts led to a decrease in prevalence from 2.7 percent in 1994 to 2.3 percent in 1997, a 15 percent decline. Using information from research studies about prevention strategies that work, UNAIDS is working to set up new prevention programs in a number of African countries.

Greater attention is also being focused on the need for better prevention programs that specifically target minority communities in the United States. Some black leaders have been reluctant to address the problem of AIDS, but there are signs that this is changing. United States surgeon general David Satcher, the first African American male to hold that post, has pressed black leaders to mobilize against the epidemic. The Congressional Black Caucus in 1998 urged the administration of President Bill Clinton to declare the HIV/AIDS epidemic among African Americans a public health emergency. And the CDC, which provides $253 million a year to state and local government for HIV prevention programs, is funneling some of those funds directly to groups that focus on minorities.

However, some widespread social and behavioral practices that contribute to the spread of HIV have proven resistant to change. For example, women in many countries and cultures are unable to insist that a sex partner use a condom, which would help protect them from infection. To combat this problem, many public health experts support development of an effective and inexpensive “stealth” method such as a *microbicide,* an HIV-killing gel or cream that a woman could use with or without a partner's knowledge. Such research has lagged, but the OAR's Nathanson says the NIH is now supporting a major program to develop effective microbicides.

Some controversial measures that public health experts say would help reduce the spread of the virus—notably needle exchange and drug addiction treatment programs for injection drug users, and school-based sex-education programs that provide information about ways of reducing HIV risk—lack the necessary political support. Building such support is one of the major challenges facing public health experts and the AIDS community today, many observers believe.

“The biggest AIDS gap of all is the gap between what we know we can do today and what we're actually doing,” Peter Piot, head of UNAIDS, told delegates at the Geneva conference. “We have the tools; now we must build the political will to use them.”

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