Denise Myshko

30 Years of AIDS Research

Antiretroviral agents have revolutionized treatment for HIV/AIDS. But there is still a tremendous need for prevention and less-costly therapies.

Much progress has been made over the last 30 years in the HIV/AIDS arena. HIV infection is no longer considered a death sentence, thanks to antitretroviral "cocktail" medications. Experts say the biggest advance over the last three decades has been these agents, which have been able to stop the replication of the virus. This, they say, has transformed what was once a fatal disease to more of a chronic illness.

Daria Hazuda, Ph.D., VP and worldwide discovery head of infectious diseases franchise at Merck Research Laboratories, says the development of combination antiretroviral therapy is truly remarkable.

"The time frame from when the virus was first identified to when the first antiretroviral agents were developed and then to the advent of combination therapies has been remarkably short," she says. "It is incredibly hard to make one drug; to have made a cocktail comprised of multiple agents in such a short period of time has been a remarkable achievement."

But experts are quick to point out that there is still a tremendous need for preventive therapies, drugs with fewer side effects, and less-expensive drugs. While deaths from AIDS have decreased, the incidence of HIV remains unchanged. And while medications have had a tremendous impact, they often have side effects and are costly.

The Centers for Disease Control and Prevention estimates that more than 1 million people are living with HIV in the United States. The annual number of new HIV infections has remained relatively stable, with an estimated 56,300 Americans becoming infected with HIV each year.

> **"HIV studies are very much lab driven; therefore, a central lab is important to standardizing the reporting of the data."**
>
> **ELISHA TALLEY-ROITHNER** / PPD

Globally, 33.3 million people are living with HIV/AIDS, and there were 2.6 million new infections in 2009. That year, there were 1.8 million deaths as a result of AIDS.

"HIV is debilitating in many ways and is an expensive disease to treat," says Robert McNally, Ph.D., president and CEO of GeoVax Labs. "Our estimate is that oral medications cost about $1,500 a month for an individual or insurance company. In addition, current medications, even though they are effective, have a multitude of side effects."

Current Research

Biopharmaceutical companies are conducting research on 100 medicines to treat HIV/AIDS and related conditions and they are intensifying their efforts to develop preventive vaccines, according to a report issued last year by the Pharmaceutical Research and Manufacturers of America (PhRMA). Since HIV was first identified, 31 medicines have been approved to treat HIV infection.

One of the most anticipated HIV drugs in the pipeline is a highly active antiretroviral therapy, which requires patients to take different classes of drugs. This has succeeded in achieving near-zero levels of HIV in infected people.

Bristol-Myers Squibb is one company researching HIV medicines.

"We are actively researching pediatric applications of medicines, including Reyataz, in collaboration with the Pediatric AIDS Clinical Trials Group; we are also in the process of developing a powder formulation of Reyataz for oral use in pediatric patients," says Awny Farajallah, executive director, atazanavir development at Bristol-Myers Squibb. "We recognize that development is a long-term com-

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> **"To be successful in the HIV market, companies need strong and continuing collaborations with external stakeholders to create public-private partnerships to make sure antiretroviral medications get to the patients who need them most."**
>
> **DR. DARIA HAZUDA**
> Merck Research Laboratories

mitment, as it is an ongoing process to learn and apply new therapies in the most appropriate ways."

While Bristol-Myers Squibb is not focused on preventive vaccines for HIV, company researchers are working to advance the company's understanding of HIV immunology, which in turn has made research into therapeutic vaccines and immunomodulation more promising, says George Hanna, M.D., VP of HIV development at Bristol-Myers Squibb.

The company has three HIV treatments on the market — Sustiva, Reyataz, and Atripla (marketed by Bristol-Myers Squibb and Gilead) — and a portfolio of investigational compounds in HIV, including an attachment inhibitor prodrug and an NRTI in Phase II development.

"We continue to have a focus on investigational compounds in HIV and we are actively working in the disease area to bring forward new development candidates that will deliver true advances to patient care," he says.

Bristol-Myers Squibb has development programs that are in line with the company's focus to address the treatment of HIV by evolving antiretroviral therapy to deliver true advances to patient care and developing interventions to enable a return of immunological health and virologic eradication or control in people with HIV infection.

Company experts say new research is likely to lead to new treatments for HIV/AIDS, as well as vaccines for the prevention of HIV infection.

"In the future, my opinion is that we'll see more and more development around prevention and vaccines and hopefully a true cure, and I think the most promising area is in vaccines for HIV," says Elisha Talley-Roithner, executive director, project management, and global therapeutic area head for infectious diseases, at PPD.

PPD is so committed to HIV/AIDS research, it has created a Vaccines & Biologics Center of Excellence to provide laboratory services devoted solely to vaccines and biologics drug development.

The center integrates two decades of laboratory expertise in a single, comprehensive resource that can support vaccine and biologic development programs from preclinical to postapproval.

Researchers at several organizations, including the AIDS Research Alliance (ARA) and Merck, are studying the mechanisms that the AIDS virus uses to stay dormant and hide in "reservoirs" in the body.

"In 10 years within the treatment field, we have been able to suppress infection in a large majority of patients with drugs that are tolerated," says Stephen Brown, M.D., VP and medical director at ARA. "At the same time, there are studies looking at drugs and immune therapies to attack the reservoir where HIV hides."

Researchers now believe that HIV stays hidden throughout the bodies of people infected with the virus in reservoirs comprised of long-lived blood cells. The cells are infected with HIV, yet the virus is dormant — or latent — within these cells, so the cells appear to be "normal" and thus escape the reach of anti-HIV drugs and the immune system.

These reservoirs of HIV are located throughout the body, including in the brain, lymphoid tissue, bone marrow, and genital tract. These reservoirs persist, even in the presence of antiretroviral therapies.

"In the reservoir, the virus only contains information on how to replicate itself," Dr. Brown says. "Those cells are invisible to the immune system, and we need a way of activating them."

The organization is using the revenue from its work as a clinical site and, with additional funding, is pursuing its own research. The organization licensed prostratin from the National Institutes of Health in 2001. ARA's research using prostratin has taken a huge step forward in reservoir depletion strategy.

30 Years of Progress: HIV/AIDS Medication Facts

- Life with HIV/AIDS has changed dramatically. Patients diagnosed with AIDS in 1990 could expect to live only months, during which time they would be likely to contract a number of opportunistic infections. Since the approval of the first antiretroviral therapy (ART) in 1995, the AIDS death rate has dropped by 78%.
- HIV death rates continue to fall. From 1999 to 2008, death rates continued to drop by 5% per year. The most recent data show a continued decline in death rates. Between 2008 and 2009, death rates fell another 9%. Among people 25 to 44, death rates fell by more than one half in 2007 alone (the most recent age-group-specific data).
- AIDS-related hospitalizations have dropped. Since ARTs became available, the number of people with HIV increased by 28% between 1996 and 2000, primarily because of rising survival rates. Hospitalization rates, however, fell by 32% over the same period.
- University of Chicago economists report that patients with HIV now live 15 years longer than they would have in the 1980s.
- Use of HIV medicines helps prevent transmission. A recent study in The Lancet reported that initiation of ART reduces the risk of transmission from an infected individual to his or her partner by 92%. A large new study sponsored by the National Institute of Allergy and Infectious Disease echoes this result, finding that early initiation of ART reduced transmission by 96%.
- Medicines have become easier to use, adding to their effectiveness. The first once-daily, one-pill combination tablet was approved for treatment of HIV in 2006. This medicine combines the active ingredients of three widely used antiretroviral drugs into a single dose.

Source: Pharmaceutical Research and Manufacturers of America. For more information, visit phrma.org.

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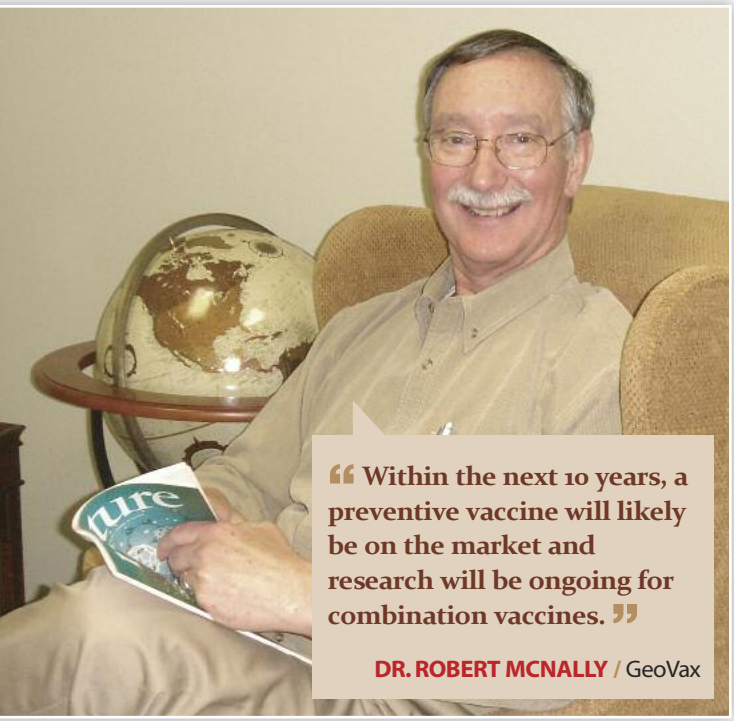

> **"Within the next 10 years, a preventive vaccine will likely be on the market and research will be ongoing for combination vaccines."**
>
> **DR. ROBERT MCNALLY** / GeoVax

"We filed our own patent on certain aspects of the drug," Dr. Brown says. "We are in the process of bringing it through the preclinical process."

Animal studies show prostratin prevents the virus from infecting cells. It attacks the virus at a different stage than other classes of FDA-approved anti-HIV drugs. It also appears to work on a cellular target rather than a viral target.

"Prostratin activates latently infected cells," Dr. Brown says. He says the alliance plans to conduct Phase I studies and will then look for a partner.

Merck is another company researching HIV reservoirs. In July 2011, Merck announced two new collaborations with the University of North Carolina and the University of California. The collaborations aim to develop new approaches toward eradicating HIV.

The goal of these collaborations is to identify where the virus hides and how it can be awakened, Dr. Hazuda says. She says this research of the HIV reservoirs aims to make the virus actively expressed in cells so that the antiretroviral agents can then eradicate them.

"As long as HIV expression is activated in the context of highly effective antiviral therapy, the virus being expressed will not be able to replicate in subsequent cells," she says. "If we can block the subsequent rounds of infection, ultimately the cells in which we've awakened the expression of HIV will eventually die.

"The goal is to help investigators develop animal models so we can look at where the virus is hiding," Dr. Hazuda continues. "Once the animal models are developed and validated, we will begin testing various interventions.

"There are several hypotheses right now about where the virus is and different ways to wake it up. Merck is also going to be involved in the collaboration with interventions to help test some of these hypotheses," Dr. Hazuda concludes.

HIV Vaccine Research

Researchers also are developing and testing potential HIV vaccines with the goal of developing a vaccine that can prevent HIV infection.

Dr. McNally says within the next 10 years, a preventive vaccine will likely be on the market and research will likely be ongoing for combination vaccines to fight the virus in other parts of the world.

GeoVax is developing two vaccine components: a recombinant DNA-vectored vaccine and a recombinant MVA-vectored vaccine. Both produce non-infectious, virus-like particles in the body of a vaccine recipient. These non-infectious particles are designed to "train" the immune system of the vaccinated person to recognize HIV should this person be exposed to the real virus.

"For HIV prevention, we have completed all of our safety studies in humans, and we are planning an efficacy trial," Dr. McNally says. "In primates, our vaccines have demonstrated 70% protection. On the therapeutic side, we are conducting a Phase I trial for people who are recently HIV-infected. Individuals participating in this trial will be vaccinated and monitored for safety and viral control.

"We have shown avidity, which is how well the antibody adheres to the virus," Dr. McNally continues. "The antibody is a blocking mechanism. We have demonstrated in primate models that high avidity correlates with protection. In our primate models, protection lasted nearly a year and the viral load stayed in check without any assistance."

The search for an HIV preventive vaccine has been disappointing, and there have been several failures in this area of research, but Dr. Hazuda says researchers learn from projects that fail.

"The history of both preventive and therapeutic vaccinations shows there are many failures, but recently there are significant reports of success," she says.

In the early days of HIV vaccine research, the part of the immune system that needed to be stimulated was unknown, Dr. McNally says.

"Now we know antibody and T cells are important," he says.

> **"In the next five years, using drugs and microbicides to prevent HIV will move into the mainstream."**
>
> **DR. STEPHEN BROWN** / AIDS Research Alliance

HIV vaccine research continues. Dr. Brown says one vaccine study was being done by the HIV Vaccine Trials Network (HVTN). The HVTN is a global partnership of researchers, academic institutions, and community members.

HVTN 505 is a combination of two experimental HIV vaccines being tested in a trial of 2,200 people. This study was sponsored and paid for by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH).

The original aim of HVTN 505 was to evaluate whether the vaccines lowered viral load or changed the course of disease progression in people who became infected with HIV. But an HIV vaccine study in Thailand showed some reduction in HIV infections among people who got a different but similar vaccine. The HVTN 505 study was expanded to 2,200 patients to test whether the 505 vaccines might also protect against HIV infection.

The trial in Thailand began in 2003 and ended in 2006, with results released in 2009. Those who received the vaccine saw a 31% drop in HIV infection compared with those who received placebo.

The vaccine, ALVAC-HIV, is manufactured by Sanofi Pasteur.

Challenges in HIV Research

HIV is unique to drug development because treatments are generally combination products. Addressing the challenges associated with HIV research requires collaboration among the various stakeholders.

"Therapies are now so successful that this is actually the biggest challenge for developing new medications," Dr. Hazuda says, "Because there are far fewer patients who are failing therapy and who are desperately in need of something new, there is a shortage of patients available for trials."

Merck is addressing this challenge through partnerships with community groups. In the early days of HIV research, there was a close collaboration between the patient community, the academic medical community, the regulatory authorities, and pharma.

"Without this close collaboration, as researchers in this field we would not have been able to achieve what we did in such a short period of time," she says. "This should be a model of collaboration for other disease areas."

Dr. Brown agrees that a community-based approach is critical.

"Early community education is important," he says. "If we can educate communities about the new products that are being studied, patient recruitment can be faster. Working with the communities to provide education about new drugs is critical for the pipeline process to proceed."

Ms. Talley-Roithner says the medical infrastructure within the different countries throughout Africa is a critical consideration when conducting HIV research.

"Getting patients to come back to the clinic is a challenge," she says. "We've invested a lot of time and training with investigators and we provide tools to help them bring their patients back for follow-up visits." PV

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