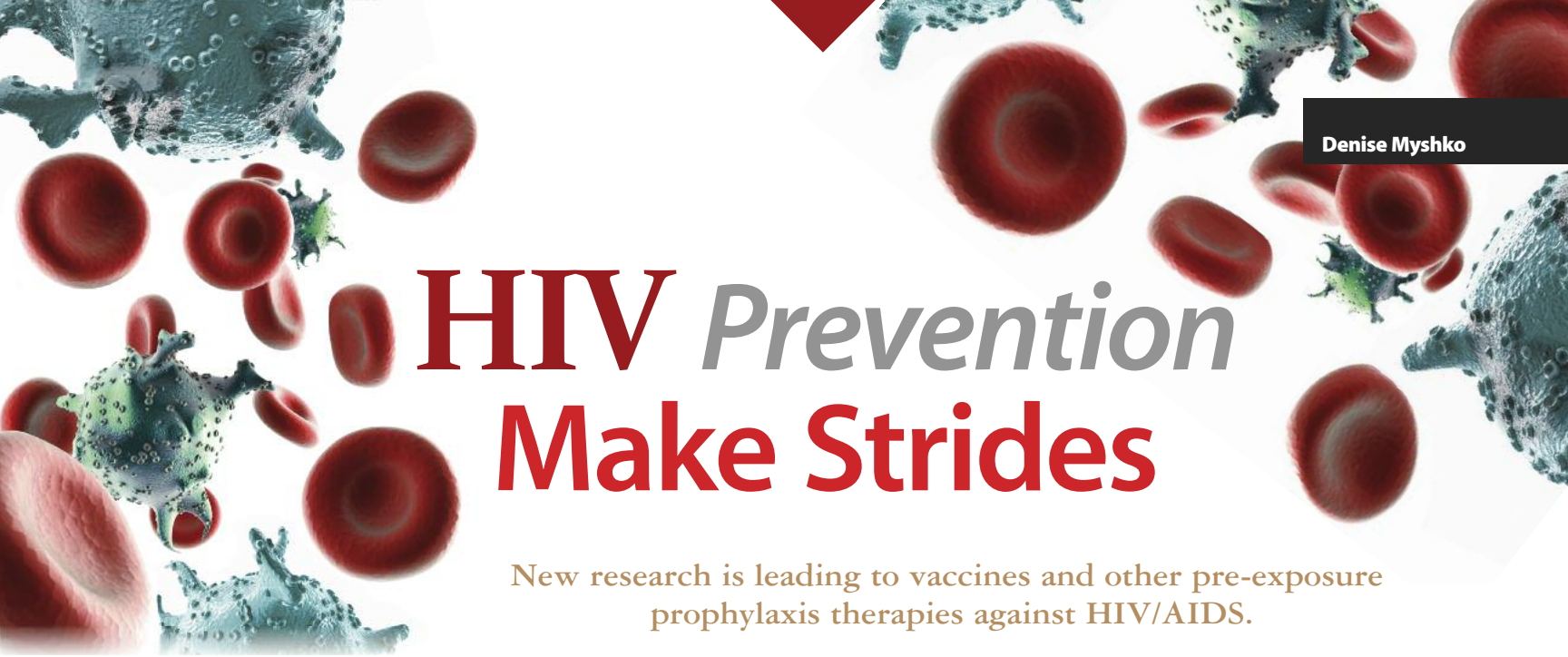


Denise Myshko

HIV Prevention Make Strides

New research is leading to vaccines and other pre-exposure prophylaxis therapies against HIV/AIDS.

A modern day plague unchecked. That's how the Centers for Disease Control describes HIV/AIDS. HIV, along with malaria and tuberculosis, represents a huge area of unmet need. These diseases continue to be serious health issues for some parts of the world. For HIV alone, there were about 2.5 million new cases worldwide in 2011. About 34 million people around the world are living with HIV.

By 2005, the epidemic had become so pervasive that four people died from HIV/AIDS every minute. Since 2005, progress has been made, and 25 countries have seen a 50% drop in new HIV infections since 2001. But progress has been uneven. Since 2001, the number of people newly infected in the Middle East and North Africa increased by more than 35%. In Eastern Europe and Central Asia, there has been an increase in new HIV infections in recent years.

For many years, researchers have been working not only to find new treatments but also therapies that could prevent HIV infection. Companies are working on vaccines and other pre-exposure prophylaxis therapies to bring this plague under control. While developing a vaccine for HIV has met with many challenges, companies are making progress.

Last year, Gilead Sciences was the first company to receive approval for a therapy to reduce the risk of HIV infection. Truvada, approved in July 2012, is not a vaccine, but a combination of antiretroviral drugs — tenofovir disoproxil fumarate and emtricitabine. The product is also approved as a treatment for HIV. When Truvada is used as a treatment rather than a preventive, the patient also takes a third drug. For 2012, Truvada sales were $3.18 billion.

Daily use of Truvada was shown to reduce the risk of HIV infection by 42% in a study sponsored by the National Institutes of Health of about 2,500 HIV-negative gay and bisexual men and transgender women, and by 75% in a study sponsored by the University of Washington of about 4,800 heterosexual couples in which one partner was HIV positive and the other was not.

In June of this year, trial results were released that showed Truvada can reduce HIV risk among people who inject drugs. In some regions of the world, such as Eastern Europe and Central Asia, this route of transmission accounts for up to 80% of new infections.

Keith Rawlings, M.D., director of medical affairs at Gilead, says pre-exposure prophylaxis (PrEP) is an important public health intervention that may have the potential to reduce the number of new HIV infections and is not a commercial opportunity.

"As part of the approval of Truvada for PrEP, Gilead worked with the FDA to develop a risk evaluation and mitigation strategy (REMS) to help ensure safe use of Truvada for PrEP as part of a comprehensive prevention strategy," Dr. Rawlings says. "Gilead also developed FDA-approved materials to educate and inform healthcare providers and uninfected individuals about Truvada for PrEP. These materials highlight the importance of strict adherence to the dosing regimen, emphasize that Truvada must be considered as only one part of a comprehensive prevention strategy to reduce the risk of HIV-1 infection, and convey that Truvada for PrEP should only be used in individuals who are confirmed HIV negative."

Some experts, however, note that adherence could be a challenging issue with the product because it must be taken daily.

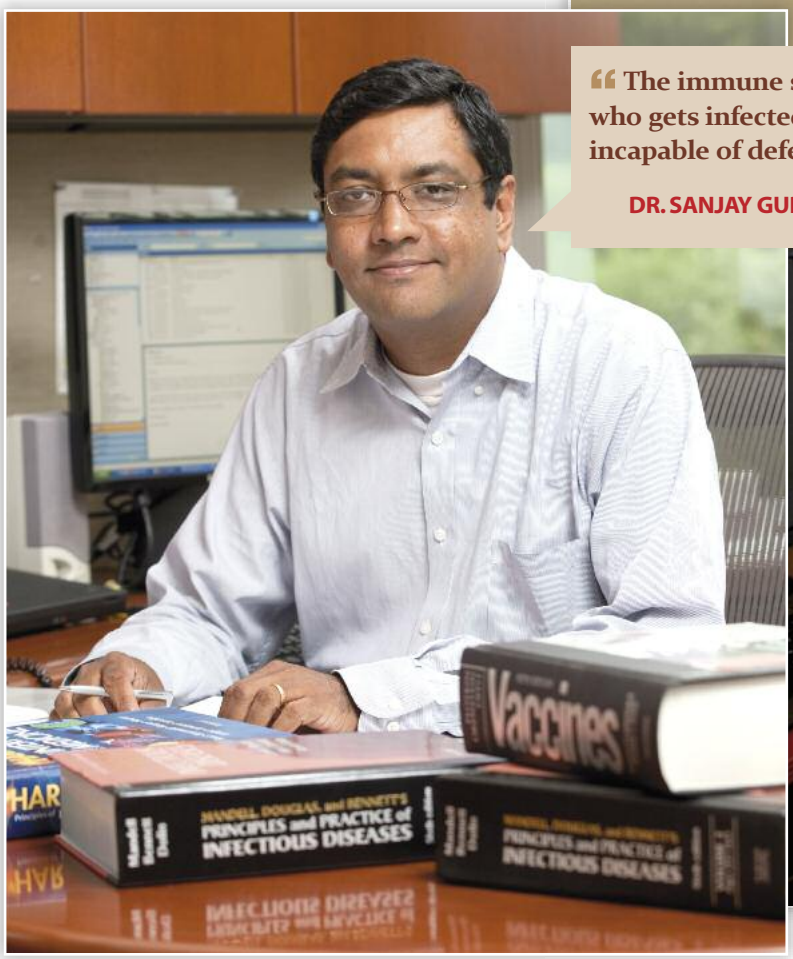
"In many cases, those who are most at risk for HIV infection are not in the best position to be fully adherent," says John Adams, Pharm.D., senior director of clinical development at INC Research. "Most experts would agree that the proposed benefit of pre-exposure prophylaxis hasn't translated into a lot of demand globally, a least not yet. Whether that market potential will increase significantly or not is going to be largely dependent on overcoming many of the implementation challenges. We have a drug combination that can suppress viral replication exceedingly well. Can we implement its optimal use to truly impact HIV incidence on a broader scale? That remains to be seen."

Dr. Adams points to the results of a survey published in the New England Journal of Medicine last October. The survey presented two different cases, one of which was a 46-year-old male who had sex with many male partners in New York and the other case was an 18-year-old heterosexual female in South Africa. Readers were asked if they would recommend pre-exposure prophylaxis in either of these cases. Readers, with 1,115 votes cast, were divided: 51% of respondents favored PrEP for the homosexual man and 49% favored it for the South African woman.

"Readers from the developing world were a bit less inclined to recommend PrEP," Dr. Adams says. "This may be because, in areas of high risk, if adherence isn't going to be optimal, we can argue that PrEP could do more harm than good."

Vaccine Research Continues

Experts say if behavior could be taken out of the equation, pre-exposure prophylaxis could meet with better success. A vaccine that requires few injections could have better potential for success in many parts of the world.



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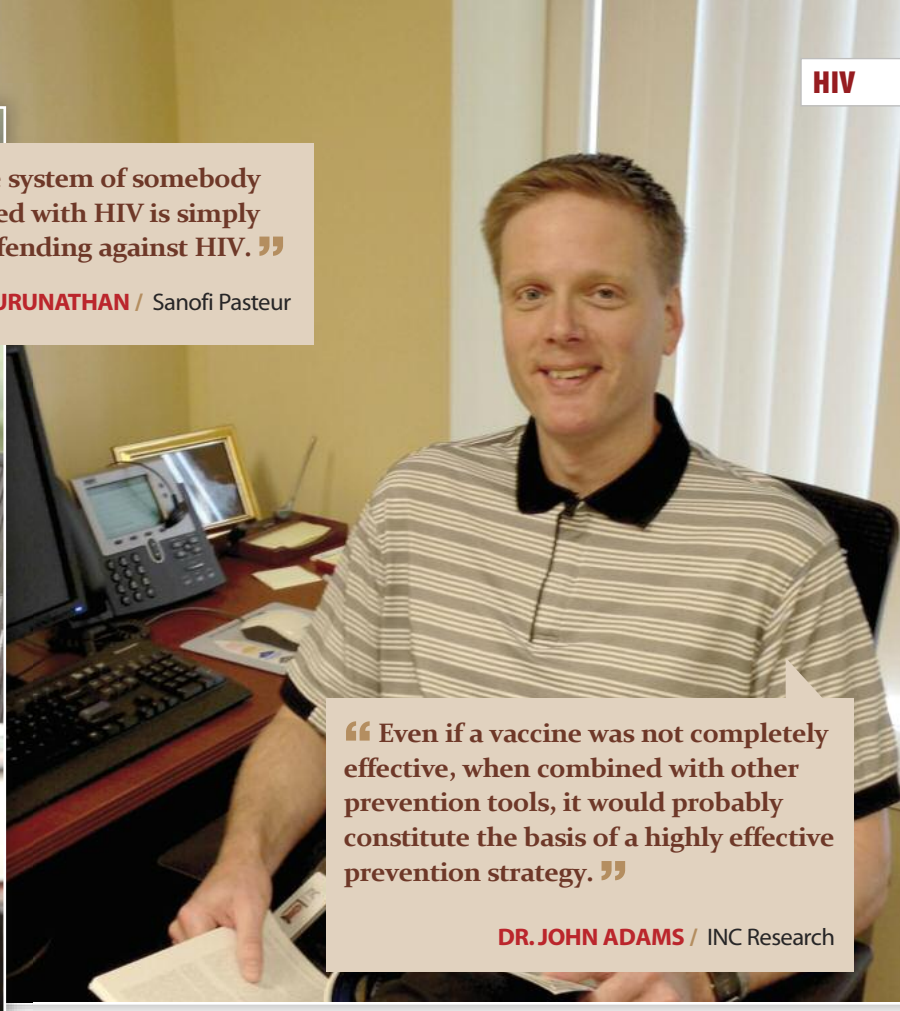
> **DR. SANJAY GURUNATHAN** / Sanofi Pasteur



> "Even if a vaccine was not completely effective, when combined with other prevention tools, it would probably constitute the basis of a highly effective prevention strategy."
>
> **DR. JOHN ADAMS** / INC Research

"A vaccine wouldn't have to be 100% effective to be useful," Dr. Adams says. "Even if a vaccine was not completely effective, when combined with other prevention tools, it would probably constitute the basis of a highly effective prevention strategy."

But HIV is one of the most difficult targets to develop a vaccine against. HIV mostly infects cells in the immune system. In fact, HIV attacks the "command center" of the immune system, the CD4 T-cells. HIV searches for cells that have CD4 surface receptors. The T4 cell is responsible for warning the immune system that there are invaders in the system.

For many infections, the body seems to be able to produce an immune response that can typically fend off the pathogen, says Sanjay Gurunathan, M.D., associate VP for clinical development, at Sanofi Pasteur.

"The immune system of somebody who becomes infected with HIV is simply incapable of defending against HIV," Dr. Gurunathan says. "HIV is a very clever virus, and it keeps changing itself. Before the host's immune system can react to the virus, it's already changed its nature and the immune response that it generates is not effective."

Additionally, HIV targets the immune cells that are the very basis for immunity.

"This poses significant challenges for designing a vaccine that can overcome the diversity piece and be in a position to boost the immune system in a way that it can protect," Dr. Gurunathan says.

Developing a vaccine for HIV remains challenging, and failures continue. In April of this year, the National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, stopped its clinical trial of an investigational HIV vaccine because it did not prevent HIV infection or reduce viral load.

The failure of this trial was related to the vector used in the product. This particular vaccine used an adenovirus, a common cold virus. As a result of this study, the NIAID delayed or modified vaccinations in 11 of its preventive and therapeutic HIV/AIDS, malaria, and Ebola virus vaccine clinical trials involving adenovirus-based vaccine vectors.

But other researchers have been making progress in the HIV vaccine area, either using different vectors (primarily pox vectors) or proprietary systems for delivering or triggering immune response.

Early Vaccine Successes

It's now well-understood that to be successful, vaccines against HIV need to stimulate both antibody and T cell responses. Antibodies work as the "border guards" for our bodies, says J. Joseph Kim, Ph.D., president and CEO, Inovio Pharmaceuticals.

"Antibodies protect the boundaries of our bodies to make sure infection doesn't occur and if it occurs, it gets cleared up quickly. T-cells, on the other hand, are like a police force, our SWAT teams," he says. "Once our own body cells are infected, we need the SWAT team of the immune system to clear the infected cells out of the body."

One of the first trials to demonstrate that a vaccine could prevent HIV is RV144. In 2009, the sponsor of the trial, the U.S. Military's HIV Research Program, released results of the trial — commonly referred to as the Thai trial — that showed efficacy of 31%. The product tested was a prime-boost combination of Sanofi Pasteur's Alvac HIV vaccine and AIDSVAX B/E, in more than16,000 healthy adult volunteers at relatively low risk for HIV infection in Thailand. Sanofi Pasteur's HIV vaccine uses a canary pox — a virus that cannot infect or harm humans — to carry select HIV genes, but not the whole virus, into the body.

Dr. Gurunathan says the approach the company has followed is a prime boost, which primes the body with a pox virus and then immunizes with a different agent.

"It is a one-two hit to get the broadest possible response to give protection," Dr. Gurunathan says. "The first injection targets both

HIV Facts

- About 50,000 people in the United States are newly infected with HIV each year. In 2010 (the most recent year that data are available), there were an estimated 47,500 new HIV infections. Nearly two-thirds of these new infections occurred in gay and bisexual men
- Worldwide, in 2011, about 34 million adults and children were living with HIV.
- In 2011, 1.7 million people died from AIDS-related causes worldwide, 24% fewer deaths than in 2005.
- 25 countries have seen a 50% or greater drop in new HIV infections since 2001.
- There has been a 50% or greater drop in HIV/AIDS-related deaths between 2005 and 2011 in 14 countries, with another 29 countries achieving a reduction of 25% to 49%.
- Progress worldwide is uneven. Since 2001, the number of people newly infected in the Middle East and North Africa increased by more than 35%. In Eastern Europe and Central Asia, there has been an increase in new HIV infections in recent years.

Sources: Centers for Disease Control and Prevention, United Nations Programme on HIV/AIDS (UNAIDS)

T-cells and antibodies and then we come back with a boost that preferentially targets the antibody response."

Sanofi Pasteur continues to study Alvac HIV through a public-private partnership called P5 — Pox-Protein Public Private Partnership. Current P5 members include the National Institute for Allergy and Infectious Diseases (NIAID), the Bill & Melinda Gates Foundation, the NIAID-supported HIV Vaccine Trials Network (HVTN), the U.S. Military HIV Research Program, Sanofi Pasteur, and Novartis. Established in 2010, the P5 partnership assembled teams across four continents to drive a focused approach to developing HIV vaccines based on the pox-prime, pox-protein-boost concept.

Sanofi Pasteur also has another investigational HIV vaccine called NYVAC. The clinical development of NYVAC-HIV vaccine has, to date, been conducted in Europe primarily through the EuroVacc Program. It is an attenuated recombinant pox virus-based smallpox vaccine derived from vaccinia virus strains.

Together with the P5, the partnership will substantiate and extend further the findings of study RV 144 with additional studies planned in South Africa.

"We are going to have to do some run-in studies before we do additional Phase III studies," Dr. Gurunathan says. "There is going to be some early Phase I studies to make sure that everything is working as we expect it to work. Those run-in studies will begin over the next few years. That will be quickly followed by a Phase III study. At Sanofi Pasteur, we believe that a vaccine to prevent HIV infection is in sight and we are doing everything we can to make that vision a reality."

Another company using a pox vector is GeoVax. The company has completed patient enrollment for the Phase I clinical trial testing the safety of its second-generation prevention vaccine. The 48-patient clinical trial is looking to assess safety and immunogenicity of the vaccine at low-dose and full-dose regimens. This trial should be completed by the end of this year, with Phase II trials planned for 2014.

GeoVax's two component vaccine, a recombinant DNA and a recombinant modified vaccinia Ankara (MVA), is designed to stimulate both anti-HIV T cell and anti-HIV antibody immune responses.

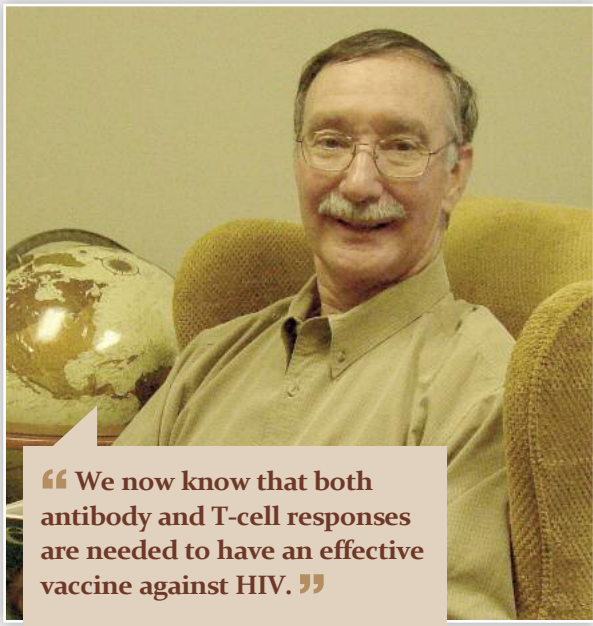
"We insert genetic material from the HIV to stimulate the immune system," says Robert McNally, Ph.D., president and CEO. "We added an adjuvant to the DNA portion — adjuvants typically help stimulate the immune response — and in this case, we used GM-CSF. This has given us a huge boost in protection against the virus. The second-generation product has shown data in nonhuman primates that we get better protection than the product without the adjuvant."

GeoVax has received grants from the NIH and has done trials through the U.S.-sponsored HIV Vaccine Trials Network.

GeoVax is evaluating the product in a Phase I trial for "treatment interruption" to determine if the therapeutic vaccine has the ability to treat individuals already infected with HIV; data are expected in the second half of 2013. The primary goals of this small clinical trial are to document the safety and immunogenicity of the vaccine in patients with well-controlled infections. Vaccine efficacy will be directly assessed through a brief period of anti-retroviral drug cessation. These results might indicate the vaccine's potential ability to treat HIV infection either as a stand-alone therapy or in conjunction with an oral drug.

Other Vaccines

Other companies are working on vaccines that don't use vectors. One company, Inovio Pharmaceuticals, developed its own proprietary delivery system called Cellectra. The company in July announced the results of two Phase I trials of its PennVax-B preventive HIV DNA vaccine delivered with a DNA adjuvant and with or without Inovio's Cellectra electroporation delivery device. Inovio's HIV DNA vaccine together with the Cellectra device significantly increased the number of responders producing CD4 and CD8 T-cell responses in humans.



"We now know that both antibody and T-cell responses are needed to have an effective vaccine against HIV."

DR. ROBERT MCNALLY / Geo Vax

"We use snippets of DNA as a genetic code that encodes for a protein from HIV," Dr. Kim says. "There are several important proteins. Ours is comprised of the envelope protein, which is the outside coating of the virus and enzymatic protein within that."

Dr. Kim says the plasmids, or the circular backbone DNA itself, is the carrier.

"In this plasmid, there is cassettes for an insert that encodes for the envelope protein," he explains. "But the backbone closes the loop and it carries the DNA sequence. The cassette then gets translated into a protein in our body and that's where our Cellectra delivery system comes in. This is a proprietary delivery system device that we have been using to deliver all of our cancer and HIV products. This system opens up cell membranes at the site of the injection to allow the plasmids to get in more efficiently and rapidly."

The PennVax was designed to be a T-cell emphasized vaccine. The next generation of the vaccine, PennVax GP, is designed with additional antibody generating components built into the sequences.

Inovio will soon begin a Phase I safety and immunogenicity study of PennVax GP involving about 130 patients that will be funded with a grant from the NIH and conducted by the HIV Vaccine Trials Network. Overall, the company has received about $25 million from the NIH for its vaccine research.

"Our PennVax GP is designed to cover all of the major HIV strains and subtypes that are present in North America, Europe, Asia, and Africa," Dr. Kim says. PV

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