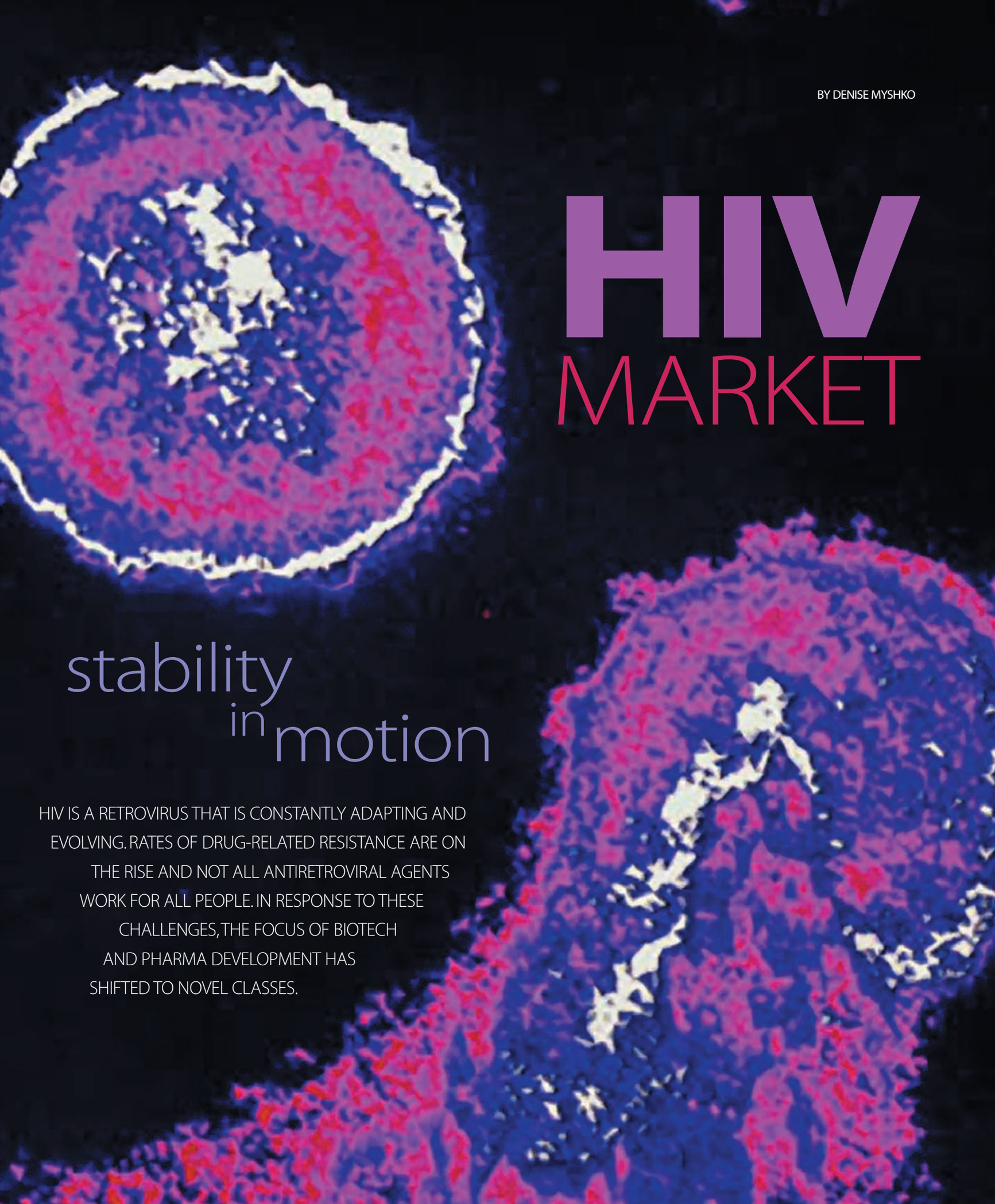
BY DENISE MYSHKO

# HIV MARKET



## stability in motion

HIV IS A RETROVIRUS THAT IS CONSTANTLY ADAPTING AND EVOLVING. RATES OF DRUG-RELATED RESISTANCE ARE ON THE RISE AND NOT ALL ANTIRETROVIRAL AGENTS WORK FOR ALL PEOPLE. IN RESPONSE TO THESE CHALLENGES, THE FOCUS OF BIOTECH AND PHARMA DEVELOPMENT HAS SHIFTED TO NOVEL CLASSES.

**Brad Aufderheide**
HealthEd

The HIV/AIDS information landscape is very large and can be confusing for patients, providers, and allied healthcare professionals. **THERE IS A STRONG NEED FOR RELIABLE EDUCATION THAT IS TARGETED, EASY TO UNDERSTAND, AND AUDIENCE APPROPRIATE.**

At first glance, the HIV market may appear to be crowded, with 88 available products for HIV/AIDS and related conditions and 77 more medicines in development. But HIV/AIDS is a complicated disease category. Rates of drug-related resistance are on the rise, and not all antiretroviral agents work for all people. People need more treatment options, and research continues, particularly into treatments that offer improved efficacy, have limited toxicities, and that help stave off treatment resistance.

The focus of biotech and pharma development has shifted to novel classes, says John M. Lebbos, M.D., director of infectious diseases at Decision Resources Inc.

"Indeed, the research investment in novel drug classes and mechanisms of action are bearing fruit with several new approaches in advanced stages of development," he says. "The most prominent of these classes are the integrase inhibitors and CCR5 antagonists. These novel approaches will address major unmet needs in the HIV market for patients with resistant virus and lack of treatment options."

The human immunodeficiency virus (HIV) market is the largest antiviral market, representing one of the most active areas of research and development within the specialty of infectious disease, according to Decision Resources Inc.

More than 20 years after the launch of the first antiretroviral (ARV) agent, zidovudine (AZT), significant advances have been achieved, although substantial unmet needs remain. The intense R&D efforts over the past two decades have yielded a rich and diverse pipeline comprising product candidates from both conventional and novel drug classes.

The near-term launch of two new drug classes — CCR5 antagonists and integrase inhibitors — demonstrates significant clinical advancement, as these novel classes will expand the therapeutic options for highly treatment-experienced patients and potentially improve upon the safety and efficacy of current ARVs.

The numbers of HIV patients demonstrate just how important these breakthroughs are. At the end of 2003, an estimated 1,039,000 to 1,185,000 people in the United States were living with HIV/AIDS, with between 24% and 27% undiagnosed and unaware of their HIV infection, according to the Centers for Disease Control and Prevention. In 2005, the estimated number of persons living with AIDS in the United States and dependent areas was 433,760.

**Without a dramatic breakthrough, about 45 million new people could be infected with HIV by 2010.**

**PhRMA**

Worldwide, there are about 39.5 million people living with HIV, and in 2006 there were 4.3 million people newly infected with HIV, according to a December 2006 report by the Joint United Nations Programme on HIV/AIDS and the World Health Organization.

## THE HIV MARKET

"The HIV market is mature and crowded, but there is still substantial opportunity to improve drugs in terms of their long-term safety profile, more convenient fixed-dose coformulated products, as well as novel classes or mechanisms of action," Dr. Lebbos says. "The major challenge is that the virus is inherently prone to mutate and develop resistance against different treatment approaches. Furthermore, vaccine development is constrained by the lack of an efficient animal model."

Dr. Lebbos says the needs and opportunities lie in developing products with improved long-term efficacy and safety as well as novel classes, which might include follow-on integrase or CCR5 inhibitors that potentially improve upon the candidates about to enter the market.

Sales of drugs to treat HIV were $7.1 billion in 2005, according to Datamonitor. The launch of new drugs and an increase in the number of people diagnosed with HIV is set to make AIDS medicine a $10.6 billion market by 2015, according to an April 2007 report by Datamonitor. Factors driving this growth include an increase in the number of people diagnosed, and the launch of several new drugs and drug classes that offer new hope to patients who otherwise would have at best limited, but perhaps no therapeutic options left at all.

Datamonitor researchers say the HIV/AIDS market is set to undergo significant changes during the next 10 years as drugs that work through novel mechanisms and next-generation versions of existing drugs are launched.

"This is very dynamic time in the HIV/AIDS market," says Glenn Mattes, president of Tibotec Therapeutics. "I would almost call it stability in motion, where we have patients who are doing well yet this market is evolving to the point where perhaps the goals of therapy should be reassessed and become a little more aggressive."

Decision Resources forecasts a 4.6% annual growth in the 2006-2011 HIV therapies market attributable to the launch of novel classes of anti-retrovirals; thereafter, annual

### MEDICINES IN DEVELOPMENT FOR AIDS*

| | |
|---|---|
| 35 | Antivirals |
| 19 | Vaccines |
| 7 | Immuno-modulators |
| 4 | Anticancer agents |
| 2 | Anti-Infectives |
| 2 | Gene Therapies |
| 1 | Antifungals |
| 9 | Others |

* Some medicines are listed in more than one category.

Source: PhRMA, Washington, D.C. For more information, visit phrma.org.

**Dr. Brigitte Sanders**
Southern Research Institute

The current issue with HIV drugs is that they are only directed against four targets. **THE DRUG PIPELINE NEEDS TO BE EXPANDED TO INCLUDE OTHER HIV PROTEINS AND ENZYMES.**


market growth will slow to less than 1% through 2016 and 2021, as patents on key HIV products expire.

According to Decision Resources, commercial opportunity in the treatment-naive patient segment lies in developing convenient products with high barriers to resistance and favorable long-term toxicity profiles. The market for treatment-experienced patients offers opportunity for agents with novel mechanisms of action and for follow-on therapies with activity against multidrug-resistant HIV strains.

The continuing uptake of new therapies — including the very recently approved Pfizer drug Selzentry (maraviroc, which received FDA approval Aug. 6, 2007); Bristol-Myers Squibb/Gilead's Atripla (approved in the United States July 12, 2006); and Tibotec's Prezista (darunavir, approved by the FDA in June 23, 2006) — and the launch of several novel agents, such as Merck's Isentress (raltegravir, previously known as MK-0518) will drive near-term expansion of the HIV market, according to Decision Resources.

## THE PUBLIC SUPPORTS BREAKING PATENTS TO ENSURE ACCESS TO HIV/AIDS DRUGS IN POORER COUNTRIES

In May 2007, Brazil's President Luiz Inacio Lula da Silva took steps to make an inexpensive generic version of a patented AIDS drug manufactured by Merck & Co. by issuing a compulsory license that would bypass Merck's patent. A compulsory license is a legal mechanism that allows a country to manufacture or buy generic versions of patented drugs while paying the patent holder only a small royalty.

Most adults in the United States (57%) say they are in favor of the country's decision, while 20% say they are opposed, according to a recent poll by Harris Interactive for The Wall Street Journal Online's Health Industry Edition.

Overall, 61% of U.S. adults believe poorer countries should be allowed to break companies' patents on HIV/AIDS drugs if doing so would help them treat more of their population; 33% say they believe that ignoring companies' patents on HIV/AIDS drugs hinders the development of new drugs, while 40% say they disagree with this statement.

Compared with five years ago, fewer U.S. adults believe that the global HIV/AIDS epidemic is worsening; 40% think the global HIV/AIDS epidemic has worsened in the last five years, down from 58% in 2004 who said the same and 16% say they feel the global HIV/AIDS epidemic has gotten better, while 32% say things have stayed about the same.

Source: Harris Interactive for The Wall Street Journal Online's Health Industry Edition, Rochester, N.Y.
For more information, visit harrisinteractive.com.

According to the new Pharmacor report Emerging HIV Therapies, Atripla will address the significant need for a more-convenient therapy, while the efficacy of Prezista, Isentress, and Selzentry will benefit highly treatment-experienced patients.

"There is plenty of room for innovation to improve treatment: products that are robust and durable around resistance and genetic barrier, those that have better tolerability, or ones that can help patients get their viral load down and their CD4 count up quickly and as comfortably as possible," Mr. Mattes says. "That's where the real opportunity lies."

Atripla, which is commercialized in the United States by Bristol-Myers Squibb and Gilead Sciences through a joint venture, is a once-daily single tablet regimen approved for the treatment of HIV-1 infection in adults for use either as stand-alone therapy or in combination with other antiretroviral agents. The product is a combination of efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI), emtricitabine, and tenofovir disoproxil fumarate, both nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs). Efavirenz is marketed by Bristol-Myers Squibb as Sustiva in the United States, Canada, and six European countries. Emtricitabine and tenofovir disoproxil fumarate are commercialized by Gilead Sciences as Emtriva and Viread, respectively.

Tibotec Therapeutic's Prezista, co-administered with low-dose ritonavir, is indicated in combination with other antiretroviral medici-

**Glenn Mattes**
Tibotec Therapeutics

**THIS IS A VERY DYNAMIC PERIOD IN THE HISTORY OF AIDS THERAPY.** There are a lot of options available for physicians and patients to consider, and it is a period of time when therapeutic options are evolving.

nal products for the treatment of human immunodeficiency virus (HIV-1) infection in highly pretreated adult patients who failed more than one regimen containing a protease inhibitor. Prezista is currently approved in several areas, including the United States, Canada, and the European Union. Tibotec Therapeutics is a division of Ortho Biotech L.P., a Johnson & Johnson company.

Tibotec continues to conduct research on Prezista and other HIV/AIDS therapeutics. For Prezista, the company is conducting the GRACE study (Gender, Race And Clinical Experience) to look at treatment-experienced adult women with HIV to evaluate gender and race differences in response to Prezista. GRACE, a multicenter, open-label Phase IIIb trial, is looking at gender differences in the efficacy, safety, and tolerability of Prezista during a 48-week treatment period.

The study also will explore racial differences in treatment outcomes. Today, women account for almost one-third of new HIV diagnoses in the United States, and rates of HIV infection are particularly high among women of color. African-American women, who represent only 13% of the U.S. female population, account for 64% of female AIDS cases.

**The HIV market will grow from $7.1 billion in 2005 to an estimated $10.6 billion in 2015.**
**Datamonitor**

In July, the company submitted an NDA for its next-generation NNRTI, TMC125 (etravirine), which has shown antiviral activity in patients with NNRTI resistance.

The August 2007 approval of Selzentry, a CCR5 antagonist, for use along with other antiretroviral agents for treatment-experienced patients infected with CCR5-tropic HIV-1, makes the Pfizer drug the first member of a new class of oral HIV medicines.

Discovered by Pfizer scientists in 1997, Selzentry works by blocking viral entry into human cells. Rather than fighting HIV inside white blood cells, it prevents the virus from entering uninfected cells by blocking its predominant entry route, the CCR5 co-receptor.

In Europe, the product, to be known as Celsentri, has been recommended for approval by the Committee for Medicinal Products for Human Use (CHMP) of the Medicines Evaluation Agency (EMEA).

Though innovation is crucial for patients, drug developers understand the intricacies and challenges involved in breakthrough developments.

"Any drug that is first in class is going to have a higher hurdle for safety because there is no experience with blocking that particular target," says Randy Tressler, M.D., director and team leader of the global HIV medical team at Pfizer. "Long-term safety is going to require a large database to follow patients for many years to address the concerns that patients, prescribers, and regulators have."

He says the preliminary data that have been presented in small numbers of patients indicate that the safety profile for the new classes looks good compared with the other agents that are currently on the market.

"We have to recognize that these are small databases; small numbers of patients followed for a short period of time," Dr. Tressler says. "Long-term toxicities will not be known for a number of years. Rare events may not be understood until larger numbers of patients have been dosed."

Another product under review at the FDA is Merck's Isentress, which would be used in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy (ART). U.S. regulators have granted Isentress priority review.

If approved, Isentress would be the first in a new class of antiretroviral agents called integrase inhibitors that inhibit the insertion of

HIV DNA into human DNA. Inhibiting integrase from performing this essential function blocks the ability of the virus to replicate and infect new cells. There are drugs in use that inhibit two other enzymes critical to the HIV replication process — protease and reverse transcriptase — but currently no approved drugs inhibit integrase.

"The major issues with HIV drug development are drug resistance and toxicity development," says Brigitte Sanders, D.V.M., Ph.D., senior project leader, infectious disease research, drug development division, Southern Research Institute. "A new drug needs to be active against multidrug resistant strains of HIV, and resistance development against the new drug needs to be nonexistent or slow. The drug needs to have an additive or synergistic effect in combination with other FDA-approved drugs, since today's HIV therapies almost always are administered in combination. Since the current medications against HIV have severe toxicities, such as lipodystrophy and liver toxicities, the newly developed drugs need to have a favorable toxicity profile because they are taken for years."

**As many as 1.2 million U.S. residents are estimated to be living with HIV infection. It is estimated that close to 40 million people worldwide live with HIV, yet the vast majority are unaware of their status.**

**PhRMA**

Some products that are receiving attention have new mechanisms of action.

"The drugs with new mechanisms of action are the entry inhibitors that target the molecules involved with HIV entering into the cell, such as the envelope protein and the HIV cell receptors CD4, CCR5, and CXCR4," Dr. Sanders says. "Other hot drugs currently in the clinical trial phase are the ones that inhibit the enzyme integrase."

Biopharmaceutical researchers also are intensifying their work toward the development of vaccines, according to a November 2006 report from the Pharmaceutical Research and Manufacturers of America (PhRMA).

In addition to the 19 vaccines in development there are 35 antivirals, two anti-infectives, four cancer treatments, seven immunomodulators, one antifungal, two gene therapies, and nine other medicines in human clinical trials or before the FDA awaiting approval.

## MARKETING ISSUES

When launching a new HIV product, pharmaceutical marketers need to understand and know their patient populations better, says Brad Aufderheide, VP, strategic planner, HealthEd.

"Not only has the virus evolved but the marketplace has evolved dramatically over time," he says. "The industry standard has shifted, and the patient populations have shifted. Over time, the hot topics have shifted as well. Initially we were just trying to find a drug that was going to save lives. There was a horrible immediacy. Then we wanted to make sure people were comfortable with their therapy and that they understood the risk of transmission. And we wanted to help people successfully stay on the treatment regimen."

He says the HIV/AIDS therapeutic options have gotten so much better that patients can oftentimes enjoy long, fulfilling lives.

"The role of the provider being responsible for telling the patient to take his or her medications has evolved to one where the patient and the provider are partners in a treatment team," Mr. Aufderheide says. "That has been a big paradigm shift."

Pharmaceutical companies can play a role in that treatment relationship by providing the necessary information about their products that patients would not normally have access to.

"What we do here at HealthEd is to take that information and put it in a context that is user-friendly, of appropriate health literacy, and is culturally appropriate so that people can readily understand and act on the information for better health outcomes," Mr. Aufderheide says.

Getting share of voice in a crowded marketplace and a narrower target audience base — several thousand doctors prescribe most of the antiretrovirals in the entire country — will be a challenge as well, he says.

"The more complicated the marketplace becomes, the more message niches come into being that require education and understanding for our audiences," he says. "Many of our clients have recognized this fact and have chosen to take a focused approach on initiatives that have measurable outcomes, are patient-tested and driven, and are rooted in proven behavioral models."

He says shifting patient education earlier is yet another important strategy that the industry is moving toward.

"Patients play such a critical, active role in treatment decisions and adherence that there need to be sound patient marketing strategies in place before launch to expedite product adoption and ensure appropriate, ethical use," Mr. Aufderheide says. "There is a need to prime the market before launch and clearly explain how to best use the product, manage side effects, and plan for potential drug-drug interactions." ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

## Experts on this topic

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