

The Changing HIV/AIDS Landscape:

The number of therapies available to improve and extend the lives of HIV/AIDS patients is increasing. So is the cost of providing them. Biotechs and others are working on HIV blockers, vaccines, and gene therapies that may one day benefit patients and keep the cost of staying healthy down.

BY LOLA BUTCHER

B iotechnology, a superhero for treating some autoimmune conditions and cancers, has yet to fully brandish its cape in the face of an arch-villain named HIV/AIDS. But in laboratories around the world, scientists are working on biologic approaches to treating and preventing this devastating scourge.

Their work is progressing slowly, and, even in optimistic America, there is not much hype about a near-term breakthrough. Though the words *cure* and *prevention* are not even whispered, the number of therapies available to improve and prolong the lives of HIV/AIDS patients is increasing steadily — along with the expense of providing them.

“The foreseeable future does not give much hope to a cure or vaccine for this disease,” says Mesfin Tegenu, RPh, president of Philadelphia-based PerformRx, the pharmacy benefit management division of Ameri-Health Mercy, the largest Medicaid managed care plan in the country. “We anticipate increased enrollment of individuals with HIV/AIDS and a

Progenics’ CCR5 entry inhibitor, PRO-140, is in a class of products that blocks the HIV virus instead of targeting it. Richard W. Krawiec, PhD, Progenics’ V.P. of corporate affairs, says PRO-140 may require injections only monthly.



PHOTOGRAPH BY PETER HVIZDAK

Where Do Biologics Fit In?

corresponding increase in the number of drugs used during treatment, and an escalation in the overall cost of therapy.”

In a Pharmaceutical Research and Manufacturers of America survey last year, its members were testing 77 drugs and biologic therapies for HIV/AIDS. Some of those will join the arsenal of treatments approved in the last two decades.

Most of this activity is taking place in the antiviral category, where biotechnology is heavily represented with novel approaches to slowing HIV's progress in infected patients. The second busiest front is vaccines, where biotechs are in the early phases of testing preventive and therapeutic candidates. The biotechnology industry also is advancing gene therapies, which are in the early stages of development but offer a promising approach.

HIV BLOCKERS

So far, biotech's biggest contribution to the HIV/AIDS challenge may be enfuvirtide (Fuzeon), approved in 2003 to treat HIV infection in patients who have detectable viral loads even though they are already taking anti-HIV drugs.

Developed by Trimeris, a biotechnology company in Morrisville, N.C., enfuvirtide is the first in a class of medications known as fusion (or entry) inhibitors, which block HIV before it can infect healthy T cells. Other antivirals work inside T cells, after HIV has infected them and begun to replicate.

Tony Zappa, PharmD, executive vice president at BioScrip, a spe-

cialty pharmacy in Eden Prairie, Minn., says many of the more than 25,000 HIV patients who receive therapies through his company each month use enfuvirtide.

“Clinically, it's probably one of the most promising therapies because it stops the virus from infecting the cells in the first place,” Zappa says. “It really stops the game.”

That said, he and others find enfuvirtide less attractive than other new therapies because it requires a twice-daily injection. That makes adherence difficult, considering that some patients experience severe injection reactions. Some patients struggle with the out-of-pocket cost of enfuvirtide, which is used in conjunction with other anti-HIV drugs.

“Those patients who were cruising along at \$12,000 to \$15,000 a year for their drugs all of a sudden had \$20,000 a year added on top,” says Zappa.

While the biggest hit goes to the health plan or government agency that covers the patients, many of those insured have substantial copayments on specialty items such as enfuvirtide.

“If you're looking at 20 percent of about \$1,900 a month, it gets pretty expensive for people,” Zappa says.

As Trimeris and its partner Hoffmann-La Roche work on a next-generation therapy that has greater longevity and fewer side effects, other biotechnology companies are developing entry inhibitors as well. Tanox, based in Houston, was excited about the results of its phase 2 trial for TNX 355, a monoclonal antibody designed to block

HIV infection further upstream than enfuvirtide.

Brian Abrahams, MD, an analyst who tracks biotechnology companies for CIBC World Markets, thinks Tanox' recent acquisition by Genentech, its partner in the development of another product, will slow TNX 355's path to market. A planned phase 3 trial in 2006 didn't happen, and a Tanox spokesperson said the company is still discussing the results of the phase 2 trial with the U.S. Food and Drug Administration.

Although he thinks TNX 355 has shown “a lot of promise,” Abrahams doubts that Genentech will pursue its development, and, because it would be an infusion, he is not sure anyone else will, either.

“It's sort of a potential new step forward with a different mechanism of treating the disease,” Abrahams says. “But given the fact that there are so many other drugs in development that have similar activity and can be taken orally, I think the market potential for TNX 355 would be limited.”

Most notably, Pfizer is conducting phase 3 trials on its small-molecule drug maraviroc, which blocks HIV infection in a slightly different way than TNX 355 or enfuvirtide. Pfizer is expected to file a new drug application for maraviroc this year. Another company, Progenics Pharmaceuticals of Tarrytown, N.Y., achieved fast-track status for PRO-140, a monoclonal antibody now in phase 1b trials. The two companies are traveling a difficult road — one pockmarked by developmental delays and aban-

done therapies stemming from the discoveries of liver diseases and increased viral loads in patients who enrolled in trials of other small-molecule compounds.

Richard W. Krawiec, PhD, Progenics' vice president of corporate affairs, says PRO-140 appears to sidestep some of the problems found with enfuvirtide and the small-molecule HIV blockers. PRO-140 may require injection only once a month or even less, and the toxic side effects and adherence challenges as-

sociated with small-molecule drugs might be avoided, he says.

"With monoclonal antibodies, we expect no drug or food interactions, so it wouldn't be 'Take it after a meal or before a meal,'" he says. "You wouldn't expect interactions between drugs, nor would you expect liver toxicity, because it's not metabolized by the liver."

Zappa expects the new entry inhibitors to hit the market in 2008 or 2009 at the earliest. Based on past experience, he expects 10 to 15 per-

cent of patients now being treated to receive one of the new therapies as an add-on to their regimen.

"You'll see the cost for those people jump by, I'm guessing, \$10,000 a year or more, depending on how those drugs are priced," he says.

VACCINES

Michael Wong, MD, board policy chair for the American Academy of HIV Medicine and an HIV/AIDS researcher at Beth Israel Deaconess Medical Center in Boston, calls find-

HIV/AIDS: The lay of the land for patients and payers

Like the constantly mutating virus underlying it, the HIV/AIDS landscape is hard to describe in any definitive way. With many HIV/AIDS patients living long and productive lives, the situation seems promising in some ways — and devastating in others.

In the 26 years that have passed since the first AIDS death in the United States, more than 550,000 Americans have died of the disease, and an estimated 1.2 million living are living with HIV/AIDS today, according to the U.S. Centers for Disease Control and Prevention. Of those, an estimated 34 percent have AIDS, 42 percent are HIV positive but have not yet progressed to AIDS, and the remaining 24 percent are undiagnosed. The CDC estimates about 40,000 new HIV infections occur in the United States each year, a figure far below the peak of the mid-1990s but one that has held steady for nearly a decade.

Worldwide, the picture is much more grim. More than 39 million people were living with HIV at the end of 2005, a year in which 2.8 million lost their lives to AIDS and more than 4 million became newly infected with HIV, according to the United Nations Programme on HIV/AIDS.

Sub-Saharan Africa, the global epicenter of the HIV/AIDS pandemic, is home to almost 64 percent of all people living with HIV, although only about one tenth of the world's population lives there. Two million of the HIV/AIDS victims are children younger than 15, and some 12 million orphans lived in sub-Saharan Africa in 2006.

The better news is that drug therapies — at least for those who have access to them — have changed an HIV diagnosis from a death sentence to a chronic condition with a wide array of treatment options. Currently, three classes of products — reverse transcriptase inhibitors, protease inhibitors, and entry inhibitors — have received FDA approval, and combination therapy has proven most effective. Over time, however, patients begin to develop resistance to the drugs, creating a continuing need for new treatment strategies.

The antiretroviral therapies, as they are called, slow the progression of HIV infection to AIDS and, as a result, lead to an increase in the number of people living with AIDS. In fact, the estimated number of people living with AIDS increased by 30 percent from 2000 to 2004, according to the Pharmaceutical Research and Manufacturers of America.

EFFECT ON PAYERS

Compared to chronic conditions like diabetes and cardiovascular conditions, which affect far larger populations, HIV/AIDS is an almost negligible expense for many health plans. In fact, the Kaiser Family Foundation reports that spending on HIV care was estimated to account for less than 1 percent of all direct personal healthcare expenditures in the nation in 1998, the most recent year for which information is available.

But for payers in areas with a high incidence

ing a vaccine that either prevents or treats HIV infection “the holy grail.”

“In spite of a lot of good research, we still don’t really know exactly what parts of the immune system are truly needed to control or prevent infection,” he says.

The search for a vaccine dates back to the late 1980s, but it is difficult to find anyone who sees light at the end of a dark tunnel.

“It’s not to say we’re nowhere closer to a vaccine, but it’s been really elusive,” Wong says. “It’s not as easy

as making a vaccine for influenza.”

The traditional approach to developing a vaccine — using a weakened version of a virus to trigger an immune response against the real disease — does not work for HIV. Thus, the International AIDS Vaccine Initiative (IAVI) characterizes its challenge as one “to develop a vaccine without a definitive road map.”

Development of any new vaccine usually takes 10 to 15 years and up to \$200 million, but IAVI lists barriers beyond time and money:

- HIV is one of the most complicated viruses ever identified because it targets and destroys the very immune system that a vaccine traditionally triggers.
- The genetic instability of HIV is daunting in that millions of viruses are constantly produced with high mutation rates.
- Scientists lack a good model for early testing of vaccine candidates in animals.
- Questions linger about the most effective approach — or combi-

of HIV/AIDS — and for most payers looking into the future — the cost of treating HIV/AIDS patients cannot be ignored, says Tony Zappa, PharmD, executive vice president at BioScrip, a specialty pharmacy in Eden Prairie, Minn.

Drug therapy accounts for more than 70 percent of the cost of treating HIV/AIDS patients. Zappa expects annual cost increases between 8 and 10 percent, reflecting both higher prices and utilization levels to continue for the next few years.

“If there were no products launched into the marketplace, that’s probably what we’d see for at least the next four or five years because there are no products waiting to go generic,” he says. “All of these are branded products. They’re all very expensive.”

With a current life expectancy of 24.2 years following diagnosis, the lifetime cost of HIV treatment and care is estimated at \$385,200, according to a study published in the November 2006 issue of *Medical Care*. The study, conducted by Cornell University researcher Bruce Shackman, MD, used 2004 prices, discounted for future inflation. Mesfin Tegenu, RPh, president of PerformRx, the pharmacy benefit manager for AmeriHealth Mercy, a Philadelphia Medicaid managed care plan, notes that newer drugs that have become available since 2004 are likely to result in longer life expectancy — and higher costs.

The financial burden associated with the HIV/AIDS epidemic is of particular concern to government agencies and Medicaid managed care plans. More than 70 percent of HIV/AIDS

patients depend on Medicaid, Medicare, or state-level AIDS drug assistance programs, or are uninsured.

Of particular concern to Tegenu and others responsible for Medicaid managed care plans is the relationship between behavioral health issues and HIV/AIDS. Citing research that suggests the prevalence of HIV/AIDS is between 5 and 15 percent in the behavioral health population, versus less than 1 percent in the general population, Tegenu says Medicaid managed care enrollment typically includes the higher incidence of — and cost associated with — HIV/AIDS.

Zappa, whose pharmacy markets to HIV/AIDS patients, says that HIV infection rates are higher among low-income and indigent people than other socioeconomic groups.

Those infection rates, which were flat or even decreasing for a few years, are growing again, Zappa says. In fact, the two groups with the fastest-growing infection rates are those aged 18 to 25 and people over age 50, many of whom are still in the workplace.

“The infection rates are growing in age categories that are still highly productive,” Zappa says, pointing out that trend has implications for many employer-sponsored health plans.

“If you’ve got a 100,000-life plan, you probably have 500 to 1,000 people in your plan currently with HIV,” he says. “And given the rates [of new infection], you could be adding 50 to 75 new cases a year, depending on how your member mix breaks out by age, ethnicity, and gender.”

nation of approaches — to triggering an immune response to HIV.

- Scientists do not know whether a universal vaccine could immunize against the different subtypes of the HIV virus or whether a different vaccine must be developed for each.

PhRMA identifies 19 HIV vaccines — some preventive and some therapeutic — in the pipeline. Of those, only one is in a phase 3 trial, and Sanofi Pasteur, its lead developer, is reluctant to talk about its efforts.

The study, sponsored by the U.S. Army, includes four immunizations with Sanofi Pasteur's vaccine and two immunizations with the AIDSVAX vaccine from VaxGen, a biotechnology company in Brisbane, Calif. Final results are expected in 2009.

Despite its phase 3 status, a Sanofi Pasteur spokesperson noted that even under the best circumstances, a product emerging from its clinical trial of 16,000 volunteers in Thailand is "years and years" away.

VaxGen's own phase 3 trial of AIDSVAX ended with disappointment in 2003 when the vaccine candidate was not shown to prevent HIV infection or slow the progression of the disease among those who received the vaccine but later became infected.

GENE THERAPY

At least two companies — Enzo Biochem and VIRxSYS — are pursuing a gene-based immunotherapy for the treatment of HIV. VIRxSYS, a Gaithersburg, Md., company with phase 2 trials under way for its VRX496 therapy, received nearly

VIRxSYS is confident about its VRX496 gene therapy, and apparently, so are investors. "It's very encouraging to see about 60 percent of our investors from 2004 and 2005 come back in 2006 based on our phase 1 results," says Riku Rautsola, PhD, the company's president and CEO.



PHOTOGRAPH BY ROB CRANDALL

\$32 million in venture capital, a record for a gene therapy company, in 2005. Last year, investors offered another \$20 million, in a follow-up warrant round to the 2005 financing, bringing the total investment to date to \$87 million.

VRX496 modifies a patient's own CD4 T cells with a lentiviral vector that is equipped with an anti-HIV gene that blocks HIV replication by targeting the HIV envelope gene. In addition to blocking HIV replication to reduce viral load, it appears that VRX496 repopulates a patient's immune system with HIV-resistant CD4 T cells, restoring normal immune function against HIV and other infections.

Riku Rautsola, PhD, the company's president and CEO, does not call the therapy a cure for HIV, but says in theory it could be a cure for AIDS because the therapy may prevent and perhaps even reverse the progression of HIV to AIDS. He believes the therapy eventually may be appropriate for all HIV patients, but current plans call for seeking initial approval to treat early-stage HIV

patients, patients who experience toxicity from current treatments, and those in whom the HIV virus has become resistant to other therapy. Results of a phase 1 study, published in the *Proceedings of the National Academy of Sciences*, were encouraging.

From a payer perspective, Rautsola says, the cost would be comparable to bone marrow transplantation. "Those treatments usually cost about \$100,000 to \$125,000, so that's where our benchmark will be. Because the VRX496 therapy is designed to be a one-time treatment, we believe that this will represent a significant total cost savings during the anticipated life of a patient, while, at the same time, relieving patients from the burden of daily drug regimens."

None of these developments have come easily. Those that make it to market, though, may represent an enormous step forward in the treatment of the epidemic. **BH**

Lola Butcher, who writes about health policy and the business of healthcare, lives in Springfield, Mo.