Emerging Drugs Show Promise Against HIV

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After a dearth of new drugs for people infected with HIV, this year promises a bumper crop of medicines that may help combat rising resistance to older therapies.

Two of the experimental medicines take entirely new approaches in thwarting the HIV virus; a third overcomes resistant viruses by taking a new tack on an enzyme many older drugs target.

Amid scores of drugs in the pipeline presented this week at the annual Conference on Retroviruses and Opportunistic Infections in Los Angeles, several drugs look promising in pivotal efficacy studies including Merck & Co.'s MK-518 and Pfizer Inc.'s maraviroc. University of Pittsburgh researcher John Mellors called the drugs' performance "a really remarkable development" and the best he'd seen since the debut of AIDS cocktail therapy over a decade ago. They, and another that's garnering attention, Johnson & Johnson's TMC125, are heading for review by the Food and Drug Administration this year.

Because HIV mutates quickly to outwit drugs, cocktails of two or three drugs are used to simultaneously attack the virus in different spots. The effectiveness of these cocktails is greater than the sum of their parts.

But doctors estimate tens of thousands of American patients are infected with viruses that have become resistant to at least one class of HIV drug, weakening the cocktail approach. Some patients who have fought HIV for years have now run through the roughly two dozen drugs available.

In these patients, the mutant HIV is rebounding, suppressing their immune systems and making them vulnerable to infections from other viruses, bacteria and fungi. So the need for fresh medicines is growing more acute. Now years of research and testing appear ready to pay off.

Data on clinical tests of the new drugs buoyed spirits at the conference. "It's very exciting," said Houston-based activist **Nelson Vergel**, who has wrestled with HIV since 1983. "This is the first time we've had so many agents for multidrug resistance from one meeting," he said.

The arrival of new medicines at the same time is especially heartening, doctors say. Introducing new drugs one at a time can make it easier for the virus to fight them off. Cocktails with two new ingredients, for instance, could remain potent longer.

The new drugs may all be on the market by the end of 2007, and some patients in need can get access already. The drugs usually aren't priced until they are approved.

Among the most advanced and promising of the new drugs is one from Merck, known until now by the code name MK-518. The company yesterday announced it will carry the generic name raltegravir and the tentative brand name Isentress, under review by the FDA. The drug, which inhibits an enzyme that HIV uses to copy itself into the DNA of white blood cells, is the first in a new class called integrase inhibitors.

Mr. Vergel, a 48-year-old retired chemical engineer, started taking the drug last May as part of an antiviral cocktail in a trial, and three weeks later his virus dropped to an undetectable level. The HIV rebounded after six months, but a rise in his infection-fighting white blood cells, called CD-4 cells, has persisted.

Robin Isaacs, Merck's executive director of infectious-disease clinical development, said the two latest studies show the drug, taken twice a day, helped drive virus levels down to undetectable in slightly more than 60% of volunteers when added to an antiviral cocktail. Only 33% to 36% of patients receiving a placebo had similar reductions. Volunteers taking the new drug also saw higher levels of CD-4 cells than patients receiving placebo. A Merck spokesman said the company expects to file for FDA approval in the second quarter of this year.

Gilead Sciences Inc. is testing a once-a-day integrase inhibitor dubbed GS-9137, which might make it easier to combine with other medicines taken on the same schedule.

Another class of drugs, called entry inhibitors, may also debut this year. These medicines keep HIV out of white blood cells. One door to these cells, called CCR5, has been the object of research by several drug companies, but side effects have marred some of the early work. Pfizer's maraviroc is beginning to convert some skeptics and is on a fast track for FDA approval. "Though this class has gotten beaten up a bit over the last year, the data on maraviroc is substantially better than anyone was expecting," said Martin Delaney, a founder of the treatment advocacy group Project Inform in San Francisco.

Two new studies at the meeting found that maraviroc taken with an antiviral cocktail was twice as likely to suppress HIV virus to undetectable levels as a placebo taken with the cocktail. It also doubled the rise in disease-fighting CD-4 cells.

The ranks of patients resistant to existing drugs are growing. With about one million Americans infected with HIV, and roughly 400,000 patients in treatment, Harvard University researcher Daniel Kuritzkes says 40,000 people harbor multidrug-resistant HIV.

But fewer than half of all such patients could expect to benefit from maraviroc, because most patients on long-term treatment harbor HIV strains that enter through a different

portal, known as CXCR4, which is unaffected by the drug, said Dr. Steven Deeks, an HIV specialist at the University of California, San Francisco.

For Pfizer's clinical trials, South San Francisco-based Monogram Biosciences tested potential patients to determine which portal HIV used to enter the cell. Only patients whose HIV entered through CCR5 were admitted to the trial. In a first for AIDS drugs, FDA approval might require doctors to ship samples to Monogram's headquarters for testing before prescribing maraviroc.

"This is going to be a logistical nightmare," said Dr. Deeks. But Monogram Chief Financial Officer Alfred Merriweather noted Pfizer is paying for the company's costs to set up collection systems.

In Boston, Stephen Boswell, head of Fenway Community Health, a group of nonprofit community health clinics, says those lab tests could prove expensive. Monogram hasn't yet set a price, but it now sells similar tests for $1,000 to $1,500 per patient.

Another compound, TMC125, from Johnson & Johnson's Tibotec unit, has been developed to overcome viruses that have become resistant to other drugs in a class known as non-nucleoside reverse transcriptase inhibitors. The company expects to file for FDA approval in the second half of 2007.