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## Chemical & Engineering News

### Cover Story

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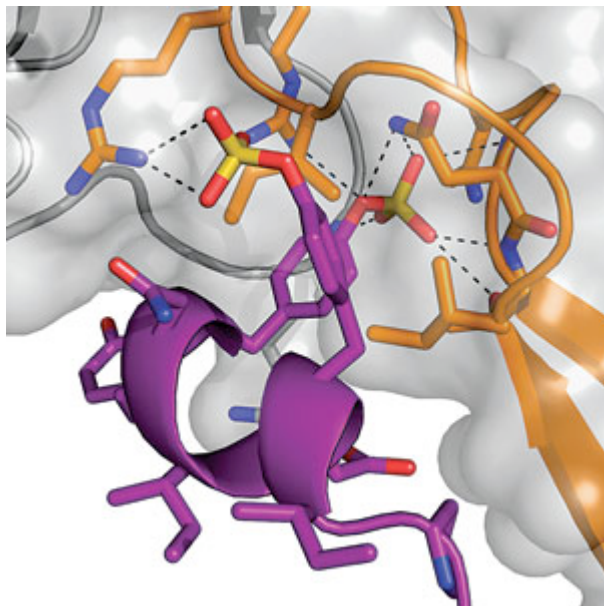
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## New Antiretrovirals

### In recent years, new drugs have brought better options for controlling HIV

Ann Thayer

"**IN THE 1980s**, if you could give people three months with a monotherapy, it was a big deal," says Roger J. Pomerantz, a doctor who has worked in the HIV arena since 1982. The first anti-HIV drug, GlaxoSmithKline's zidovudine (AZT), was approved in 1987. In the early 1990s, more drugs emerged and helped increase life expectancy to maybe a year, Pomerantz says.



Jonathan Stuckey/NIAID and *Science*

**POTENT INHIBITORS** Some HIV drugs work by blocking the interaction between the CCR5 cell coreceptor (purple) and the virus's gp120 envelope protein (gray).

By the mid- to late-1990s, more-effective combinations, called highly active antiretroviral therapy (HAART), brought dramatic changes that meant HIV was no longer an immediate death sentence for

many patients. Today, a 20-year-old HIV-positive person starting HAART can expect to live to be about 69 years old, according to a recent analysis of 43,000 people in wealthy countries.

Although a tremendous prospect for many HIV-infected people, the life expectancy is still below the 80-year average for an uninfected person. Moreover, these statistics don't reflect undeveloped countries where the disease burden is high. Despite the variety of powerful drugs, there is still room for better ones that more effectively attack HIV and give long-term patients a better quality of life.

Worldwide, death rates from HIV have started falling, according to the [Joint United Nations Program on HIV/AIDS \(UNAIDS\)](#). In 2007, about 3 million people were on drug therapy in low- and middle-income countries, a 10-fold increase over six years ago but representing only about 30% of those considered most in need. For those with access to treatment, HIV has become a manageable condition.

HAART combines different drugs that inhibit key stages of the HIV life cycle. If taken correctly and consistently, HAART can make the amount of virus, or viral load, undetectable in a person's bloodstream, an achievement that not only improves health but also is believed to reduce transmission. However, adherence to the drugs must be a daily and lifelong commitment because missed doses can lead to viral resistance.

More than 20 antiretroviral drugs are on the market for use in a variety of recommended combinations. Even so, no drug is perfect, and they differ in potency, ease of use, interactions with other drugs, and side-effect and safety profiles. For these reasons, and to help patients who have been failed by previous drug regimens, researchers still see a need for new agents with different mechanisms of action.

Since late 2005, Pomerantz has been president of [Tibotec](#), an infectious diseases company that [Johnson & Johnson](#) acquired in 2002. In the past two years, Tibotec has brought two new antiretrovirals to the market, and it has another in advanced development. When approved in January, Intelence (etravirine) was the first nonnucleoside reverse transcriptase inhibitor (NNRTI) approved in a decade.

NNRTIs inhibit reverse transcriptase, the enzyme that the HIV virus uses to make DNA from its RNA template. HIV invades human immune system cells by binding to and fusing with them. Once inside, HIV transcribes its RNA into DNA and then irreversibly integrates its genetic material into the human cells' genome. The process may stop at this stage, leaving the integrated viral DNA dormant in reservoirs of cells within the body.

**ALTERNATIVELY**, in CD4<sup>+</sup> T cells, which the body uses to fight infections, the cells' machinery and HIV's protease work together to churn out viral proteins and assemble them into new viral copies that can go off to infect other immune cells. This process kills the CD4<sup>+</sup> T cells, and eventually, HIV destroys enough cells that the immune system becomes deficient. In other words, a person progresses to AIDS and is indefensible against other infections and diseases.

Along with several virus subtypes or "clades" around the world, HIV is highly mutable, which allows it to escape the drugs trying to stop it. Before Intelence, scientists thought that just one mutation in the reverse transcriptase enzyme would knock out the whole NNRTI class of drugs, Pomerantz says.

"Many of the single mutations from the first generation won't have any effect on the drug's performance," Pomerantz says of Intelence. In fact, the genetic barrier is high, and it may take

several mutations to stop Intelence and similar drugs from working (C&EN, Feb. 11, page 14).

Intelence was approved for use in treatment-experienced patients who have failed other drug regimens. Tibotec is developing TMC278 (rilpivirine), a similar compound, as a first-line therapy for newly diagnosed, or treatment-naïve, patients.

TMC278 is slightly more powerful than Intelence and can be given just once per day, Pomerantz says. It is also a good candidate for a fixed-dose combination with other HIV drugs. Tibotec has just started Phase III clinical trials that will test the drug's durability as a therapy for 48 weeks to gain U.S. approval and for 96 weeks for European approval.

DRUG THERAPIES			
Antiretrovirals emerging over the past two decades have changed HIV therapy			
PRODUCT	GENERIC NAME	MANUFACTURER	APPROVED
<b>Nucleoside/Nucleotide Reverse Transcriptase Inhibitors</b>			
Retrovir	Zidovudine (AZT)	GlaxoSmithKline	1987
Videx	Didanosine (ddI)	Bristol-Myers Squibb	1991
Hivid <sup>®</sup>	Zalcitabine (ddC)	Roche	1992
Zerit	Stavudine (d4T)	Bristol-Myers Squibb	1994
Epivir	Lamivudine (3TC)	GlaxoSmithKline	1995
Combivir	Lamivudine, zidovudine	GlaxoSmithKline	1997
Ziagen	Abacavir	GlaxoSmithKline	1998
Trizvir	Abacavir, zidovudine, lamivudine	GlaxoSmithKline	2000
Viread	Tenofovir	Gilead Sciences	2001
Emtriva	Emtricitabine	Gilead Sciences	2003
Epzicom	Abacavir, lamivudine	GlaxoSmithKline	2004
Truvada	Tenofovir, emtricitabine	Gilead Sciences	2004
<b>Nonnucleoside Reverse Transcriptase Inhibitors</b>			
Viramune	Nevirapine	Boehringer Ingelheim	1996
Rescriptor	Delavirdine	Pfizer	1997
Sustiva	Efavirenz	Bristol-Myers Squibb	1998
Intelence	Etravirine	Tibotec	2008
<b>Protease Inhibitors</b>			
Invirase	Saquinavir	Roche	1995
Crixivan	Indinavir	Merck	1996
Norvir	Ritonavir	Abbott Laboratories	1996
Viracept	Nelfinavir	Agouron Pharmaceuticals/Pfizer/Roche	1997
Agenerase <sup>®</sup>	Amprenavir	GlaxoSmithKline	1999
Kaletra	Lopinavir, ritonavir	Abbott Laboratories	2000
Lexva	Fosamprenavir	GlaxoSmithKline	2003
Reyataz	Atazanavir	Bristol-Myers Squibb	2003
Aptivus	Tipranavir	Boehringer Ingelheim	2005
Prezista	Darunavir	Tibotec	2006
<b>Entry and Fusion Inhibitors</b>			
Fuzon	Enfuvirtide	Roche/Trimeris	2003
Selzentry	Maraviroc	Pfizer	2007
<b>Integrase Inhibitors</b>			
Isetress	Raltegravir	Merck	2007
<b>Multiclass Combination</b>			
Atripla	Efavirenz, emtricitabine, tenofovir	Gilead Sciences/Bristol-Myers Squibb	2006

■ Discontinued by manufacturer. SOURCE: U.S. Food & Drug Administration

[View Enlarged Table](#)

The NNRTI class has been dominated by Bristol-Myers Squibb's first-line drug Sustiva, also sold by Merck & Co. as Stocrin in some parts of the world. Two new NNRTI candidates are attracting interest. This month, Idenix Pharmaceuticals reported potent antiviral activity and a promising safety profile for IDX899 from Phase I/II studies. And Ardea Biosciences has RDEA806 in Phase II trials. The firm says the drug is active against resistant strains and doesn't show typical NNRTI side effects, such as abnormal dreams and rashes.

The first anti-HIV drugs approved were nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), which are faulty genetic building blocks that make the enzyme grind to a halt. An entirely new one hasn't come along in a few years. Australia's Avexa has moved apricitabine into Phase III trials. Others in Phase II trials include Achillion Pharmaceutical's elvucitabine; Pharmasset's racivir, the racemic form of emtricitabine; and RFS Pharma's prodrug amdoxovir.

Until the first inhibitor of HIV's protease enzyme came along in 1995, there wasn't any opportunity to combine drugs from different mechanistic classes. HAART is predicated on the highly unlikely chance that mutations will simultaneously emerge against at least three drugs with different targets. Before

starting therapy, a patient may have their virus type tested for its resistance to different drugs. Typical combination therapies for treatment-naïve patients use two NRTIs with either an NNRTI or a protease inhibitor.

Approved in mid-2006, Tibotec's Prezista is the newest protease inhibitor. The drug has a high genetic barrier to resistance and was approved for treatment-experienced patients. Tibotec is also collecting data for a broader approval for treatment-naïve patients.

Likewise, Boehringer Ingelheim's Aptivus (tipranavir) was approved in 2005. It is a nonpeptidic protease inhibitor active against HIV strains that are resistant to other such inhibitors, explains Scott Morrow, senior associate director for therapeutic operations in virology at the company. Boehringer also sells Viramune, which was the first NNRTI when it was approved in 1996.

**THIS SUMMER**, however, Boehringer closed down three clinical trials of tipranavir. The problem, Morrow explains, came in recruiting treatment-experienced patients in a reasonable amount of time. The company estimated it would take 10 to 15 years to enroll enough patients to get meaningful results.

"These people tend to be on successful treatment, and so there's a very limited population that you can get into your trials," Morrow says.

"Obviously, it is great news for patients if they are on successful therapy," Morrow adds. "But we may have to move a little slower because I don't really foresee decreasing the number of patients in a trial.

"Companies need to be prepared that when they reach a big Phase III trial they may need to extend their development timelines," Morrow cautions. And as HAART has gotten more effective, drug regulators have been asking for increasingly longer term data on viral load reduction, a request that lengthens trials.

In addition to improving drugs' effectiveness, developers are trying to make HIV drugs easier to take. Adherence calls for convenient and well-tolerated regimens, says Norbert W. Bischofberger, chief scientific officer at Gilead Sciences. To avoid patients taking many pills at varying times and under different conditions, he says, Gilead's focus has been "one pill, once a day."

Following this path, Gilead developed the NRTI Viread, approved in 2001; followed it in 2003 with the NRTI Emtriva, which is (–)emtricitabine; and then in 2004 supplied the one-pill combination Truvada. Gilead next worked with Bristol-Myers Squibb to combine Truvada and Sustiva into Atripla, approved in 2006. Today, according to Gilead, about 50% of treatment-naïve patients are started on Atripla, while another 30% are put on Truvada. Such therapies, Bischofberger says, "really signify the progress we have made in the past 10 years."

Along with convenience, the thinking about treatment guidelines has shifted, as well. "In the early days, the mantra was 'hit hard and hit early,' " Bischofberger says, but the complex, multidose regimens were impossible for the normal person to take long term. As a result, people became conservative and waited until the disease was more advanced to start treatment. "With more-convenient and better tolerated regimens, the pendulum has swung in the other direction," he says.

Boehringer's Morrow agrees. A decade ago, patients would start therapy when their CD4<sup>+</sup> cell count fell below 500 cells/mm<sup>3</sup>, he explains. The cell count in a healthy, uninfected person is between 500

and 1,450 cells/mm<sup>3</sup>. After seeing how effective HAART could be, doctors let the disease progress longer on recommendations that shifted to a count of 200, although some started therapy for patients with less than 300.

**BUT EXPERIENCE** is beginning to show that patients who start treatment earlier tend to live longer. "Last year, we saw the guidelines updated, and the cutoff is 350," Morrow says. "There are rumors that next year it may increase back to 500."

**“We knew that no matter how good our molecule was that we would see resistance to it.”**

In recent years, alternatives in three new classes of drugs have emerged for patients with drug-resistant forms of the virus. Fuzeon, a fusion inhibitor that blocks the virus from merging with T cells, was the first such drug approved in 2003.

Developed by [Roche](#) and the biotech firm [Trimeris](#), Fuzeon is a complex and difficult-to-manufacture peptide. It is costly to use and requires twice daily injections with side effects. Nevertheless, "it continues to have a niche," says Tim Horn, president of the informational website [AIDSmeds.com](#).

Although Roche came out with the first drug in a new class, it discontinued its HIV efforts in July after determining that nothing in its pipeline offered enough benefit over existing drugs to continue development ([C&EN](#), July 21, page 12). Anything it had was at the preclinical stage and at least six years away from the market. Besides Fuzeon, Roche will still sell HIV diagnostics and the protease inhibitors Invirase and Viracept.

Trimeris had a next-generation fusion inhibitor in early clinical development. But the company's revenues have fallen as Fuzeon's sales declined in the face of competition. It has stopped R&D and is looking to license the compound.

Meanwhile, August 2007 was the debut of the first entry inhibitor, [Pfizer's](#) Selzentry (maraviroc). The CCR5 antagonist doesn't go after the virus, but instead blocks one of two coreceptors on human immune cells that HIV uses to gain entry. Before using the drug, patients must be tested to see whether their virus type uses the CCR5 or the CXCR4 coreceptor. About 50 to 60% of highly treatment-experienced patients have the R5-type virus and would benefit from the drug.

[Monogram Biosciences](#) markets the only widely used test. It is expensive, takes a few weeks to get results, and has had problems with sensitivity, Horn explains. "That becomes a huge wrench in the works for doctors, and the additional testing has created a barrier in terms of using the drug effectively," he adds. As a consequence, Pfizer's sales of maraviroc have been lower than expected. The company has a next-generation CCR5 antagonist that it says works against maraviroc-resistant viruses in Phase II development.

Other companies have been developing entry inhibitors, too. In 2005, GlaxoSmithKline halted Phase III trials of its entry inhibitor, aplaviroc, because of liver toxicity. And [Incyte](#), in a move to conserve resources, stopped development of its leading CCR5 drug as it was about to enter late Phase II trials. It is looking to out-license its CCR5 program. Still moving ahead is [Schering-Plough](#), which has vicriviroc in Phase III trials involving treatment-experienced patients with the R5-type virus.

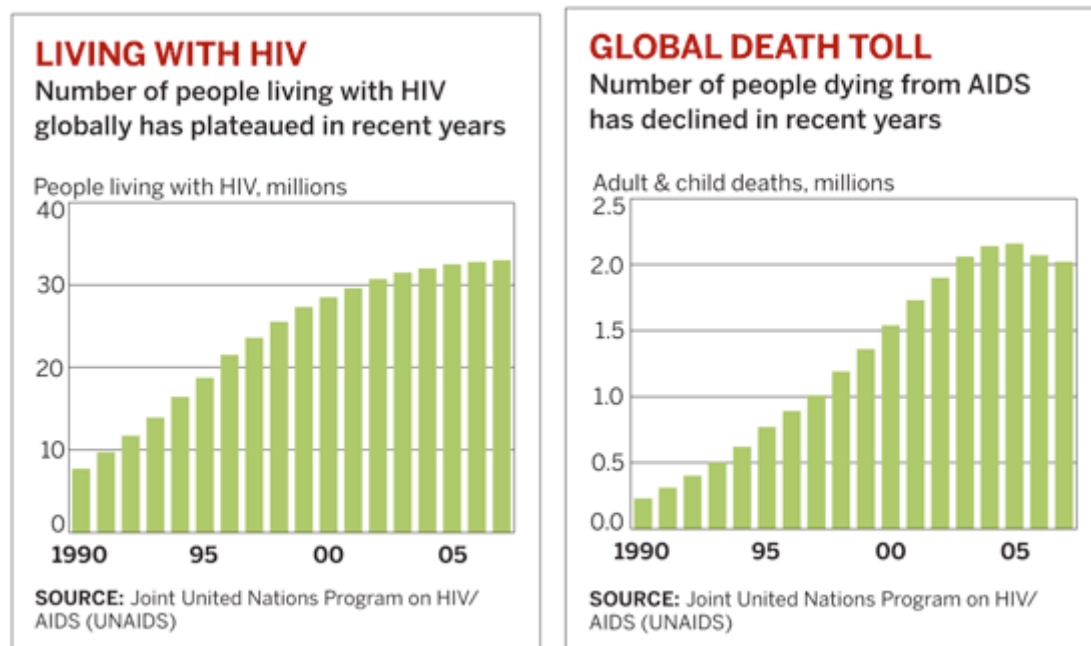
The importance of the CCR5 coreceptor came to light in the mid-1990s. Blocking it doesn't seem to

significantly alter the normal functions of a person's immune system, explains Lisa Dunkle, senior director of global clinical research for HIV at the Schering-Plough Research Institute. Many people lack the CCR5 receptor because of genetic mutation, and they suffer no ill effects.

Schering-Plough developed vicriviroc in-house. "We had a discovery program that focused on chemokine receptors and were able to identify a whole series of compounds that had potent activity," Dunkle says. "Vicriviroc also is active against all of the different clades and against strains of HIV resistant to other classes of antiretroviral agents." The compound has promising synergistic activity when combined with certain other drugs for treatment-naïve patients, she adds.

Soon after the entry inhibitors emerged came the first inhibitor of the HIV integrase enzyme, which integrates HIV's genetic material into that of the immune cell. Merck began its integrase inhibitor program more than a decade ago.

"People argued that it was impossible to inhibit an irreversible reaction with a reversible inhibitor because you can't inhibit something 100%, 100% of the time," says Daria Hazuda, vice president of Merck's antiviral franchise.



However, from their own work and that of others, Merck scientists learned that integration has to occur within a window of opportunity in the infection process. "If it doesn't occur, then the cell metabolizes the DNA into products that are essentially dead ends in the infection process." Hazuda explains. "So all you have to do is stall the process long enough so that cell's machinery gets a leg up and wins the race between integration and degradation."

The inhibition is effective, she adds, and stalls the infection process irreversibly, even after the inhibitor is removed. These findings also have relevance for inhibiting RNase H, which is a subdomain of the HIV reverse transcriptase. "None of the reverse transcriptase inhibitors target the RNase H activity; they all target the polymerization activity," Hazuda says. A new distinct target within the reverse transcription machinery offers the potential for novel antiretrovirals.

Eventually, the Merck scientists found the integrase inhibitor raltegravir; it was approved in late 2007 under the name Isentress for treatment-experienced patients. According to the AIDS research and policy organization Treatment Action Group (TAG), the drug has been well received in the marketplace. Merck is also testing the compound in combination with two NRTIs for use in treatment-naïve patients where, Hazuda says, clinical researchers saw 90% efficacy over 96 weeks in Phase II studies.

One potential problem is that it takes only a single mutation to make the drug ineffective. "It's always a race between the chemists and the virus, and so we knew that no matter how good our molecule was that we would see resistance to it," Hazuda says. Planning ahead, as raltegravir was moving into Phase II trials, Merck scientists were already looking at next-generation compounds that could work against a raltegravir-resistant virus.

Gilead also has an integrase inhibitor, elvitegravir, in Phase III clinical trials. In treatment-experienced patients the drug is used in combination with ritonavir, an early protease inhibitor developed by Abbott Laboratories. Ritonavir is frequently used as a boosting agent because its strong interaction with drug-metabolizing enzymes helps block the breakdown of other HIV drugs and allows their levels in the blood to remain high.

For treatment-naïve patients, Gilead is developing its own proprietary booster to coformulate with its two NRTIs and elvitegravir, Bischofberger says. It wants one that doesn't have HIV activity, can be dosed once daily, is in solid form, and is stable at room temperature. If a regimen contained elvitegravir, Truvada, and a ritonavir booster, he points out, patients failing therapy could become resistant to drugs in the integrase inhibitor, NRTI, and protease inhibitor classes, respectively.

Other new classes are being explored, including maturation inhibitors, which prevent the final stages of HIV's cycle. Panacos Pharmaceuticals recently presented Phase II results for bevirimat, an agent that works best in patients without specific mutations in a target viral protein. The drug is effective for about 60% of patients, who would be tested to see whether the mutations are present.

Many other candidates are being explored, as well as new strategies including immune-system-based therapies that target human responses rather than the virus. But despite the number of new drugs recently approved, TAG's annual report suggests that the remaining pipeline is thin, and no approvals are likely before 2010. In addition, TAG expresses concern that other companies may exit HIV R&D as Roche did.

Because HIV is a large chronic-disease market, companies still have an incentive to develop new drugs, even though patent expirations are expected to slow overall sales growth. In 2007, the global HIV drug market exceeded \$9 billion in sales, according to the market research firm Datamonitor. The top 10 products accounted for 80% of sales, Datamonitor says, and Gilead is the market leader. HIV research is a strong growth area for both Merck and Tibotec, while companies with mature products in the more-populated classes are losing ground.

Although HIV research has been ongoing for 25 years, "it's still very much a work in progress," AIDSmeds.com's Horn says. "A lot of the medications we're using today have been around for a while, but we are continuing to see how best to use them and learning very quickly about some of the advantages and drawbacks. And some of the newest medications have really made a tremendous difference in our ability to treat people."

To compete, new drugs have to be efficacious, safe, and have few side effects so they can be used

over long periods. Convenience and a high genetic barrier to resistance are important. Many of the drugs being used in poorer countries are older agents falling out of favor.

Prices for first-line antiretrovirals decreased by 30% to 60% between 2004 and 2007 because of drug company price cuts and availability of generics, reports UNAIDS. But the immense cost and difficult logistics of delivering therapies around the world make treatment an unlikely long-term solution to the HIV problem.

For all the success antiretrovirals have brought, there is still no cure or vaccine to prevent HIV infection ([see page 17](#)). HAART can stop HIV but doesn't do anything to rid the body of latent virus. Researchers are still tackling the most difficult challenges: finding and eliminating all the hidden viral reservoirs and learning how to intercede quickly enough after infection to prevent these reservoirs from forming in the first place.

### Cover Story

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