In 1982, men would sometimes line up outside the Scaife Hall laboratory of immunologist Charles Rinaldo. Their hands grasped semen samples covered with plastic wrap or placed in glass jars, specimens they had brought from home. They were waiting so that second-year med student David Lyter could draw their blood in Rinaldo’s tiny office. The immunologist had scraped together some money and joined forces with the student—they put out flyers and gave talks in local gay bars, asking men to come in and donate samples for a study. A mysterious new disease which seemed to target gay men had first been reported the year before.
Charles Rinaldo posed for this cover of Out, a local gay newspaper, in 1983. His goal was to recruit 10,000 men into a study of AIDS. (The goal was later scaled back; about 1,300 men enrolled in a national study.) Those volunteers made possible 800 scientific articles.

Soon, Rinaldo, now a PhD professor of pathology at the University of Pittsburgh School of Medicine and chair of infectious diseases and microbiology at the Graduate School of Public Health (GSPH), had garnered funding from the National Institutes of Health (NIH) to study the new disease, which had come to be called AIDS. The Pitt Men’s Study, housed in GSPH, was born.

Rinaldo and his team began recruiting gay and bisexual men into the NIH study in 1984. One or two nights a week, they would go to gay bars, coffeehouses, bathhouses. One of their haunts was the nightclub Pegasus. Arriving around 10 p.m., the researchers would walk past the dance floor, with its glittering disco ball and flashing, colored lights, to a back room, normally used for storage or as a dressing room for drag shows. The team would set up shop—taking out their informed consent forms and blood-drawing equipment. The club owner would announce that the Pitt Men’s Study was there for the night. In some venues, the researchers would draw blood from an arm extended along a pool table or a keg of beer, all the while hearing the pounding beat of dance music through the walls. The recruiters usually stopped enrolling participants around midnight, but sometimes stayed until two in the morning answering questions.

In the clubs, standing on the edge of the dance floor, Rinaldo often wondered: How many of these men will be alive in a few years?

“I felt that we had to do something to stop the spread of this epidemic and learn more about it,” he says.

The initial recruitment period lasted 12 months and resulted in the enrollment of 1,300 men. Every six months for the past 18 years, the study participants have come in for clinic visits. Since 1983, Rinaldo’s study has received more than $47 million from NIH and has been used for more than 800 scientific articles—both epidemiological and biomedical. He is one of four sites in NIH’s Multicenter AIDS Cohort Study, which is the largest study of AIDS among gay men in the United States.

In 1981, Rinaldo learned that the mysterious new disease involved T cell destruction, relating directly to his area of expertise. “To study the disease, I had to have volunteers giving us samples. Starting the Pitt Men’s Study was a perfect opportunity for me as a scientist to do something constructive and important with this disease.”

With the samples he has collected, Rinaldo studies how to give the immune system a better chance against HIV.

When the body is infected with a virus, the immune system’s dendritic cells go into action, engulfing a few of the foreign invaders, tearing their proteins into small pieces. The dendritic cells then present these pieces of protein to the T cells, whose job is to hunt down and destroy the invader. The cells set out on a search mission, knowing what to look for—the piece of protein that the dendritic cell has shown them.

But, if the virus is HIV, the immune system can’t get rid of it, not even with the help of drugs. If the patient is treated, the HIV simply goes into hiding. Rinaldo believes the T cells, in effect, can’t see the hiding HIV. He wants to engineer the dendritic cells so that the immune system can better locate the virus.

The end result, he hopes, will be a treatment tailored to each individual: Extract some of a person’s residual HIV, along with some of their dendritic cells. Expose the dendritic cells to bits of HIV protein that are not normally exposed to the immune system inside the body: Give them new ways to identify the lurking HIV. Put the dendritic cells back into the person’s body. The theory is that the engineered cells will be better able to show the T cells how to find the hiding HIV.

Later this year, Rinaldo hopes to begin a Phase I clinical trial of the experimental treatment.

“We want to turn the T cell system on against this virus in a more potent and broader way,” says Rinaldo.

The current standard of care for HIV infection is highly active antiretroviral therapy (HAART). For 50 percent of patients being treated with HAART, HIV infection is a chronic disease—requiring a lifelong regimen of multiple drugs, all of which are toxic and pose potential side effects like anemia and disturbances to the peripheral nervous system. If the patient stops treatment—even if the virus has been suppressed to barely detectable levels for years—the virus will come roaring back, wreaking destruction, within weeks. Even so, in half of the patient population, the treatment is controlling the virus so far.

In the other half, the HIV has mutated and become resistant to the drugs being used, and therapy is less effective. In these cases, clinicians experiment with the patient’s drug regimen, trying to find a treatment to which the patient will respond. Some patients now have what is called multidrug resistant HIV—implacable to all of the 17 drugs currently available to treat the disease. The number of patients with multidrug resistant HIV is low, but growing.

More chilling: Some people are passing along multidrug resistant HIV to others.

“These patients, they’re newly infected, they never had any drug exposure, but they’re already precluded from any drug regimen because they have a virus which is resistant,” says Michael Parniak, professor of medicine at the University of Pittsburgh School of Medicine.

“If we start getting widespread transmission of multidrug resistant virus, we’re going to be back, possibly, to where we were in 1984, when people had a short life span once they were diagnosed, because there was no effective treatment.”
In the clubs, standing on the edge of the dance floor, Rinaldo often wondered: How many of these men will be alive in a few years?

Seventy percent of the drugs currently available to treat HIV infection target the viral enzyme reverse transcriptase, the molecular structure of which is depicted right. Existing reverse transcriptase inhibitors affect the part of the molecule shown in yellow. Pitt’s Michael Parniak (above) and collaborators discovered compounds that disable another region of the molecule, called ribonuclease H (RNase H), shown in red. Because the new compounds target a different region of the molecule, they may prove effective against strains of HIV that are resistant to existing drugs.

Working with Pitt chemistry professor Dennis Curran, Parniak has found compounds that inhibit ribonuclease H. In initial studies, the inhibitors have proven effective against all known mutations of resistant HIV. The scientists hope to compile enough information to interest a pharmaceutical company in trying to develop a drug.

Such a drug, or a treatment involving Rinaldo’s genetically engineered dendritic cells, would likely offer little hope in developing countries that cannot afford the drugs currently available in North America and Europe. Parniak believes the greatest promise for stemming the worldwide epidemic lies in prevention—and reverse transcriptase may be relevant there, too.

A few years ago, Parniak investigated an experimental reverse transcriptase inhibitor. He treated cells with the compound and then washed it off the cells. Then he tried to infect the cells with HIV. The cells were protected against infection. “The compound turned out to be spectacular, unbelievably good,” says Parniak.

Parniak’s hope is that the compound can be used as one component of a vaginal cream that would prevent infection by the virus. A team of Pitt and other researchers recently has formed to work on the project.

Parniak believes such a cream could help control the epidemic. Heterosexual transmission is the primary mode for the spread of HIV worldwide; women account for 48 percent of those infected. “In a lot of relationships, a woman doesn’t have a lot of say in whether the man uses a condom,” he says. “A microbicide, like a cream, could be used by the woman to

says Parniak. “I’m getting scared. It’s potentially a very devastating scenario.”

Current drugs available for use against HIV target one of two viral enzymes—viral protease or reverse transcriptase. In an effort to stop multidrug resistant HIV, researchers are looking for new targets within the virus.

Parniak believes he has found a new target—even though it doesn’t sound new. It’s reverse transcriptase.

Once HIV infects a cell, reverse transcriptase goes to work. First, it produces, from the virus’ single strand of RNA, a corresponding strand of DNA. Then, reverse transcriptase degrades the RNA, which enables a second matching strand of DNA to be produced. (These double strands are then inserted into the cell’s DNA, where they produce viral proteins.)

“Quite frankly, reverse transcriptase is the most beautiful enzyme I’ve ever come across,” says Parniak, a PhD who first became fascinated with the enzyme under the auspices of Canada’s Lady Davis Institute, directed by leading AIDS researcher Mark Wainberg.

Existing reverse transcriptase inhibitors target the part of the enzyme that performs the first job—producing the strand of DNA. But, the second job—degrading the RNA—is performed by a distinct and separate region of the enzyme. That region is called ribonuclease H.

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provide a degree of protection even in the absence of a condom.” A vaccine would be ideal to stop the spread of HIV, yet the possibility is years away. “A microbicide is a potential stop-gap measure to minimize the spread of the disease until an effective vaccine can be developed,” he says.

The company licensing the drug believes it can go into clinical trials with the compound in about a year. Parniak is almost afraid to hope. “It’s possible it’ll go into clinical trials,” he says. “One side of me is saying—Please let that be the case. The other side is saying—Well be real lucky if we get there. But I’m leaning toward the optimistic side right now.”

In dim rooms with dance floors and flashing strobes, Rinaldo in 1984 wondered how many in the local gay community would survive the new disease. Soon enough, he would get an answer. About one in five men who enrolled in his study (251 men) were already HIV-infected.

We’ll be real lucky if we get there. The other side is saying—

The increasing rates of infection, the emergence of multidrug resistant virus, these are some of the reasons why the Pitt Men’s Study, after 18 years, is enrolling participants again. With the help of a $4 million NIH grant, Rinaldo’s study will expand to look at AIDS in young people and African Americans. (In the United States, 50 percent of new infections are in African Americans, who make up 12 percent of the population.)

Contrary to US public perception, AIDS is not under control, says Parniak—not even at home. “In the developed countries, I think we place too much faith in research—that we’re always going to have a treatment. That may not be the case. This virus has proven to be unbelievably plastic. It gets around everything we’ve thrown at it,” he says. “You don’t know who’s infected. Be cautious.”

More chilling: Some people are passing along multidrug resistant HIV to others.

One Saturday morning in 1985, John Mellors, who was then medical director of the emergency room at Yale-New Haven Hospital, was working when his brother-in-law Ruddy walked in. Ruddy, the youngest member of the family, was in his early 20s. Mellors evaluated him and immediately became worried. Ruddy had a cough and recurrent fever. That weekend, he developed pneumocystis carinii pneumonia. On Monday, blood test results came in, showing that Ruddy had no T cells. He was diagnosed with AIDS.

At the time, there was no treatment for the disease. “He unfortunately passed away a little over a year after he was diagnosed,” says Mellors, hesitating slightly as he tells the story. “That inspired me, the loss of my brother-in-law, to work on AIDS.

“I set out on what in retrospect was a naive course of events to become an HIV researcher,” says Mellors. “I basically taught myself everything. Here’s the autoclave, here are the gloves—that was my training, along with instruction in rudimentary techniques in a virology laboratory.”

Mellors came to the University of Pittsburgh School of Medicine as a professor of medicine in 1991. Soon after, he began looking at data collected on 180 men in the Pitt Men’s Study. Using frozen samples, he measured the amount of HIV in study participants’ blood (the viral load) from the early ’80s. With coinvestigators in the Men’s Study, he discovered that viral load correlated with the clinical outcomes of patients throughout the next 10 years.

“It showed that you could tell the probability of developing AIDS over a decade by one measurement,” says Mellors. “John demonstrated that it was a continuum—the lower the viral load, the better the clinical outcome,” says Emilio Emini, senior vice president for vaccine research at Merck. Mellors’ breakthrough gave clinicians the ability to gauge prognosis; it also told researchers working on drug development what to aim for—a lower viral load.

His current research focuses on trying to understand why treatment fails in some AIDS patients. Mellors is looking at the molecular level to find out how the virus changes so that it can bypass the destructive action of the drug.

Ultimately, Mellors believes, research and human ingenuity will develop a solution to AIDS, but he’s not optimistic the epidemic will be controlled in his lifetime. “AIDS is a test for humankind, and so far, we as a human race are not dealing with it very effectively,” he says. “We’re in slow motion.”

The crisis, he believes, calls for a sustained, unified, well-led global strategy, the cooperation of governments, and billions of dollars. It also calls for reinforcements among the ranks of researchers. Whenever he has a chance, Mellors tries to inspire students to focus their careers on AIDS: “For this generation, born into a world impacted by AIDS, the question is, not having seen it evolve and spread from nonexistence to global pandemic, will they be more complacent about it?”

Many Americans, he notes, are dispassionate about the disease because they’ve never had a friend or family member die of AIDS—the majority of the three million who died last year from HIV/AIDS were in other countries (20,000 died in North America). Or Americans think AIDS is practically cured with the right medications.

“Here, sitting in Pittsburgh, most people can’t relate to it,” he says. “We’re amazing creatures. Unless we have to step over the bodies on the way to work, we don’t notice.” —DH
America has become complacent about AIDS, believes John Mellors.