# Whatever Happened to AIDS? Pharmaceuticals

*By ACSH Staff — April 7, 2005*

Rock Hudson, Arthur Ashe, Ryan White, Liberace, Alvin Ailey, Freddie Mercury, Anthony Perkins, Rudolf Nureyev. Remember when you could hardly go a month without hearing about someone famous dying of AIDS? And the *New York Times* obituary page was filled with thirtyish men, often in the arts, who had died "after a short illness." When is the last time you heard this? Probably about eight years ago. So what happened?

The pharmaceutical industry is what happened.

**"The Gay Plague"**

I remember precisely the first time I ever heard of AIDS. In June 1982, a bunch of us were sitting on a deck on Fire Island reading the May 31st issue of *New York* magazine, which documented a horrible new disease. The article was called "The Gay Plague." We had no idea at the time, but we happened to be an hour's walk from the summerhouse in Fire Island Pines, where Gaetan Dugas (a.k.a. Patient Zero), a Canadian airline steward, was sharing a house. We were four miles from the epicenter of the AIDS epidemic on the East Coast. The disease didn't have a name yet, nor did anyone know what caused it. All that doctors knew was that it affected mostly gay people and they all died terrible deaths from infections that were normally present but harmless in people with healthy immune systems.

About a year later, two different labs determined that the disease was caused by a virus (this story itself is fascinating, involving furious allegations of theft and credit-grabbing). By this time the disease was routinely called AIDS. The name of the causative virus (HIV) was officially assigned in 1986. There had been at least four other names prior to that.

**AZT**

The first specific treatment for AIDS, AZT, didn't arrive until five years after that article. AZT was a twenty-year-old compound prepared at the National Institutes of Health for cancer research (for which purpose it didn't work), but in 1985 they found it to be effective in inhibiting HIV replication. The NIH licensed it to Burroughs-Wellcome (now Glaxo), and it received FDA approval in 1987. AZT alone was ineffective in treating AIDS, and subsequent clinical trials showed no increases in survival for those patients taking the drug. It does have some utility in prevention from needle sticks and decreasing mother-to-fetus transmission, but as a therapy for people who already had full-blown AIDS it was a poor option. The fatality rate for AIDS patients was 100% at this time.

The reason that AZT didn't work well was that HIV quickly mutated to form viruses that were resistant to the drug. These mutants then continued to attack the immune system. Mutation is quite common with viruses, but HIV happens to be especially good at it. It is now known that to curb resistance one needs to use at least two different drugs together. But what can you do when

there is only one drug available? To understand this, you need to know a little about how viruses work.

**Combating Nature**

Most viruses function in about the same way. They float around until they find the appropriate host cell that fits the particular virus. Then, they attach to the cell and chemically drill a hole into the surface, entering the cell. The viruses then fall apart, releasing their contents. These contents find the normal reproductive machinery of the host cell and trick it into making new genetic material of the *virus*, instead of that of the *cell* itself. This new DNA (or RNA) now takes control of the cell, causing it to make many copies of the viral proteins, which are then assembled into new virus particles. The new viruses then break out of the cell and start the process over again. Each of these steps works by a different mechanism. These processes can theoretically be interrupted by the presence of a drug and are referred to as *targets*.

After intense study, molecular biologists at universities and drug companies methodically uncovered each of these targets and learned how they contributed to the replication of HIV. They also figured out how to set up screens (tests) to see if chemicals could be identified that would inhibit a certain target. And if so, would this inhibit the replication of the virus?

The short answer is yes--you can set up screens. They do enable you to identify potential drugs that inhibit specific targets. Inhibition of these processes *does* stop the replication of HIV. And combining different drugs *does* suppress resistance--resulting in a profound effect on the outcome of AIDS.

**Turning the Tide**

Beginning in the 1990s, drug companies launched huge campaigns to study HIV and address the lack of effective therapies. New techniques in drug discovery (X-ray crystallography and computer-assisted drug design) were used, and these would very quickly help change the course of the disease. Almost every drug company was involved, including a number of my friends and colleagues.

Before this time, AZT and a few close relatives (a class called RTIs) were the only AIDS drugs available. Other medicines were also used to treat some of the opportunistic infections (but not HIV itself). The results were unimpressive, and people kept dying. This would soon change.

In 1995, Roche received approval for Invirase, the first in a new class of AIDS drugs called protease inhibitors (PIs). Invirase operated by mechanisms completely different from AZT. Within two years, four other PIs were available. Using the PIs combined with one or more RTIs, the death rate from AIDS began to drop for the first time (New England Journal of Medicine, p. 1764, 2001).

There are now seventeen AIDS drugs available, collectively inhibiting HIV by four different mechanisms. Sixteen of these were discovered by the drug companies (AZT came from the National Institutes of Health). Of course, they did this just to make lots of money, right? Not exactly--of the top twenty best-selling drugs in the U.S., none are AIDS medications (Associated Press, 9/30/04). In fact, the best-selling AIDS drug in 2003 was Combivir, which ranked 74th (that's less than 10% of Lipitor sales [1], for example).

The mortality rate for AIDS is now 20%, compared to 100% ten years ago (WHO report, 2002). In 1991, Magic Johnson announced that he was HIV positive. Had this happened in 1986, he would have certainly joined the list of deceased celebrities rather than being alive now. Although AIDS is by no means cured and the drug regimen is unpleasant, the hopelessness of the 1980s has given way to the possibility of manageable chronic disease.

**Short-Term and Long-Term Incentives for Progress**

The story in the developing world is quite different. The catastrophe in Africa and Asia is well known, but given the existence of effective drugs, the problem is now more political and economic than scientific. Clearly, victims of AIDS in these areas would greatly benefit from drugs that we have here. But how to accomplish this is far from a trivial question. It also raises some interesting ethical and practical questions.

In 2002, Indian companies started making cheaper generic copies of *patented* AIDS drugs for use in poor countries. Despite noble intentions, there is no question that this is, in fact, theft of intellectual property, much the same as putting your name on an author's book and selling it as yours. But does the extreme need make this practice right? I recently sent this question to Randy Cohen (who writes "The Ethicist" for *New York Times Magazine*). He called the question "interesting" but wouldn't touch it. Before you answer it, you might want to ask yourself the following: if someone stole your checkbook, cashed a check, and sent _that_ to Africa, would that be okay? It's much easier to be generous with other people's money.

More practically, since most anti-infectives will eventually fail over time (due to resistance), new generations of antiviral drugs must continually be developed to keep AIDS in check. If you are the CEO of Glaxo and just spent $1 billion to develop an AIDS drug only to have the patent violated abroad, are you going to be anxious to do this again? And if that answer is no, then who *will* do it?

I work in the pharmaceutical industry, and it's no secret that my industry is generally disliked (obnoxious commercials, pricing, certain business practices, politics, etc). Some of this is deserved and some is not. But the AIDS drugs didn't come from the government or universities or hospitals or nutritionists. And there are thousands of people walking around today that otherwise wouldn't be. Just something to think about.

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**Links**
[1] http://www.drugs.com/top200sales.html