SPECIAL REPORT

# Whatever Happened to AIDS?

## How the Pharmaceutical Industry Tamed HIV

*Presented by the*

AMERICAN COUNCIL ON SCIENCE AND HEALTH

Written by **Josh Bloom, Ph.D.**

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February 2011

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# Introduction

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 thirty-ish men, often in the arts, who had died "after a short illness." When is the last time you heard this? Probably about fifteen years ago. So what happened?

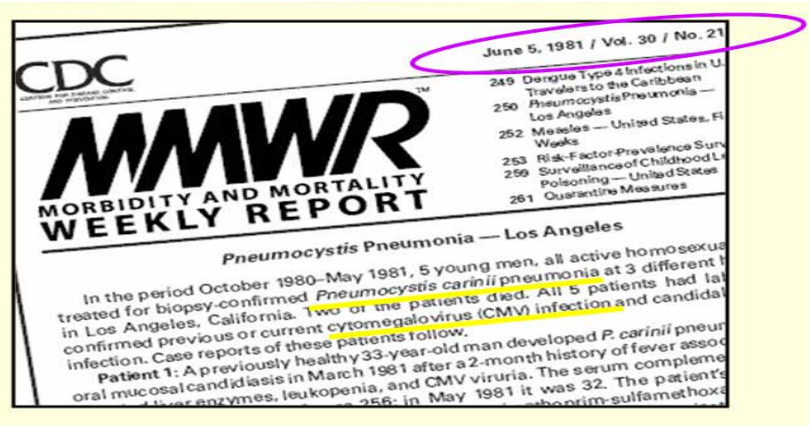
**The pharmaceutical industry is what happened.** Using state-of-the-art techniques in drug design, virology and biotechnology, the industry delivered a revolutionary series of novel therapies in an exceptionally short period of time. This campaign is arguably among the most impressive in medical history in its scope, scientific sophistication and outcome, yet is largely taken for granted—when it is noted at all. The highlights of this effort are outlined in the following review.

# "The Gay Plague"

The first publication relating to AIDS (June 5, 1981) was a short report in the Morbidity and Mortality Weekly Report (MMWR). This journal is published by the Centers for Disease Control to track epidemics, disease trends, and other public health issues. The article noted a cluster of five cases of homosexual men having pneumocystis carinii pneumonia at three different hospitals in Los Angeles. Pneumocystis carinii was, until then, a rare infection found in patients with severely compromised immune systems. In addition, the patients had other very rare infections, including cytomegalovirus (CMV) retinitis, which causes blindness, and oral candidiasis, also known as thrush. All of these pathogens co-exist happily with healthy people. They make a "deal" with our immune system — "you leave us alone and we'll leave you alone." Since this deal was being breached, it quickly became clear that whatever was going on involved the immune system.

The addendum following the article noted "Pneumocystis pneumonia in the United States is almost exclusively limited to severely immunosuppressed patients. The occurrence of pneumocystosis in these five previously healthy individuals without a clinically apparent underlying immunodeficiency is unusual. The fact that these patients were all homosexuals suggests an association between some aspect of a homosexual lifestyle or disease acquired through sexual contact and Pneumocystis pneumonia in this population." There was clearly something new and nasty going around, but no one knew what it was.

One of the first mentions of AIDS in the popular press was in the June 1982 issue of *New York Magazine*. The article was called "The Gay Plague." Readers learned about gay men dying from gruesome diseases with bizarre



CDC

MMWR

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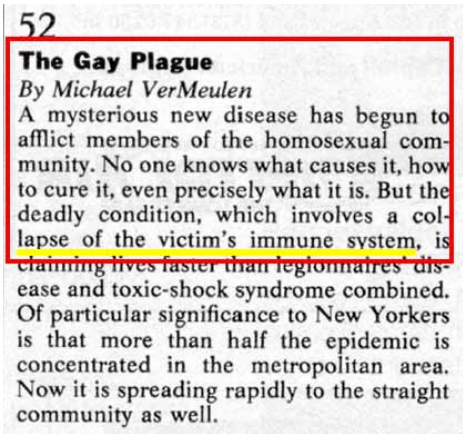
*Pneumocystis* Pneumonia — Los Angeles

In the period October 1980–May 1981, 5 young men, all active homosexuals, treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal infection. Case reports of these patients follow.

**Patient 1:** A previously healthy 33-year-old man developed *P. carinii* pneumonia, oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with liver enzymes, leukopenia, and CMV viruria. The serum complement [illegible] 256; in May 1981 it was 32. The patient's [illegible] sulfamethoxazole-trimethoprim

The first published report on AIDS, MMWR, June 5, 1981.



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**The Gay Plague**

*By Michael VerMeulen*

A mysterious new disease has begun to afflict members of the homosexual community. No one knows what causes it, how to cure it, even precisely what it is. But the deadly condition, which involves a collapse of the victim's immune system, is claiming lives faster than legionnaires' disease and toxic-shock syndrome combined. Of particular significance to New Yorkers is that more than half the epidemic is concentrated in the metropolitan area. Now it is spreading rapidly to the straight community as well.

New York Magazine, May 31, 1982.

The hopeless nature of the AIDS situation at that time was impossible to overlook, and it cast a pall over a large segment of the United States.

symptoms. The article offered detailed accounts of their deaths, which sounded like something from a science fiction novel. One patient had such a large growth of oral thrush (Candida albicans) that he had to sleep sitting up in a chair so the mass wouldn't block his windpipe. There were also reports of cytomegalovirus (CMV), a normally benign member of the herpes family, infecting patient's eyes, causing CMV retinitis and ultimately blindness. CMV was also attacking other body organs (bowels, liver, lungs), leading to deaths. Kaposi's sarcoma, a very rare skin cancer caused by another member of the herpes family, was frequently observed, as well as toxoplasmosis, a protozoan infection spread by contact with cat feces. These normally benign pathogens were termed "opportunistic infections" since they only flourished in the absence of a healthy immune system. Beyond this, no one knew the causative agent of the disease. Early speculation included the use of "poppers" (*iso*-butyl nitrite), a commonly used stimulant at gay parties. Much of the early history of AIDS is chronicled in "And the Band Played On" (1987) by Randy Shilts, a reporter for the *San Francisco Chronicle*, who himself died from the disease in 1994. The hopeless nature of the situation at that time was impossible to overlook, and it cast a pall over a large segment of the United States.

About a year later, two different labs determined that the disease was caused by a virus. (This story itself is fascinating, involving bitter allegations of theft and credit grabbing.) Luc Montagnier of The Pasteur Institute in Paris is generally recognized as the first scientist to isolate and identify HIV (he named it LAV, short for lymphadenopathy-associated virus). Robert Gallo of the National Cancer Institute also claimed to be first. Gallo's group named the virus HTLV-III, short for human T-lymphotropic virus type III suggesting (incorrectly) that HIV was in a class of viruses that causes leukemia. In 1987, the American and French governments decided to share the credit and patent rights to the HIV test, and the two groups resumed collaborating, even co-publishing papers. By this time, the disease was routinely called AIDS, replacing all other names, including the more judgmental (and incorrect) term GRID (Gay-Related Immune Syndrome). The first blood testing for the virus began in 1985, and the name of the causative virus HIV (human immunodeficiency virus) was officially assigned in 1986. Montagnier shared the Nobel Prize in Medicine in 2008 with several colleagues for his pioneering work in AIDS. Gallo was conspicuously omitted.

# How Viruses Work

In order to understand the magnitude of the work involved in bringing AIDS under control, it is instructive to know a bit about how viruses work. Most viruses attack only specific cells. For example, cold viruses attack the nasal passages, not the stomach. The stomach flu (erroneously named, since it is actually called norovirus and is not related to influenza) attacks the small intestine but not the throat. The three principal hepatitis viruses go after the liver, but not the kidneys. This specificity occurs because the spikes (Fig. 1) on the outside of any given virus (antigens) recognize only specific, complementary structures on the host cell called receptors. In order for attachment to take place, there must be an exact fit between a particular viral antigen and the cell receptor. This binding can be depicted as a jigsaw puzzle: the exact shape of one piece must match the next piece in order for attachment to occur. This antigen-receptor binding and specificity is the basis for all viral infections.

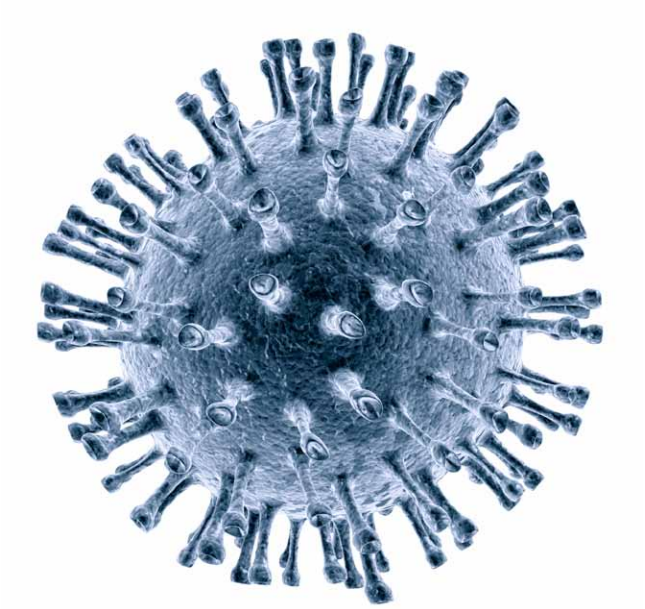


***Figure 1.*** *Representation of a virus. The spikes (antigens) bind to the target cell, initiating infection. Antigens are different for all viruses.*

Despite their exquisite specificity, all viruses function in more or less the same manner (Fig. 2). They float around in the air or bodily fluids until they find the required receptor on a cell. Then, they attach to the membrane of the cell. This is called binding or attachment (step 1). After binding, the virus chemically drills a hole through the membrane, fusion (step 2) and enters the cell. Once inside the cytoplasm, the coating of the virus dissolves, releasing the viral contents into the cell. The free viral components typically migrate to and penetrate the cell nucleus. Once inside, these components "hijack" the normal reproductive machinery of the host cell and trick it into manufacturing multiple copies of the new gene of the virus, instead of that of the host cell (step 3, transcription). This material consists of nucleic acids — either DNA or RNA, depending on the particular virus. The newly formed nucleic acid then works in conjunction with the reproductive machinery of the host cell to produce multiple copies of all the proteins required to manufacture new virus particles (step 4, translation). Within the cell, the new viral proteins and nucleic acids are

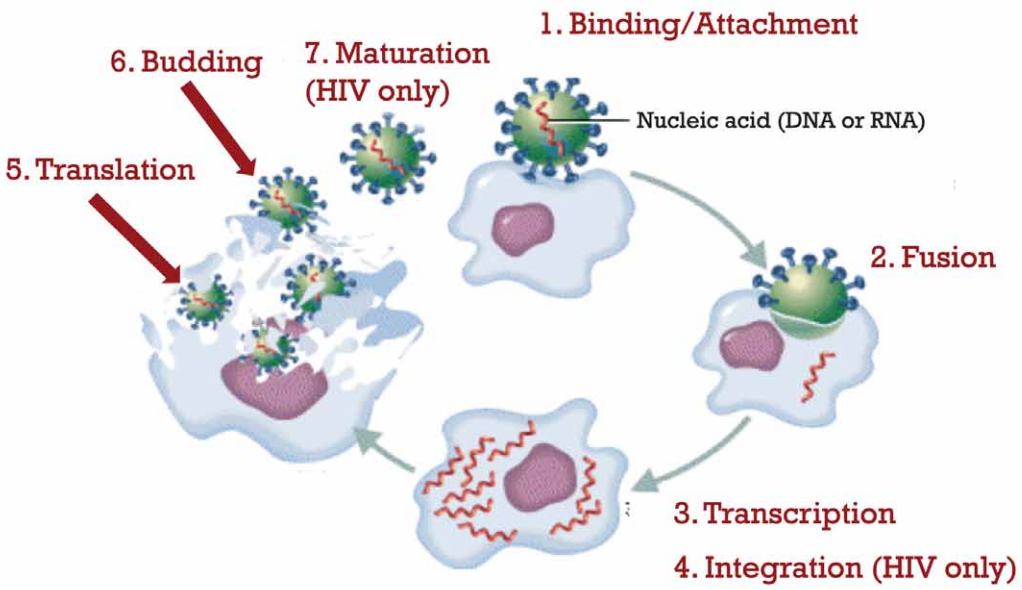



***Figure 2.*** *Life cycle of a typical virus.*

then assembled into progeny virus particles. The new viruses migrate back to the inner cell membrane and then break out of the cell (Step 5, budding), usually killing the cell in the process. This process then starts over again, only with significantly more virus particles already present.

HIV has three key features that differentiate it from other viruses. First, the transcription step involves a viral enzyme called reverse transcriptase (RT), present only in a rare class of viruses called retroviruses. Retroviruses contain an RNA genome, but use RT to produce a DNA copy of the original viral RNA. This is of critical importance. Retroviruses (HIV being the most important of the class) throw a wrench into the works following the transcription step. Using an enzyme called integrase (Step 4), the newly-formed viral DNA inserts itself into the strands of the host cell DNA (Fig. 3), essentially changing the genetic content of the host cell (and thus, the host) such that the cell now produces viral RNA (Step 5, translation). If not for RT, the virus would simply produce its own RNA, and integration would not occur (human cells contain only DNA in their genome). In effect, this means that once you become HIV-infected, you are not really you anymore. Rather, your own white blood cells are now genetically altered to manufacture HIV as they undergo normal cell division to produce more white blood cells. In a sense, you are now a walking HIV-synthesizing

Once you become HIV-infected, you are not really you anymore. Rather, your own white blood cells are now genetically altered to manufacture HIV as they undergo normal cell division. In a sense, you are now a walking HIV-synthesizing machine.

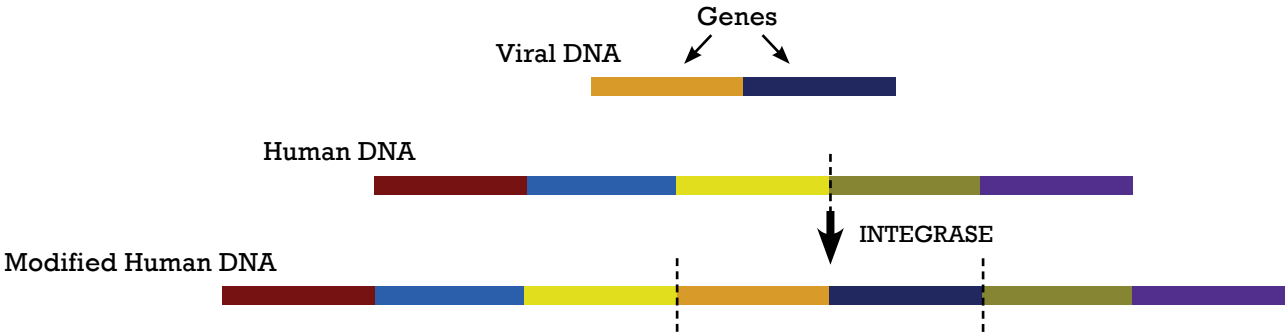



***Figure 3.*** *Representation of the alteration of human DNA by viral integrase*

machine, since the infected white blood cells can keep reproducing until they die, generating rapidly increasing numbers of HIV-making cells. This is why AIDS cannot be cured, but simply controlled. Even with the most aggressive treatment that reduces the quantity of viral particles in the blood to below measurable quantities, HIV always has a reservoir within white blood cells.

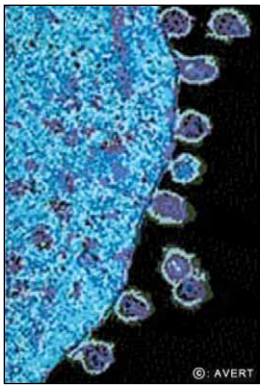



***Figure 4.*** *Electron micrograph of budding of new HIV particles (purple) from an infected T-cell.*

Following budding (Step 6), the newly formed HIV particle is not yet functional. It requires maturation to become a viable virus. This is promoted by an enzyme contained within the virus called HIV protease. As will be discussed below, this maturation requirement was superbly exploited to provide the first useful HIV therapies — protease inhibitors (PIs), which in turn enabled the use of AIDS cocktails.

Each of the seven discreet steps depicted in Fig. 2 works by a different mechanism. If any of these seven processes are interrupted by the presence of a drug that blocks that particular step, the virus will not replicate. These steps are referred to as targets, and most antiviral therapies work by attacking a specific viral target. For AIDS, each of these targets has been studied thoroughly, and there are now drugs to inhibit five of the seven targets. The reasons why several simultaneous target therapies are critical will be discussed below. Suffice it to say that the cutting edge science utilized during the course of this campaign has resulted in multiple life-saving therapies, mostly designed from scratch. This effort, most of which conducted within one decade, was the centerpiece of the massive research effort to combat HIV/AIDS. The results have been nothing short of miraculous.

# AZT (Reverse Transcriptase Inhibitor)

By the mid-1980s, a few drugs were marginally effective in treating certain AIDS opportunistic infections (e.g. pentamidine for Pneumocystis pneumonia); however, the first specific treatment for AIDS (AZT, zidovudine, Fig. 5) was not approved until the late 1980s. AZT was a twenty-year-old compound initially discovered at the National Institutes of Health (NIH) as a potential therapy for cancer (it didn't work), but in 1985, it was found to be the first drug to effectively inhibit HIV replication. The NIH licensed AZT to Burroughs-Wellcome (now GlaxoSmithKline), and it received FDA approval in 1987.

AZT works by blocking reverse transcription, (Fig. 2, step 3), thus inhibiting the formation of new viral DNA and ultimately HIV particles. Although the drug is effective in inhibiting transcription (production of new viral DNA) *in vitro* (outside the body), it was only modestly useful in treating HIV-infected patients. Although, there was some short-term benefit in some patients; however, subsequent clinical trials showed no increases in survival for those patients taking the drug. AZT was found to have some utility in prevention of infection following needle sticks and decreasing mother-to-fetus transmission of HIV, but as a therapy for people already HIV-infected it, was a poor option. The fatality rate for AIDS patients was 100% at this time. It is obvious from these observations that there is an inconsistency between AZT being a successful RT inhibitor, yet an unsuccessful HIV therapy. This can be explained by an adaptive evolutionary mechanism used by viruses to evolve and survive—rapid mutation.

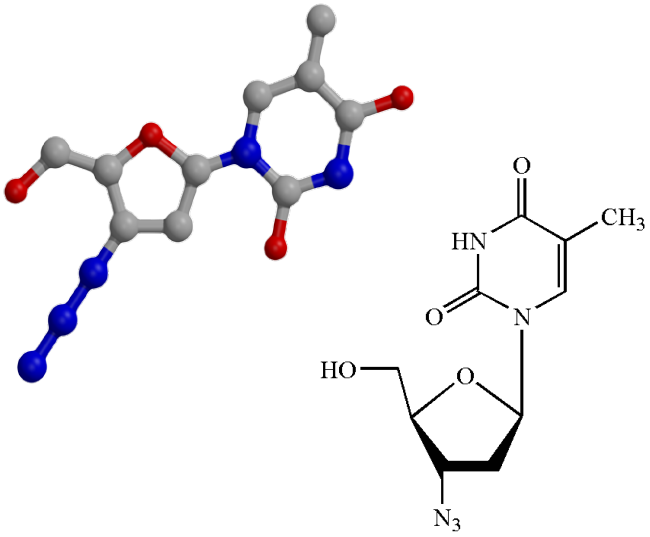



***Figure 5.*** *A chemical representation of AZT. Carbon atoms are shown in grey, oxygen in red; nitrogen in blue.*

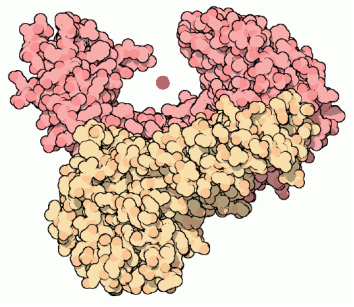


***Figure 6.*** *Molecular model of RT bound to AZT (red circle) The hole in RT is where DNA synthesis normally takes place.*

# Nature Fights Back — Resistance

The reason AZT was a poor drug was because the original strains of HIV quickly mutated to form viruses that were resistant it. These mutants then continued to attack the immune system, unaffected by the presence of AZT, and the infection spread unabated. Mutations occur with all viruses, but HIV happens to be especially adept at it. Mutation is an excellent example of natural selection — it is the way viruses continue to propagate in their never-ending battle with vaccines, drugs and immune cells. Mutation is caused by "sloppy" replication, that is, a built-in error rate that generates mutant species that are similar, but not identical to the original virus. Thus, no population of viruses is entirely homogeneous. In many cases mutant viruses are not infectious — that is, they are structurally different in such a way that they can no longer replicate. However, some mutants are fully functioning viruses, which, despite small differences in their structure, are otherwise "normal." In the case of HIV, exposure to AZT led to the rapid generation of a sub-population of mutant viruses that contained a slightly different form of RT that was the wrong shape to accommodate AZT (Fig. 7). Thus, AZT could not inhibit the replication of these mutants and they continued to replicate unchecked, eventually leading to full-blown AIDS. This is an example of selective pressure. When one population of viruses is wiped out, other sub-populations arise and attack the remaining white blood cells, initiating the propagation cycle of the mutant virus.

It is now known that in order to curb resistance, one needs to use at least two different drugs in combination. But what can be done when there is only one drug available? This is where the pharmaceutical industry made the first of many discoveries that would have an enormous impact — new RT inhibitors, non-nucleoside reverse transcription inhibitors and protease inhibitors. These new drugs would be used together as cocktails, and by 1995, the AIDS death rate began to fall for the first time (Fig. 8).

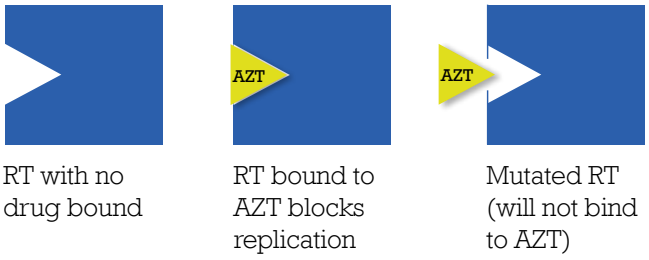
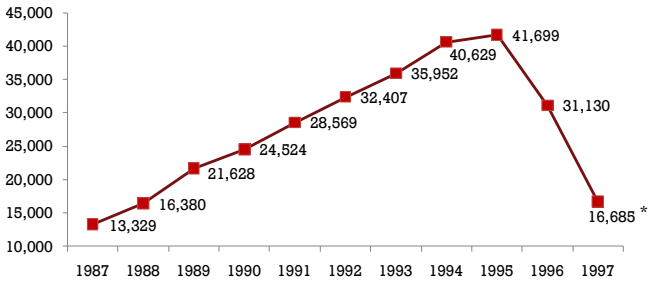



***Figure 7.*** *Depiction of HIV reverse transcriptase (left), HIV RT bound to AZT (center), mutant RT (right).*

This chart includes deaths for all ages, races, and both genders. Though the AIDS epidemic began around 1979, data on deaths were unreliable until 1987. Figures from 1997 are preliminary.




*preliminary data
Source: National Center for Health Statistics

***Figure 8.*** *AIDS Deaths from 1987-1997*

# The Tide Begins to Turn — The Advent of HAART

As scientists began to study how to disrupt the replication steps of HIV, two of the targets began to stand out as the most promising areas for new therapies. The first area to bear fruit was a series of drugs called nucleoside reverse transcription inhibitors (NRTIs). Since the first member of this class was AZT, it is not surprising that early research would be focused in drugs with similar structures. Given that the mechanism of action of AZT was known it was a relatively simple task to search for and test analogs (different chemical compounds with similar structures) of AZT.

In 1991, didanosine (ddI) became the second antiretroviral drug to be approved. Didanosine was found to have anti-HIV activity by the National Cancer Institute, which licensed the drug to Bristol- Myers Squibb, who in turn marketed the drug as Videx. Videx, however is seldom used today, having been replaced by more effective drugs. Closely following AZT and Videx were Zalcitabine (ddc, NCI and Roche, 1992, now withdrawn due to poor efficacy), Stavudine (Zerit, BMS, 1994) and Lamivudine (Epivir, Glaxo, 1995). Epivir and AZT were used in combination during this time, which was more effective than either drug alone. NRTIs are still an important component of modern AIDS cocktails, although some are omitted because of general class toxicity.

# Saquinavir (Invirase), The First HIV Protease Inhibitor

The first five antiretroviral drugs all belonged to the NRTI class, and were old compounds that pre-dated AIDS. They had previously been discovered in government or academic labs during research in other programs. Screening large numbers of similar structures and picking out those that inhibited HIV in vitro led to the identification of a similar set of compounds with activity against HIV. With the exception of Epivir (discovered at McGill University and BioChem Pharma), the main role of the pharmaceutical industry with respect to the NRTI class at this time was to license the drugs, prepare large quantities for safety and efficacy studies, and then market the drugs. As of 1994, there were no marketed drugs actually discovered by drug companies, but this changed dramatically in 1995.

In 1990, Hoffman-La Roche filed a patent claiming a class of chemical compounds, one of which would later become saquinavir (Invirase, Fig. 10), the first HIV protease inhibitor (PI). Invirase was not an old drug discovered by screening; rather, it was an extraordinary example of computer-assisted drug design (CADD), then a burgeoning field of study of drug-target interactions on the molecular level. This sophisticated process requires several successive steps (Fig. 9).

First, large amounts of the target enzyme or protein must be produced — in this case the enzyme was HIV protease (HIVP). This is accomplished by employing recombinant DNA techniques in which the genetic material of HIV is inserted into bacteria, causing the bacteria to produce HIVP, which can then be isolated

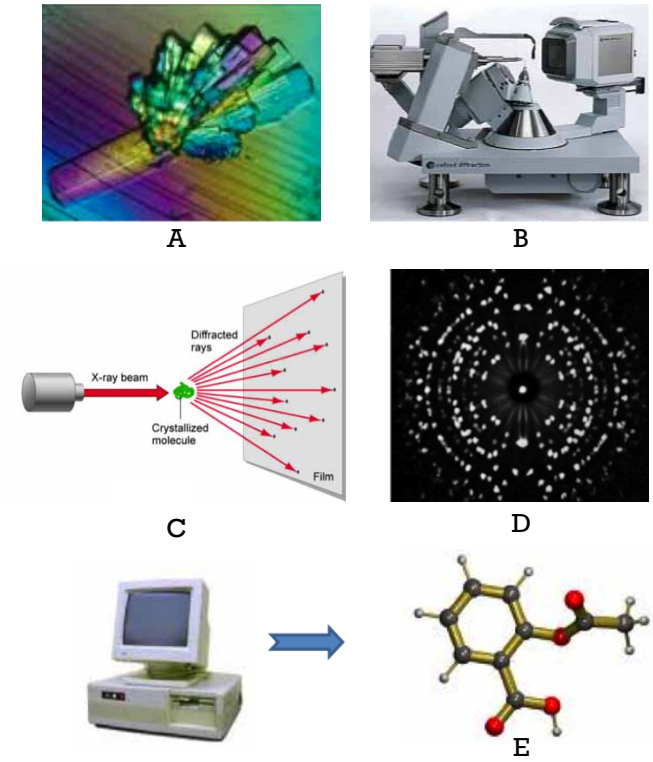



***Figure 9.*** *Depiction of Computer Assisted Drug Design. (A) Example of a crystallized chemical compound or protein; (B) An X-Ray Diffractometer; (C) An X-ray beam is focused on the crystal causing the scattering of the beam; (D) A typical diffraction pattern; (E) Using powerful computers, the diffraction pattern is translated into a three-dimensional chemical structure, showing the individual atoms of the compound. In this case, the molecular structure of aspirin is shown. Carbon atoms are shown in gray, oxygen in red and hydrogen in white.*

and purified. Then, the HIVP and new potential drug can be co-dissolved and crystallized as a complex under very specific sets of conditions. Once a co-crystal is formed, the three-dimensional structure of the complex can be solved using a technique called x-ray crystallography. This technique, which involves the use of a specialized instrument called an x-ray diffractometer enables organic chemists and molecular modelers to visualize the structure of the HIVP-inhibitor complex and see the interactions between the inhibitor and the enzyme at the atomic level. Using docking programs, molecular modelers can then design molecules that should be a good fit for the three-dimensional space of the enzyme they wish to block. The chemist can then synthesize the suggested compound(s), and biologists test them to see if they have the desired activity. After the preparation of an appropriate number (a few to several dozen, depending on the program) of analogs, chemists, molecular modelers, and biologists examine the results of the modeled target(s) to determine whether the inhibitors are, in fact, inhibiting HIVP as predicted. This process is called structure-activity relationship (SAR), and is the cornerstone of medicinal chemistry. Based on the results from the first cycle, the best new inhibitor is then co-crystallized with HIVP and the iterative cycle begins again. It is not unusual for more than 5 cycles to be required until a drug with suitable potency is found. Each of these cycles represents an enormous amount of work, and it is not uncommon for teams of 50-100 scientists to work for more than three years before a suitable drug candidate can be identified. This process is also referred to as rational drug design. The actual structure of Invirase bound to the HIVP enzyme is shown in Fig. 10.

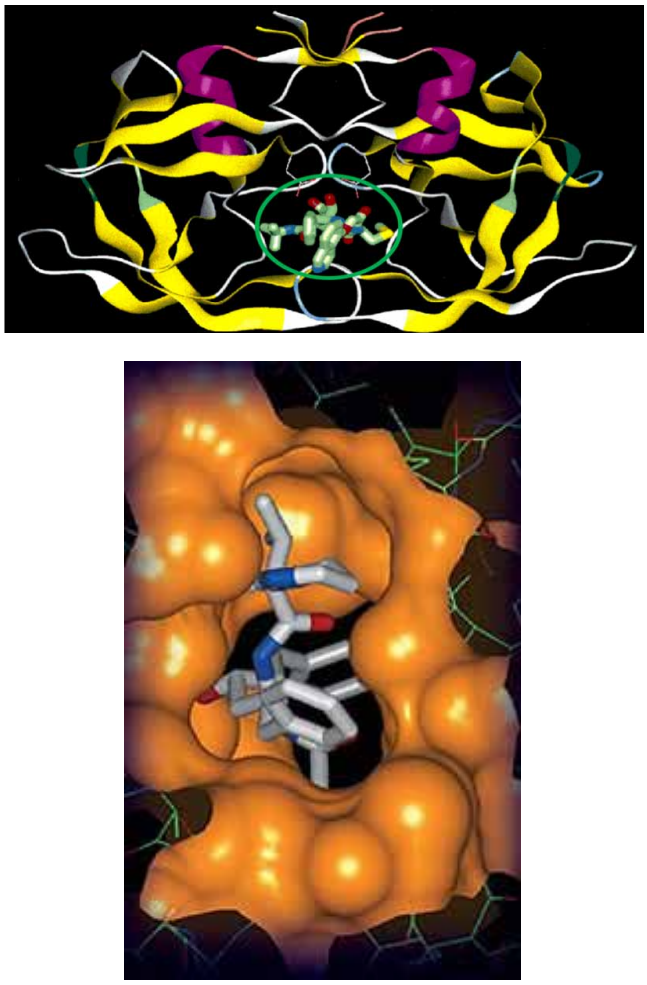


***Figure 10.*** *The X-ray structure of Invirase (top) and Kaletra (bottom). The Invirase molecule (within green circle) occupies a hole in HIVP where the normal protein substrate would sit, blocking the function of the enzyme. The colored ribbons represent protein components that make up the structure of HIVP. Note the excellent fit of the Invirase molecule in the "active site" (the "donut hole" of HIVP where the normal biochemical reaction takes place). The X-ray structure of Kaletra bound to HIVP is rotated 90 degrees relative to the Invirase structure. The orange solid is the three dimensional representation of the active site of HIVP with the inhibitor binding tightly within the donut hole.*

# Not As Easy As It Sounds

Despite the immense undertaking described above, the task of discovering a drug has only just begun. On average, it takes between 5,000 and 10,000 new chemical compounds to produce one marketed drug. Considering that a good organic chemist will prepare about 50 target molecules for testing in one year, over the course of a twenty-year career, the chances of any individual actually discovering a marketed drug are only five to ten percent. So, why is this task so difficult? It is instructive to question why an efficient process, such as rational drug design, must still overcome a massive barrier to produce a useful drug rather than just a simple (and useless) enzyme inhibitor. The answer to this question is called ADMET, an acronym for Absorption, Distribution, Metabolism, Excretion and Toxicity. This is where drugs live or die.

The most potent *in vitro* HIV inhibitor imaginable can be useless as a drug. A potential drug that fails any of the ADMET criteria will rarely be successful, especially as an oral therapy. Since most medicines are taken orally, absorption of the drug is extremely important. There are numerous factors that determine whether a drug gets absorbed. Solubility is one of them. The drug must have at least some solubility in the stomach or intestines so it can pass through the mucosal lining of the gastrointestinal tract; only then will the drug be able to enter the bloodstream. A completely insoluble drug will usually pass through the entire intestinal tract without absorption and be excreted in the feces. In certain cases when oral absorption does not occur (e.g. insulin), subcutaneous or IV administration is used; however, for the treatment of most chronic diseases, this is generally a poor option. The amount of drug getting into the blood relative to the dose of the drug is called *bioavailability*. Invirase suffers from very poor bioavailability, which means that it must be administered in large doses, which raises material costs and usually leads to more side effects. Many of the protease inhibitors that followed Invirase were prepared to address this issue.

Once absorbed from the GI tract into the bloodstream, a drug passes via the portal vein directly into the liver, the main metabolic organ in the body. At this point, several things can happen, two of which are metabolism and distribution. The liver is instrumental in processing nutrients, but it is just as good at processing foreign substances like drugs. Virtually all drugs undergo at least some hepatic (liver) metabolism, but this metabolism is manageable if the process is not too fast. The amount of time it takes to metabolize half the initial blood quantity of a drug is called the half-life. The half-life of most drugs is several hours, meaning that the drug can usually be given one to four times per day. For a chronic antiviral agent this is especially crucial. A drug with a very short half life would have to be administered ten or more times per day to maintain proper blood levels, making patient compliance and cost unfeasible. Another potential pitfall of metabolism is that a non-toxic drug can often yield a toxic metabolite after processing by the liver. Thus, metabolic

All drugs possess some toxicity. The important parameter is not absolute toxicity, but the ratio of toxicity to the seriousness of the disease it will be treating.

stability is one of the most carefully studied parameters in drug development.

Distribution is another important issue that needs to be addressed. Even with a suitable half-life, some drugs go to places where they are not useful, or are actually toxic. For instance, a drug required in the bloodstream (any AIDS drug) will be rendered useless if it is sequestered in the liver, muscle or fatty tissues. Likewise, a drug used to treat central nervous system diseases must be distributed to the brain to have any utility. Distribution is generally unpredictable and is usually studied thoroughly in animals before a drug may proceed to human trials.

Excretion is often related to metabolism. The liver usually degrades a drug into smaller fragments that are excreted in the urine or feces. Sometimes the liver attaches sugar-like substances to the drug, increasing its water solubility and facilitating its transport to the kidneys where the drug is excreted. Excretion is typically a less important issue than absorption or metabolism. At this point in the development process, it is still very common for a potent, bioavailable, stable drug to fail, despite meeting most requirements expected of a successful drug. Toxicity is by far the most common reason for failure.

The toxicity of a potential drug is carefully determined in a sequential process, which first begins in multiple cell lines, then progresses to animals and finally concludes in human clinical trials. Toxicity in certain cell lines can be enough to require the cessation of the development of a drug. Low levels of cell-based toxicity allow the drug to be evaluated in animals (usually mice and rats). Escalating doses of the drug are given either orally and/or intravenously, and the animals are observed for signs of toxicity. Necropsy also provides important data following sacrifice of the animal. If acceptable levels of toxicity are observed, another non-rodent species of animal must be used (Food and Drug Administration requirement) before any testing in humans is permissible. Eventually, escalating doses of the drug (starting with extremely small amounts) are given to healthy human volunteers, who are carefully monitored for any sign of toxicity. These studies are called Phase I clinical trials. It is not uncommon for toxicity previously unobserved in animals to show up in humans. The prediction of human toxicity based on animal toxicity is an inexact science at best. To further complicate matters, the parent drug may be non-toxic, but one of its metabolites may be toxic. Thus, any metabolites detected in significant quantity must undergo the same rigorous evaluation as the drug itself. Following Phase I trials are Phase II trials (safety and efficacy is studies in hundreds of patients with the disease), and Phase III trials, where the drug is tested in thousands of patients at multiple sites. If a drug clears all of these hurdles, it may be approved by the FDA and then marketed.

All drugs possess some toxicity. The important parameter is not absolute toxicity, but the ratio of toxicity to the seriousness of the disease it will be treating. For minor afflictions, drugs must be very safe. For life-threatening diseases, such as cancer and AIDS, greater toxicity is permissible, since the alternative is death. Nonetheless, despite the severity of the disease, the early AIDS cocktails were quite toxic and very difficult to tolerate. Regimens involved taking multiple sets of

different pills several times per day, sometimes with food and sometimes without. Side effects were numerous, including nausea and vomiting, liver toxicity, diabetes, elevated cholesterol, and lipodystrophy (Fig. 11), the deposition of large quantities of fat, usually in the upper back.

The second generation of AIDS drugs (generally after 2000) was largely developed to address ADMET issues as well as to combat viral resistance. This is where the most remarkable progress lies. Table 1 shows the nine protease inhibitors that followed saquinavir. Note that the dosages for drugs approved after 2000 are significantly lower than earlier drugs. This reflects improved potency and bioavailability. A total of ten drugs were discovered collectively by nine different companies and were developed and approved within a decade — a truly remarkable achievement. It was subsequently discovered that one of the PIs, ritonavir (Norvir) helped block the enzyme that degraded the other protease inhibitors. This effect permitted other PIs to be given in lower doses when co-administered with ritonavir. For example, the daily dose of Invirase can be cut from 2000 mg to 800 mg when a "ritonavir booster" is added. All PIs are now given with ritonavir.

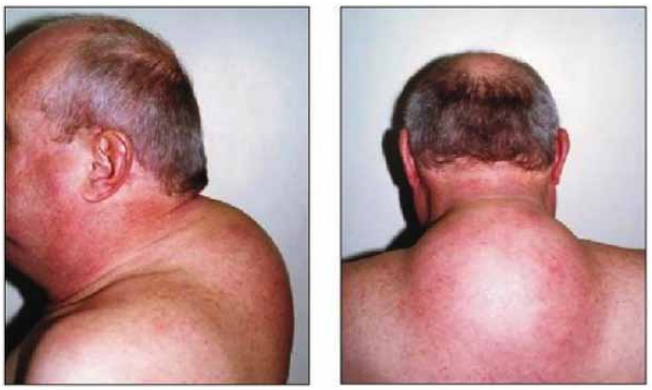


***Figure 11.*** *Lipodystrophy in an AIDS patient taking protease inhibitors*

The combination of one or more reverse transcriptase inhibitors with a protease inhibitor became the first example of HAART (highly active antiretroviral therapy). Although some of the original components have now been replaced by more potent drugs, the advent of HAART signaled the beginning of the time when science started to gain the upper hand over HIV. Patients showed impressive increases in the number of their T (immune) cells, drastic decreases in the number of virus particles in their blood, and a regression of symptoms that were unimaginable a decade before.

| Drug | Generic Name | Company | Approval Year | Typical daily dose (mg) |
|---|---|---|---|---|
| Invirase | saquinavir | Roche | 1995 | 2000 |
| Norvir | ritonavir | Abbott | 1996 | 1200 |
| Crixivan | indinavir | Merck | 1996 | 800 |
| Viracept | nelfinavir | Agouron/Japan Tobacco | 1997 | 2500 |
| Agenerase | amprenavir | Glaxo | 1999 | 2400 |
| Kaletra | lopinavir | Abbott | 2000 | 800 |
| Reyataz | atazanavir | Bristol-Meyers Squibb | 2003 | 400 |
| Lexiva | fosamprenavir | Glaxo | 2004 | 1400 |
| Aptivus | tipranavir | Boehringer-Ingelheim | 2005 | 1000 |
| Prezista | darunavir | Tibotec | 2006 | 800 |

***Table 1.*** *HIV protease inhibitors in order of date of approval. Note the lower dose requirements for newer drugs.*

# NNRTI Inhibitors

By the late 1990s, there was a sufficient number of HIV drugs available on the market to control AIDS, although improvements in the areas of resistance and tolerability were still needed. Patients had to adhere to strict regimens, involving taking as many as 40 pills per day (Fig. 12) at regular intervals (requiring awakening in the middle of the night), usually on an empty stomach with large volumes of water. The therapies were extremely unpleasant, yet attempts to allow patients a "drug holiday" by skipping treatment for a few days failed. It was clear that better therapeutic regimens were needed, especially considering the large doses of PIs required and the resulting side effects. During this time, a new, highly potent series of HAART drugs was discovered — the non-nucleoside reverse transcriptase inhibitors (NNRTIs).

The first NNRTI, Viramune (nevaripine, Boehringer Ingelheim, 1996) is still an important component of modern cocktails today. There are four marketed NNRTI drugs, the most recent being Intelence (etravirine, Tibotec), which was approved in 2008. Intelence is extremely potent, with a therapeutic dose of 200 mg per day, 5-to-10-fold less than many of the protease inhibitors (Table 2).

***Figure 12.*** *A typical pill burden for an AIDS patient ca. 2000*

The NNRTIs are related to the NRTIs in function in that they both inhibit reverse transcriptase, but they do so in a subtle but critically different manner (Fig. 13). Not only are the NNRTIs chemically unrelated to the NRTIs, but they bind to a different location on reverse transcriptase, making it possible for both drugs to simultaneously inhibit reverse transcriptase at different sites. The result is a much lower incidence of resistance since it is much more difficult for the virus to produce a viable mutant with two different mutations present. Either type of drug will generate rapid resistance when given alone, but the opposite is true when they are administered together. In fact, one of the first-line drug regimens that circumvented resistance is a

| Drug | Generic Name | Company | Approval Year | Typical daily dose (mg) |
|---|---|---|---|---|
| Viramune | nevirapine | Boehringer-Ingelheim | 1996 | 400 |
| Rescriptor | delavirdine | Pfizer | 1997 | 1200 |
| Sustiva | efavirenz | Merck | 1998 | 600 |
| Intelence | etravirine | Tibotec | 2008 | 200 |

***Table 2.*** *Marketed NNRTI drugs*

combination of two NRTIs and one NNRTI. The same holds true when a protease inhibitor is used in place of the NNRTI. The use of these regimens has had a dramatic effect on the course of the disease. Unchecked, HIV will replicate at an amazing rate, producing 10 billion new virus particles per *day*. Patients on successful HAART therapy can live for years with such a small viral load that the virus cannot be detected, let alone measured.

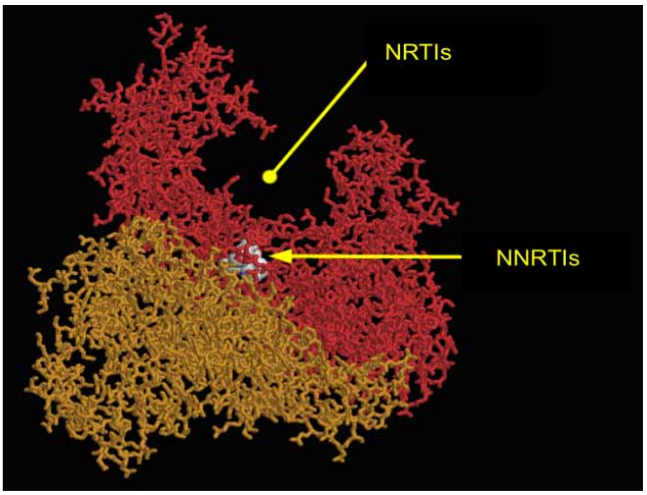



***Figure 13.*** *The binding of NRTIs and NNRTIs to reverse transcriptase. Note that the two classes of drugs bind in nearby, but distinct sites on RT.*

# Newer Therapies

Referring back to Fig. 2, we have discussed only two of the seven targets in the HIV life cycle (Step 3, transcription; Step 7, maturation). Taken together, the inhibition of these two steps and subsequent HAART therapies would constitute a remarkable breakthrough against a previously hopeless disease. But there remain therapeutic challenges (mainly resistance) that still require further study. At the time of this writing, three other targets have yielded marketed drugs in the continued campaign against HIV — integration (Step 4), fusion (Step 2) and binding (Step 1).

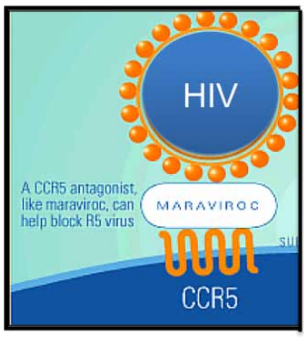



***Figure 14.*** *Maraviroc sits on the CCR5 receptor of the T-cell, preventing HIV binding*

***Fig.*** *15. Then and now.*

Enfuvirtide (Fuzeon) is usually not a first-line therapy against HIV. In addition to its high cost, the drug fails most ADMET parameters and thus must be given by injection twice daily. Its main use is for *salvage* therapy, which occurs when patients develop resistance to both RT and HIVP inhibitors, rendering them ineffective. Enfuvirtide works by disrupting the mechanism by which the virus penetrates the T-cell. Maraviroc (Selzentry) works by a similar mechanism to enfuvirtide. It binds the CCR5 receptor on the T-cell surface, one of two places where HIV would normally attach. In doing so, the T-cell receptors become occupied by the drug, leaving no room for HIV binding to occur in (Fig. 14).

Finally, scientists at Merck discovered and developed Isentress (raltegravir), the only approved HIV integrase inhibitor. Raltegravir inhibits the integration step that follows reverse transcription (Fig. 2, Step 4). As is the case with drugs that block other steps in the HIV life cycle, raltegravir suppresses viral replication, albeit by a different mechanism. The potency of Raltegravir is comparable to the PIs, but it is easier to tolerate, and lacks many of the side effects associated with the PIs. In fact, many standard-of-care therapies are *protease sparing* and consist of one or more NRTIs in combination with an NNRTI or raltegravir. Fig. 15 shows the result of the continued research into novel HIV therapies.

| Drug | Generic Name | Company | Approval Year | Target |
|---|---|---|---|---|
| Fuzeon | enfuvirtide | Trimeris/Roche | 2003 | Fusion |
| Selzentry | maraviroc | Pfizer | 2007 | Binding |
| Isentress | raltegravir | Merck | 2007 | Integration |

***Table 3.*** *Newer Therapies*

# Summary

The campaign against HIV was waged mainly by the pharmaceutical industry. Although there were significant contributions from universities and the government, neither of these has the knowledge, resources or ability to develop drugs. Drug companies are often portrayed as "evil" or "greedy", but this could not be further from the truth. As late as 1994, AIDS was a certain death sentence. Within a few years this was no longer the case, thanks to the dedication of a dozen or so companies working for a decade, often for little financial gain. Now, there are more than 20 AIDS medications on the market, and with improved modern therapies, life expectancy has increased markedly and hospitalizations have likewise decreased. The actual numbers for extended life expectancy differ greatly, and depend on factors such as the patient's age at the time of infection, the prior damage to the immune system at the start of HAART, and whether the infection arose from IV drug use or sexual activity. Nonetheless, the numbers are impressive. In 2006 at the World AIDS Conference, it was estimated that an infected 20-year-old male would have a life expectancy of 63 years in the U.S. Some studies have shown lesser benefits; however, a 2010 review estimated that a 25-year-old male non-drug user in Germany user receiving HAART today has a projected life span of 77.7 years, virtually identical to the 78.1 year life expectancy of a non-infected man. Regardless of the particular data used, by any measure, the war against AIDS is probably the greatest single accomplishment in the history of the pharmaceutical industry. So, whatever happened to AIDS? See Fig. 16.


***Figure 16.*** *This is what happened to AIDS.*

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