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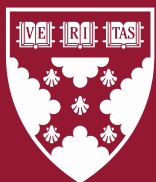
Case Histories of Transformational Advances

HIV Tests and AIDS Treatments – Containing a Fearsome Pandemic

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CASE HISTORIES OF TRANSFORMATIONAL ADVANCES

HIV Tests and AIDS Treatments – Containing a Fearsome Pandemic

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Abstract: This case history describes how a diverse cast of characters, including public health organizations, research laboratories, for-profit healthcare companies, activists, and regulators, rolled back the outbreak of HIV/AIDS in just fifteen years. Moreover, as the case history shows, a stunning reduction in deaths from the diseases was accomplished mainly through accretive advances – without developing a vaccine, an unambiguous test, or a complete cure.

Note: Like the other histories in this series, this advance is included in a list compiled by Victor Fuchs and Harold Sox (2001) of technologies produced (or significantly advanced) between 1975 and 2000 that internists in the United States said had had a significant impact on patient care. The case histories focus on advances in the 20th century (i.e., before this millennium) in the United States, Europe, and Japan -- to the degree information was available to the researchers. Limitations of space and information severely limit coverage of developments in emerging economies.

Acknowledgments: We thank Scott Podolsky for helpful information and suggestions.

HIV Tests and AIDS Treatments – Containing a Fearsome Pandemic

HIV/AIDS was discovered in the early 1980s and became a fearsome pandemic by the mid-1990s. In a stunning turnaround, mortality has dropped by eighty-five percent in the United States since 1996.¹ Today, life expectancy for Americans and Europeans infected with the virus can be the same as for those who are uninfected.

The following three sections describe how a diverse cast of participants (See **Table 1**) helped develop 1) measures to control the transmission of the disease, 2) tests to identify and monitor infections, and 3) treatments that significantly increased life expectancy. A concluding section summarizes the situation at the end of the 1990s.

Table 1 Contributors to the Control and Treatment of HIV/AIDS

Public Health Organizations	Research Laboratories	Private Health Care Companies			Activist Groups	Regulatory Agencies
		Diagnostics	Traditional Pharmaceutical	Biotech		
The Centers for Disease Control and Prevention (CDC)	Universities and hospitals throughout North America and Europe	Abbott Laboratories Electro-Nucleonics	DuPont Hoffmann-La Roche	Biotech Research Laboratories Genentech	Hundreds of local, national, and international AIDS organizations and advocacy groups	The Food and Drug Administration (FDA)
US state and local Public Health Departments	The National Cancer Institute (NCI)	Litton Bionetics Travenol	Johnson & Johnson Burroughs Wellcome	Genetic Systems Corporation		The US Patent and Trademark Office (USPTO)
The Public Health Service (PHS)	The Pasteur Institute	Pasteur	Bristol-Myers Squibb	Cambridge Biosciences (Cambridge Biotech after 1990)	AIDS Coalition to Unleash Power (ACT-UP) The Terrence Higgins Trust	US state and local Public Health Departments National European regulatory bodies
European national public health systems	The National Institutes of Health (NIH)	University Hospital Laboratories Clinical Reference Laboratory	Merck Glaxo Boehringer Ingelheim	Cetus Corporation Chiron Corporation	Individual or small group activism (e.g. buyer's clubs)	The European Medicines Agency (after 1995)
The European Centre for Disease Prevention and Control (after 2005)	Institute of Allergy and Infectious Diseases (NIAID)	Becton Dickinson Coulter Immunology Bayer Siemens		Agouron Pharmaceuticals Gilead Sciences Alere		

1. Controlling Transmission (1981-1990)

Identifying the Disease. The Human Immunodeficiency Virus (“HIV”) virus is thought to have jumped from apes to humans in the 1910s in Central Africa and then spread along ferry and rail routes to become an epidemic in the Congo in the 1950s. In the 1960s and 1970s, it arrived and spread in the West through syringes (for medical and drug use), blood banks and blood products, unprotected sex, and international travel.

The threat infections posed was not recognized for another ten years. The reason: HIV infections gradually induce AIDS (“Acquired Immunodeficiency Syndrome”) by slowly killing the immune system’s

This case history does not present original research or new thesis. Instead, it summarizes historical developments and includes questions to stimulate reflection and discussion.

“helper T-cells.” It takes about a decade to deplete helper T-cells to the point that the immune system is so impaired that patients die from infections they would otherwise have been able to resist.

Puzzling infections among gay men in California in 1981 started the process of identifying the disease. Michael Gottlieb, a Los Angeles immunologist, treated five gay males with severely depleted T-cells who had become deathly ill with a rare form of pneumonia. Rather than submit an article about the cases to a medical journal,* Gottlieb published his descriptions in the June 5, 1981, *Morbidity and Mortality Weekly Report* issued by the Centers for Disease Control and Prevention (CDC).² In July, doctors in New York and San Francisco reported two dozen similar cases.

Unexpected infections in patients with impaired immune systems were then observed outside the gay male population in 1982. The CDC and local public health departments found cases in women, hemophiliacs, and infants. The New York Public Health Department reported cases among intravenous drug users and Haitians. After this wider incidence, the CDC changed the disease’s name from GRID (“Gay Related Immune Deficiency”) to AIDS.

Immunologists, epidemiologists, and other medical researchers quickly undertook studies that eventually ruled out several possible causes, including fungal toxins, popular club drugs (amyl nitrites or “poppers”), stress, and pregnancy.³

Meanwhile, reports suggested the possibility of a blood-borne virus.⁴ CDC officials, therefore, sought to protect the blood supply by restricting donations to blood banks. At a meeting in July 1982, assistant director Jeffrey Koplan urged representatives of government organizations, blood banks, pharmaceutical manufacturers, the Hemophilia Foundation, and gay groups to back the exclusion of blood donations from gay men and Haitians. However, many participants did not want to refuse blood donations when the cause of AIDS remained uncertain.⁵

Blood supply controls were instituted in March 1983 after researchers had identified the HIV virus. (More on this in the next section.) Health officials mandated excluding blood donations from anyone with signs or symptoms of AIDS, gay and bisexual men with multiple partners, intravenous drug users, and – most controversially – recent Haitian immigrants.⁶ Heat treatment of blood and blood products became routine after researchers found high temperatures killed the virus in late 1984. And, blood banks screened donated blood once the first tests became available in 1985 (as discussed in the next section).

The CDC also recommended that doctors, nurses, and dentists use gloves, gowns, aprons, masks, eyewear, disposable needles and scalpels, and disinfectants.⁷

Some initiatives attracted controversy. Health officials helped gay bathhouses and sex clubs distribute educational pamphlets and condoms to patrons (who often used the venues for engaging in sex). These initiatives were opposed by groups promoting abstinence. San Francisco, New York, and Los Angeles city officials’ orders to shut down bathhouses faced legal challenges from bathhouse owners.[†] Volunteers

* Gottlieb had contacted the *New England Journal of Medicine* about publication, but the editor there suggested the *MMWR*, because articles in medical journals go through a lengthy refereeing process before publication, and the editor believed it was important to get the word out quickly.

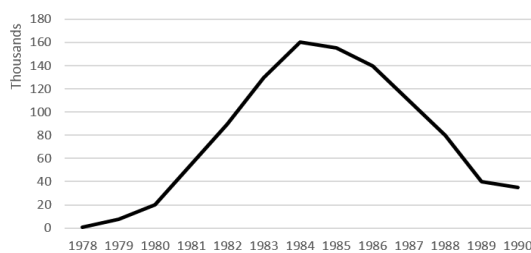
† A judicial ruling gave San Francisco bathhouses the option of staying open if owners ejected individuals engaged in risky behavior.

started needle exchange programs for drug addicts that broke laws against the possession and distribution of drug paraphernalia. A few public health departments then worked to decriminalize and expand the needle exchanges.

Screening individuals (in addition to screening blood) for HIV infections improved efforts to control risky behavior that could spread the disease. US military recruits, immigrants, and some insurance applicants were required to submit to tests.* The Public Health Service (PHS) mailed a brochure to every household in the United States in 1988 that encouraged individuals in groups considered high risk to seek tests. In 1993, the CDC advised hospitals, outpatient clinics, and emergency departments to offer HIV testing and counseling to patients, and in 1995, recommended tests for all pregnant women.⁸ HIV-positive individuals were encouraged or pressured to use condoms.⁹

These multifaceted actions undertaken by health officials and non-profit organizations (See **Exhibit 1**) helped sharply reduce infection rates before any effective treatments (described in Section 3) were developed.¹⁰ (See **Figure 1**)

Figure 1 Estimated Number of New HIV Infections per Year in the United States, 1978-1990



Source: Ron Brookmeyer, "Reconstruction and Future Trends of the AIDS Epidemic in the United States," *Science* 253, no. 5015 (1991).

Controlling Transmission in Europe. Health officials in Europe recognized the AIDS threat in the same year as in the United States. By the end of 1981, physicians in Britain, France, Denmark, and Spain had documented AIDS cases in gay men. The following year, physicians in France and Germany began to see AIDS in hemophiliacs. At the beginning of 1983, European public health officials discussed restrictions on donors to blood banks but, as with the US in 1982, decided against such restrictions.

After researchers confirmed the viral cause of AIDS, health authorities in Switzerland, France, and Germany began programs to identify individuals who engaged in risky behavior but did not exclude any groups from blood donations. Most European countries required the heat treatment of blood and blood products beginning in 1985. And, like their American counterparts, European blood banks began to screen blood for HIV once the first tests became available.

Many San Francisco bathhouses closed immediately or soon after the initial order. A few bathhouses chose to monitor patrons. One bathhouse refused all directives and fought charges brought by the city until it closed in 1987.

* Five states banned HIV antibody testing by insurers beginning in 1987, but some of these restrictions were temporary.

After 1985, European health authorities promoted voluntary testing in high-risk groups – sex workers, gay and bisexual men, intravenous drug users, migrants, prisoners, and pregnant women – rather than in the general population.¹¹ Although they were fewer than in the United States, European AIDS organizations also offered testing and counseling and encouraged the use of condoms.¹² Infection rates dropped in Europe after these measures took effect, much as rates had in the United States.¹³

Questions (for reflection and discussion):

Before reading further, please write down (in less than ten words) which decision, event, or condition you found the most significant in speeding up or slowing HIV transmission.

- _____

Be prepared to explain in class why you found this significant.

Also think about the good choices and misjudgments (not luck) made and what lessons you might draw from them.

2. Developing Tests (1981-1999)

Virologic Foundations. Developing tests for HIV posed several challenges. HIV is a “retrovirus” rather than a regular virus. And, when AIDS was first recognized, only two human retroviruses had been identified (by the NCI’s Robert Gallo in 1980 and 1981, who had found they caused cancers). HIV also had variants and mutations, which could not all be detected by a single test.¹⁴

Teams at the American National Cancer Institute (NCI) and the French Pasteur Institute took the first steps. NCI’s Robert Gallo investigated AIDS at the urging of the CDC’s task force on AIDS. The Pasteur Institute developed vaccines for infectious diseases, and Pasteur virologist Luc Montagnier had studied animal retroviruses. He focused his lab on AIDS after two physicians requested an examination of tissue samples from their AIDS patients.¹⁵

Montagnier’s team isolated and analyzed the retrovirus first, photographing it with an electron microscope. The team published its findings in May 1983. And, even before publication, the French researchers shared the virus they had isolated with Gallo’s group at the NCI. Each lab was aware of the other’s progress, and Gallo and Montagnier had close professional ties.¹⁶

Gallo’s lab at the NCI was second to identify the retrovirus, but their May 1984 publication offered stronger evidence that the retrovirus was the cause rather than a correlate of AIDS. Gallo and his colleagues reported that the retrovirus was present in some members of a high-risk group and absent in all members of a low-risk group. Follow-up studies by other researchers reinforced the causal connection.¹⁷

Other labs soon replicated Montagnier’s and Gallo’s results. Jay Levy, a physician and cancer researcher at the University of California, San Francisco, published his evidence of a retroviral cause for AIDS in *Science* in August 1984. That fall, researchers in England and Italy provided similar evidence.

The Pasteur and NCI teams then developed prototype tests for infections that relied on detecting HIV antibodies. Our immune systems produce distinctive antibodies to fight particular viruses (or retroviruses). The presence of an HIV antibody in a blood sample could be inferred from its interaction with a “conjugate”

(“antigens”) extracted from viruses cultured in a lab. (Later, as we will see, the conjugates could be synthesized, without culturing, using genetic techniques.)¹⁸

NCI researchers filed for a US patent for their test in April 1984 and received approval from the US Patent Office in May 1985. The Pasteur Institute had filed for a patent five months before the NCI but had not received any response from US patent authorities. In December, the Pasteur Institute sued the US government. It charged that the NCI (part of the US government) had based its patent in part on Pasteur’s sample, violating an agreement to use the materials for non-commercial research, and demanded royalties from the sale of tests licensed by the NCI. The US government and the Pasteur Institute eventually agreed to share licensing fees. (Presidents Ronald Reagan and Jacques Chirac announced the agreement at the White House on March 31, 1987.)¹⁹

Scientific credit was also controversial. A commission appointed by the International Committee on Taxonomy of Viruses confirmed that the virus found by the NCI team was identical to the ones discovered earlier at Pasteur.²⁰ The issue of credit resurfaced after Montagnier shared the 2008 Nobel Prize for Medicine, but Gallo was excluded.²¹

First Test Kits. In the spring of 1984, two weeks after its patent filings, the NCI solicited proposals for developing commercial test kits. The NCI offered to license its intellectual property and provide the viral samples that test developers required to produce the conjugates needed to detect HIV antibodies. However, the NCI’s supply of viral samples was limited because HIV was difficult to grow (“culture”) in a laboratory. Therefore, the NCI established criteria for selecting developers that included both technical capabilities and the capacity to market and sell high volumes of test kits.

The NCI required applications to be submitted in ten days. Twenty companies applied, of which eight satisfied the criteria. The NCI chose five.²² (See **Table 2**)

Abbott Laboratories was the first to receive the FDA’s approval to market test kits in March 1985. By October 1985, the other four NCI licensees had also received FDA approvals.

Table 2 The First Five NCI Licensees

Company (Location)	Date Founded	Related Experience
Abbott Laboratories	1894	Diagnostics, pharmaceuticals, hospital products
Electro-Nucleonics	1960	Lab equipment
Litton Bionetics	1969	Clinical diagnostics
Travenol Genentech Diagnostics	1931/1973	Clinical diagnostics
DuPont/Biotech Research Laboratories	1802/1973	Diagnostics, genetics, pharmaceuticals

Source: Barbara J. Culliton, “Crash Development of AIDS Test Nears Goal,” *Science*, New Series, 225, no. 4667 (September 14, 1984).

The Pasteur Institute gave its viral samples to just two developers. One was Pasteur’s own commercial arm that would produce tests for the European market. The other was Genetic Systems Corporation, a recent (1981) biotech startup located in Washington State, which was expected to focus on the US market. Genetic Systems obtained approval from the FDA for the kit developed with Pasteur’s viral samples in February 1986.

Advances in Screening Tests. Tests sold in 1985 and 1986 (now referred to as “first generation” tests) had limitations. They detected the antibodies to HIV-1 infection, which was common in the United States and Europe, but not to HIV-2 infection, which was less widespread but not absent.²³ The kits could not detect infections for up to twelve weeks after occurrence. And, when calibrated to minimize undetected infection (to achieve a low rate of false negatives), they produced many false positives.^{24 25}

“Second generation” tests, first introduced in 1987, improved the accuracy of test results by adding synthetically produced materials to conjugates that had previously been composed entirely of extracts from a cultured virus. The synthetic materials, produced using recent advances in genetic technologies, did not have impurities that extracts from cultured viruses contained, and purer conjugates reduced false positives. These new kits also enabled the detection of HIV-2 infections and reduced the period between the occurrence and detection of infections from up to twelve weeks to no more than six.²⁶

“Third generation” tests, first introduced in 1991, produced even more accurate results by relying entirely on synthetic conjugates (eliminating impurities from cultured viral extracts.) These new tests could also detect a variant of HIV that the second-generation tests could not and further reduced the period between occurrence and detection of infection from six weeks to three.²⁷

Confirmatory Protocols and Tests were developed to control false positive results for all three generations of screening tests. Protocols for all three generations entailed repeated testing. First generation protocols also used “Western blot” and “immunofluorescence assays” (IFA) to confirm results.²⁸ Confirmatory protocols for second and third generation tests that could detect HIV-1 and HIV-2 infections, but not distinguish between the two, used a more elaborate procedure.²⁹ (See **Table 3**)

Rapid screening tests introduced around the same time as the third-generation tests (and that also used synthetic conjugates) traded off cost for speed. A biotechnology startup, Cambridge BioScience, introduced a two-hour test in May 1990. Johnson & Johnson, an American pharmaceutical, medical device, and consumer health product company, marketed the Cambridge BioScience test to hospitals, blood banks, and commercial labs that were willing to pay a higher price for faster results.³⁰

At-home tests were technically feasible, but regulators had concerns about accuracy and inadequate counseling for those who tested positive. As early as 1986, University Hospital Laboratories (UHL), a small startup, sought FDA approval for a kit for collecting blood samples at home, which would then be sent to UHL’s lab for testing. Instead of acting on UHL’s application, however, the FDA announced rules in 1988 that made selling at-home tests nearly impossible. UHL sued the FDA in 1990. The FDA reversed its policy against home collection of samples and reviewed UHL’s application but then asked UHL to submit a revised application with more data. In 1993, Johnson & Johnson acquired UHL and resubmitted an application for home collection kits. The FDA approved Johnson & Johnson’s application in 1996; the FDA’s press release announcing the approval referred to a 1995 CDC survey that had found that twice as many patients at risk for HIV infection would seek testing with an at-home option.

Saliva- and urine-based tests, which were more convenient and cheaper than blood-based tests, were also resisted by US regulators. In 1991, the FDA ruled that the kits required full review and approval before distribution and mandated a recall of existing kits. When one company, Clinical Reference Laboratory, refused to comply, the FDA sent federal marshals to seize its kits. Then, pressured by insurance companies, The FDA approved a saliva kit in December 1994 and a urine kit in August 1996. But, it continued to restrict the use of both to hospitals, clinics, and doctors’ offices.³¹

Table 3 Overview of the First Three Generations of Test Technologies Available in the US and Europe

1.	First generation	Second generation	Third generation
Year introduced	1985	1987	1991
Conjugate	Extracted from cultured virus	Extracted from cultured virus and synthetic (recombinant)	Only synthetic (recombinant)
Can detect	HIV-1 only	HIV-1 HIV-2	HIV-1 HIV-1 (“O” variant)* HIV-2
Reliably sensitive test after	8-12 weeks	4-6 weeks	2-3 weeks
Sensitivity in reliable period (high sensitivity indicates few or no false negatives)	99%	>99.5%	>99.5%
Specificity (high specificity indicates few or no false positives)	95-98%	>99%	>99.5%
Confirmatory protocols included	HIV-1 Western blot or immunofluorescence assay (IFA)	HIV-1 WB or IFA HIV-2 ELISA** and WB if HIV-1 confirmation is negative	HIV-1 WB or IFA HIV-2 ELISA** and WB if HIV-1 confirmation is negative

Source: Thomas S. Alexander, “Human Immunodeficiency Virus Diagnostic Testing: 30 Years of Evolution,” *Clinical and Vaccine Immunology* 23, no. 4 (April 1, 2016).

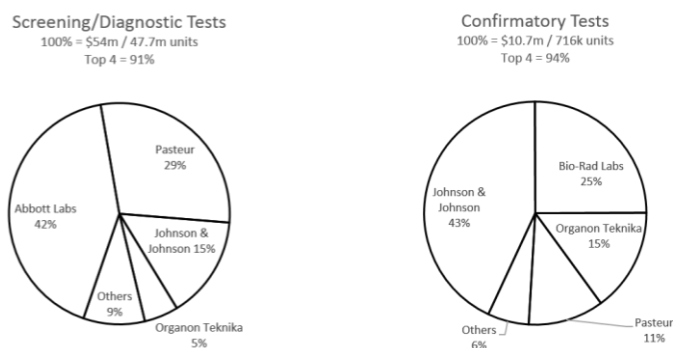
Note: This chart follows the organization of testing described in Alexander, “Human Immunodeficiency Virus Diagnostic Testing,” 251. See also: “HIV Basics - Testing” and “AIDS Diagnostic, Monitoring, and Therapeutics Markets,” Industry Research Report, 1994, Frost & Sullivan, accessed April 2016.

* The HIV-1 “O” variant is one of the four major strains of the HIV-1 virus.

** ELISA is a standard antibody-based testing method.

Markets and Competitors in the US. As of 1992, Abbott, which had been first to secure FDA approval in 1985, had maintained its lead in screening tests. Although Abbott’s tests had periodically fallen behind, switching costs had discouraged its customers from purchasing more technologically advanced alternatives.³² Pasteur’s commercial arm (which by then had acquired its American licensee, Genetic Systems Corporation)³³ ranked second. A division of Johnson & Johnson that in 1990 had acquired part of the testing business of DuPont/ Biotech, one of the five original developers of NCI-based tests, ranked third.³⁴ (Johnson and Johnson’s acquisition had also made it the leader in the smaller confirmatory test market).³⁵ Organon Teknika, an American subsidiary of the Dutch chemical company Akzo, which had acquired tests from original developer Bionetics in 1985, was fourth in screening tests and third in confirmatory tests³⁶ (See Figure 2)

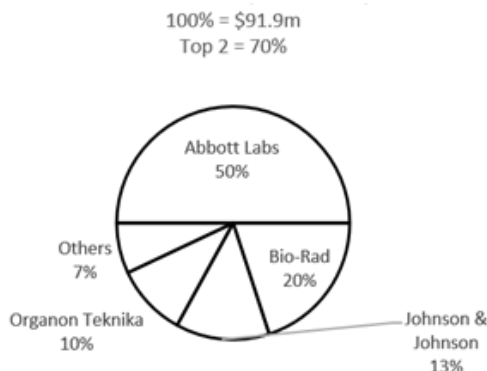
Figure 2 Market Shares of the Screening/Diagnostic and Confirmatory Tests in the United States, 1992



Source: Frost & Sullivan 1994).

The top four test producers continued to dominate the US market for screening and confirmatory tests through the 1990s. (See **Figure 3**) Abbott continued to lead, introducing faster automated testing systems.³⁷ Bio-Rad, a clinical diagnostics company, gained ground with its rapid and reliable confirmatory test (approved by the FDA in 1990). The high concentration reflected the inability of many entrants to gain a foothold – Bio-Rad being the exception – rather than a low number of entrants: by the start of the 1990s, an additional twenty-one companies, including several relatively new biotech companies, had screening or confirmatory tests in development. But by the end of the 1990s, many had exited or been acquired.*

* Five companies withdrew, including Bristol-Myers Squibb and MicroGeneSys, which both had HIV vaccine programs. Twelve companies were bought by larger companies, nearly all of which maintained the HIV test programs and products.

Figure 3 Market Shares of Screening and Confirmatory in the United States, 1999

Source: Frost & Sullivan (March 2000)

Monitoring Tests. The progression of the disease in patients already diagnosed with AIDS was initially monitored in one of two ways: one method measured distinctive protein molecules produced by the virus; the other method estimated the number of T-cells in patients, because T-cells died off as HIV infections worsened. Both were considered indirect indicators of the progress of the infection.

Advances in genetics in the late 1980s helped make monitoring more accurate and convenient. The new tests adapted a technique* to multiply genetic material rapidly. The technique had enabled forensic tests, celebrated in popular culture, that match individuals to their unique genetic material extracted from very small amounts of their blood, skin, or hair. Now, the technique was used to detect the unique genetic material of the HIV retrovirus. The tests also directly measured the quantity of HIV present in patient's bodies -- the so-called "viral load"³⁸ -- rather than indirectly through T-cell counts.³⁹

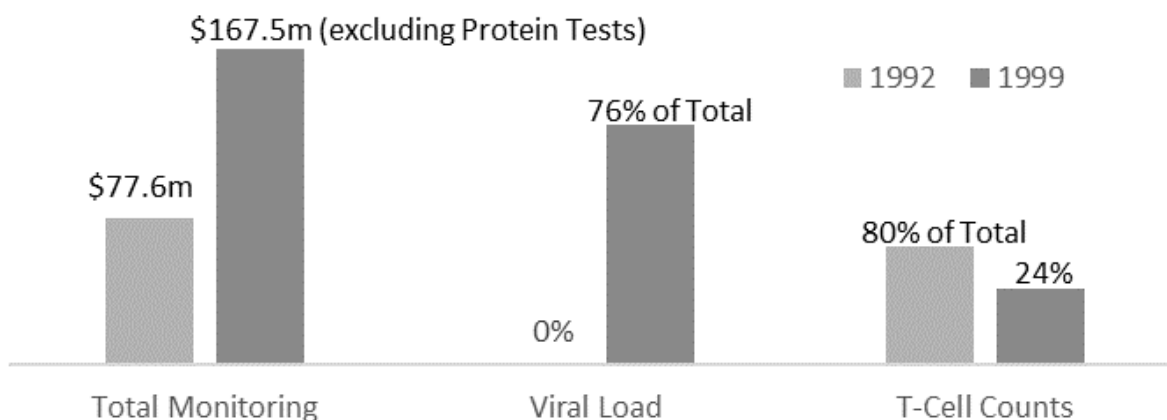
As the number of new and experimental AIDS drugs grew in the 1990s (as described in Section 3), physicians needed these monitoring tests to assess patients' responses and adjust treatments. Drug developers also needed monitoring to assess the efficacy of new drugs.

Many monitoring tests were first licensed to testing laboratories. Regulatory rules allowed laboratories to use tests that the FDA had not yet approved, provided they only used the tests in-house. Some companies, therefore, introduced new monitoring tests by granting lab licenses before seeking regulatory approvals to market them more widely. For example, in the early 1990s, Roche licensed their viral load test to labs and then went on to obtain FDA approval in 1996.⁴⁰

US sales of monitoring tests (in dollars) were more than seven times the sales of screening and confirmatory tests in 1992. Later, as sales of monitoring tests continued to grow, the mix of monitoring tests shifted from T-cell counts to more accurate measures of viral loads. (See **Figure 4**).

* Kary Mullis had conceived the underlying PCR ("polymerase chain reaction") method for multiplying genetic fragments in 1983 when he was employed by Cetus Corporation, which then developed PCR-based tests. Mullis won the Nobel Prize for Chemistry in 1993 for this work.

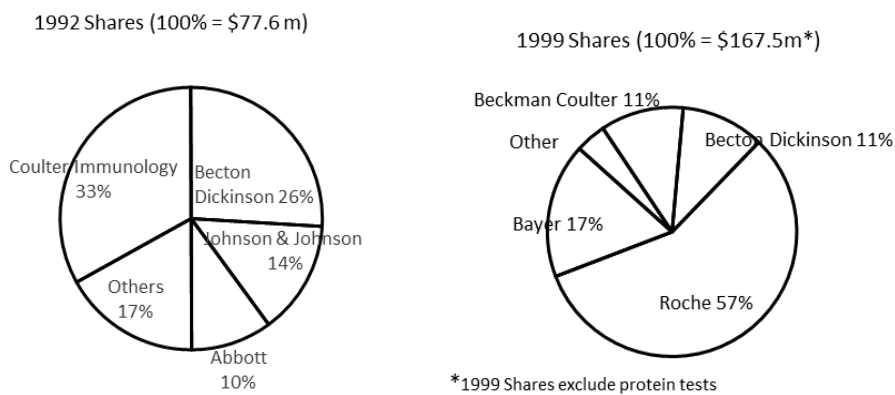
Figure 4 Growth in Sales of Monitoring Tests (\$ millions) Total and by Type of Test (1992-1999)



Source: Frost & Sullivan 1994 and March 2000).

The dominance of market leaders grew along with sales of monitoring tests. (See **Figure 5**) By the end of the 1990s, Roche sold for about three-quarters of all viral load measurement tests in the US.* (but not T-cell counting tests). And unlike the screening and confirmatory test markets, there were few new entrants in the monitoring test market.⁴¹

Figure 5 Changes in Market Shares of Monitoring Tests in the United States 1992-1999



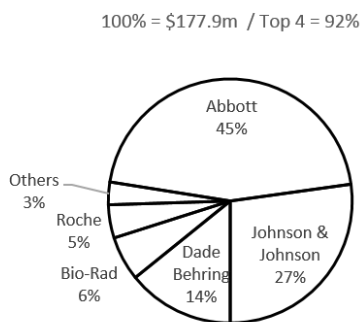
Source: Frost & Sullivan (1994, 2000)

* German pharmaceutical maker Bayer acquired Chiron’s diagnostics division in 1998, inheriting its share – the second largest – in the U.S. viral load testing market. By 2012, Roche would be ranked first among HIV test makers in Europe, and Abbott would be second.

Testing in Europe. Regulators in Europe began to approve first-generation screening tests in 1985⁴² (the same year the FDA first approved them in the US). Second and third generation tests were introduced in Europe at the same time as in the United States, in 1987 and 1991, respectively. Some European regulators were more open to at-home testing than the FDA. The United Kingdom permitted home collection kits, which allowed users to take their own blood samples and ship them to a lab for HIV testing. However, home tests without processing in a lab remained restricted. Similarly, European regulators proved more open to using saliva- and urine-based tests (allowing samples to be collected at home and processed in the lab).⁴³

Notwithstanding the differences in rules, European screening test markets exhibited similarities in market concentration and leadership. (See **Figure 6**)

Figure 6 Market Shares of European Screening Test Market 1999 (reported by blood banks)



Source: Frost & Sullivan (June 2000)

Questions (for reflection and discussion):

Before reading any further, please write down (in less than ten words) which decision, event, or condition you found the most significant in the development of AIDS tests.

- _____

Be prepared to explain why you found this significant.

3. Developing Treatments (1984-2000)

The First Effective Treatment: AZT. Initially, researchers at the NIH had tried – and failed – to treat AIDS by repairing patients’ immune systems with drugs, transfusions, and bone marrow transplants. After the retroviral cause of AIDS had been established, researchers began trial-and-testing of drugs that had shown an effect on animal retroviruses with the goal of finding at least a treatment, if not a cure. As Samuel Broder, an NCI researcher coordinating the efforts, recalled, “We were open to virtually any drug to treat this lethal and terrifying disease.”⁴⁴

In 1984, researchers at the American subsidiary of Burroughs Wellcome, a British pharmaceutical company, identified the first promising compound: AZT (azidothymidine). AZT had been synthesized in 1964 (with funding from the NCI) in an unsuccessful effort to treat leukemia. In the 1970s, German researchers found it stopped the reproduction of animal retroviruses, suggesting to Burroughs Wellcome

researchers that AZT could potentially treat AIDS. They retested it on animal retroviruses with excellent results and forwarded the drug to NCI researchers for testing on cultured HIV samples.

After NCI researchers found AZT effective against cultured HIV, Burroughs Wellcome got approval from the FDA to test and distribute the drug quickly. The agency allowed significant deviations from its normal approval process, which could take a decade to complete.⁴⁵ (See **Exhibit 3**) It approved AZT in just two years and after two instead of the traditional three phases. And, even before formal approval, the agency allowed Burroughs Wellcome to make AZT available to many patients.*

In the spring of 1987, Burroughs Wellcome began selling AZT immediately after receiving FDA approval (and a year before securing a patent). It priced the drug at almost \$10,000 per patient per year without knowing “the demand, how to produce [the drug] in high quantities, or what competing drugs might come on the market.”⁴⁶

The price provoked outrage. AIDS activists protested on the floor of the New York Stock Exchange, inside Burroughs Wellcome’s North American headquarters, and in major U.S and UK cities. Activists also organized boycotts of Wellcome’s other products, such as the cold remedy Sudafed. The drug’s price provoked scrutiny from the US Congress, as well. As part of a spring 1987 investigation into federal funding of drugs, a House Committee questioned Burroughs Wellcome executives at length about their pricing process.

Burroughs Wellcome lowered AZT’s price by twenty percent in December of 1987 and again by twenty percent in September of 1989. The company also offered free AZT to low-income patients and children and collaborated with the oldest AIDS group in the UK, the Terrence Higgins Trust, on HIV/AIDS education and prevention.

Pressure for New Treatments. AZT could extend the lives of patients by one to two years, but then patients often developed resistance to the drug. The drug also induced nausea and vomiting, damaged muscle tissues, and caused anemia.

Activists, therefore, pressured regulators and drug companies to speed development and change the testing of new drugs. (See box “Activists’ Demands”). In 1987, Writer Larry Kramer helped found the AIDS Coalition to Unleash Power (ACT-UP). In October 1988, a well-publicized ACT-UP demonstration forced the FDA to close its offices temporarily. Other activists held a sit-in at San Francisco General Hospital and blocked the Golden Gate Bridge during rush hour in 1989.

* This new procedure, which required physicians to track the outcomes of the patients receiving the drug, would become known as a “Treatment IND.”

Activists' Demands

- Access to experimental drugs to any HIV-infected person as soon as the drugs were determined safe for human consumption (after Phase I safety trials and before Phase II efficacy trials).
- Studies that tested the performance of an experimental drug against another experimental drug or a different dosage of the same drug, rather than limiting controls to testing an experimental drug against a placebo or an existing standard of care, as FDA rules then required.
- Fewer restrictions on other drugs a trial participant could take (outside of the treatment being studied).
- More women, people of color, children, intravenous drug users, and hemophiliacs of all class levels and ages, in different stages of infection, in studies, either in the main clinical trial or in a parallel clinical trial.
- Medicaid and private health insurance reimbursements for experimental treatments.
- Including indirect or "proxy" indicators of patient health, such as T-cell levels or viral load, in evaluating the results of trials

The agitations prompted several changes. The NIH expanded its network of clinical trial sites, which made it easier for more AIDS patients to join trials and get access to experimental treatments. The FDA approved larger-than-usual trials and, under new "compassionate use" and "parallel track" programs, made treatments available to patients who were not enrolled in clinical trials and did not limit other drugs such patients could take.*

The FDA also offered "accelerated approvals" based on proxy (or "surrogate") indicators, such as improved T-cell counts, and allowed patients to import unapproved drugs for personal use. (Previously, patients who could afford to travelled to Europe, Mexico, or Japan for experimental treatments unavailable in the United States. Others formed "buyer's clubs" to import and distribute unapproved drugs.)

Harnessing New Genetic Science and Technologies. As mentioned, NCI researchers had provided Burroughs Wellcome with an indication of AZT's effect on the cultured HIV retroviruses in 1984. In 1985, they published research describing the structure of the AZT molecule and how it interfered with HIV's infection of healthy T cells. In 1987, researchers at the University of California, Los Angeles, and Harvard published a basic genetic map of the HIV retrovirus⁴⁷ and a more complete description of how HIV infected T cells. A better understanding of the retrovirus's genetic structure and infection process enabled more targeted drug development.

The new science and technologies and the demand for better treatments also accelerated the growth of new biotech companies. These companies often licensed promising compounds and other discoveries from university researchers. They would then use their expertise in emerging genetic technologies to try to turn the compounds and discoveries into clinically useful treatments. Often, the founders of these biotech companies were themselves the university researchers who had made the discoveries. For instance, in 1976, Professor Herbert Boyer of the University of California, San Francisco, co-founded Genentech (that bioengineered insulin). In 1981, three professors also from the University of California, San Francisco, started Chiron (whose first drug was a treatment for kidney cancer). And, in 1984, Harvard Medical School professor William Haseltine started Cambridge BioScience (initially to develop animal vaccines).

* "Compassionate use" use granted treatments to patients who were extremely ill, but who didn't qualify for clinical trials; "parallel track" allowed companies to study the everyday use of treatments by patients not enrolled in traditional clinical trials and collect and submit data on those patients when they sought FDA approval.

Venture capitalists, who had previously hesitated, increased their investments in biotech startups. Biotech companies that advanced their licensed technologies but had not yet generated ongoing cash flow could also raise money from public stock issues when market conditions were favorable. And the NIH, which often funded the discoveries licensed by the biotech companies could also then provide research grants to the companies for further development.

For instance, in 1987, Cambridge BioScience partnered with Agouron Pharmaceuticals (the commercial arm of a research foundation) to secure an NIH grant of \$ 4.3 million to develop HIV/AIDS tests and treatments. (The agreement gave Cambridge BioScience rights to any tests and vaccines financed by the grant, and Agouron to the drugs. As mentioned, Cambridge BioScience proceeded to introduce the first rapid test in 1990, and Agouron would introduce a successful AIDS drug in 1997.)⁴⁸

Biotech companies could not, however, rely just on venture capital, stock offerings, and NIH grants to complete development, secure FDA approval, and market new drugs. Therefore, biotech companies invariably turned to alliances with traditional pharmaceutical companies for support. These pharmaceutical companies infused capital, entered into co-development agreements, or purchased rights to compounds that were not fully developed, which they would then attempt to carry forward.

Despite their limited resources, biotech companies (like large pharmaceutical companies) often worked on several development projects. Thus, many biotech companies that were developing AIDS treatments also targeted other diseases. (For instance, see box “Gilead Sciences”)

Gilead Sciences.

Michael L. Riordan, a physician who had worked in venture capital, founded the biotech company Gilead Sciences in 1987 to apply new genetic technologies to develop drugs for viral, cancer, and cardiovascular diseases.

In 1990, Gilead partnered with longtime UK pharmaceutical maker Glaxo to research genetically targeted cancer therapies. In 1991, the company licensed an antiviral molecule from a Czech chemist, Antonin Holý, and a Belgian virologist, Erik de Clercq, who had been collaborating since the 1970s.⁴⁹

Glaxo’s 1990 partnership with Gilead had included a \$20 million equity investment. In January 1992, Gilead raised over \$86 million through a public stock issue. That year, the company announced a new technology to identify drug candidates—for a wide variety of diseases—by sorting through millions of DNA molecules. This type of genetic analysis could be performed much more quickly than the traditional process of trial-and-error testing required to identify promising synthesized compounds.

By the mid-1990s, Gilead was developing drugs to prevent blood clots and to treat herpes, genital warts, influenza, hepatitis B, a viral infection that blinded many AIDS patients, and HIV/AIDS.

New Drugs Developed. By 1992, at least a dozen companies (including four startups) had new AIDS drugs in development. (See Exhibit 4) Only three would secure FDA approval for clinical use, however. The NCI had synthesized two of the three drug molecules, and researchers at Yale University had synthesized the third. All three were licensed to and marketed by large pharmaceutical companies.⁵⁰ All three had molecular structures like AZT's, and, like AZT, all three interfered with HIV's infection of healthy T cells. All three also had, again, like AZT, serious side effects.⁵¹ Two of the drugs, Videx and Zerit, were therefore approved for use only after patients developed resistance to AZT. In the case of the third – Hivid – the FDA approved its use in combination with AZT to mitigate its toxicity.

Attempts to develop better drugs to disrupt the infection of healthy cells by HIV continued through the 1990s. Developers of “protease inhibitors” took a different approach. They tried to block enzymes the retrovirus used to replicate itself. The protease inhibitors would turn out to be less toxic but also less potent than drugs that directly blocked the infection of healthy cells. Their development – that built on the earlier discovery of an enzyme target -- is considered a major success of “rational drug design.”

Six of the new AIDS drugs received rapid FDA approval under the agency's accelerated approvals program. (See **Table 4**). Four of the six were protease inhibitors, including “Viracept,” co-developed by Agouron Pharmaceuticals. As mentioned, Agouron had secured an NIH grant in 1987. It then developed Viracept as part of a joint venture with Eli Lilly. After securing FDA approval in March 1997, Viracept achieved sales of more than \$330 million in its first year, making the protease inhibitor one of the most successful introductions of a biotech drug then recorded.

Table 4 FDA Approvals for AIDS Treatments, 1995-1997

Manufacturer (Location)	Drug (Category)	Approval Date	Time to Approval
Hoffmann-La Roche (CH)	Invirase (Protease Inhibitor)	1995	3.2 months
Glaxo (UK)	Epivir	1995	4.5 months
Merck (US)	Crixivan (Protease Inhibitor)	1996	1.4 months
Abbott Labs (US)	Norvir (Protease Inhibitor)	1996	2.3 months
Boehringer Ingelheim (GER)	Viramune	1996	4 months
Agouron Pharmaceuticals (CA)	Viracept (Protease Inhibitor)	1997	2.6 months

Sources: Samuel Broder, “The Development of Antiretroviral Therapy and Its Impact on the HIV-1/AIDS Pandemic,” *Antiviral Research*, Twenty-five Years of Antiretroviral Drug Development: Progress and Prospects, 85, no. 1 (January 2010).

Large pharmaceutical companies and smaller biotech companies (who often partnered with large companies) also attempted to treat “secondary” infections: diseases that the weakened immune systems of AIDS patients could not naturally resist. Gilead, for instance, developed a drug to treat viral infections that blinded many AIDS patients. Storz Instrument Company, a subsidiary of the conglomerate American Cyanamid that had long made ophthalmic devices and drugs, produced and marketed this drug after Gilead secured FDA approval in 1996.⁵² (That year Gilead also licensed a molecule to attack influenza viruses to Hoffman-La Roche. After further development, Roche introduced the drug as Tamiflu in 1999).

Combination Therapies. In the early 1990s, researchers began investigating combinations of HIV/AIDS drugs; such combinations had previously been shown to be more effective than individual drugs in treating cancer and tuberculosis. In 1993, the NIH made combinations a “top priority,” and by 1995, over twenty combination trials had been launched in North America and Europe.⁵³

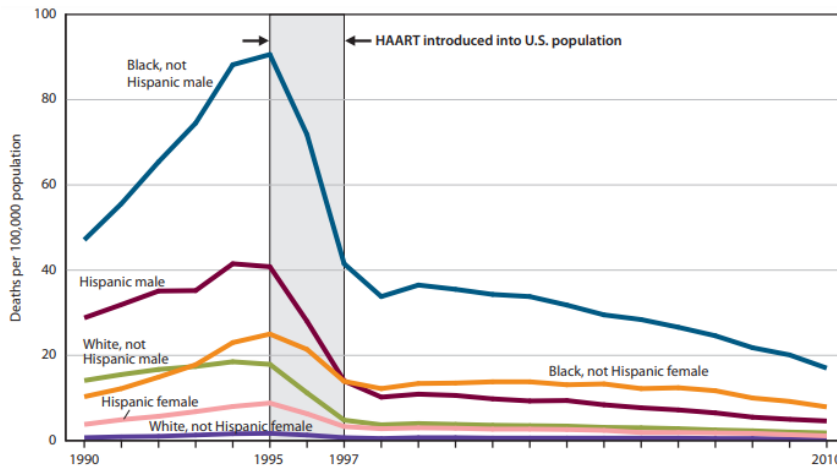
Research on two combinations presented at the 1996 International AIDS Conference in Vancouver showed they worked far better than individual drugs.⁵⁴ Conference attendees then endorsed combination treatments called “HAART” for “Highly Active Antiretroviral Therapy.” HAART combinations typically included AZT and another AZT-like drug that, as mentioned, interfered with HIV’s infection of healthy cells and a protease inhibitor that prevented replication of the HIV retrovirus. Since the FDA had already approved the individual drugs included in HAART, physicians switched tens of thousands of AIDS patients to combination therapies within weeks of the Vancouver conference.⁵⁵

In just a few years, combinations (HAART) produced a stunning reduction in death rates in the United States and in Europe.⁵⁶ (See **Figures 7 and 8**)

Many patients struggled to follow multi-pill HAART regimens, however. Glaxo Wellcome (formed through a merger between Glaxo and Wellcome in 1995) therefore created a single pill, “Combivir.” The pill contained standard doses of two of its AIDS drugs: AZT and another AZT-like drug that, as mentioned, interfered with HIV’s infection of healthy cells.

The FDA approved Combivir in October 1997. This was the first time the agency had approved drugs combined in a single pill based on improved patient compliance. FDA rules had previously required showing that combinations were therapeutically more effective than their separately taken components. Combivir obtained European regulators’ approval the following year.

Figure 7 Death Rates for HIV/AIDS for All Ages in the United States, 1990-2010



NOTES: HAART is highly active antiretroviral therapy. See data table for Figure 24 for rates for additional racial groups.

SOURCE: CDC/NCHS, National Vital Statistics System. See Appendix I, National Vital Statistics System (NVSS).

Source: Department of Health and Human Services, “Health, United States, 2013,” page 25, May 2014. Accessed June 27, 2016. <http://www.cdc.gov/nchs/data/hus/hus13.pdf>.

Revenues and Market Shares. Combinations and better drugs rapidly increased AIDS drug sales in the United States (See Exhibit 5).

Market shares (See **Figure 8**) also changed: in 1992, three companies, led by Burroughs Wellcome had accounted for nearly the entire US market. By 1999, Wellcome's share ("inherited" by Glaxo Wellcome) had fallen by more than half, despite the popularity of Combivir. Warner-Lambert had secured second place through its acquisition of Agouron and its top-selling protease inhibitor. New drugs had also increased the market shares of five other large pharmaceutical companies. One of the companies, Abbott, had introduced three new drugs, but the other four large companies offered only one new drug each.⁵⁷

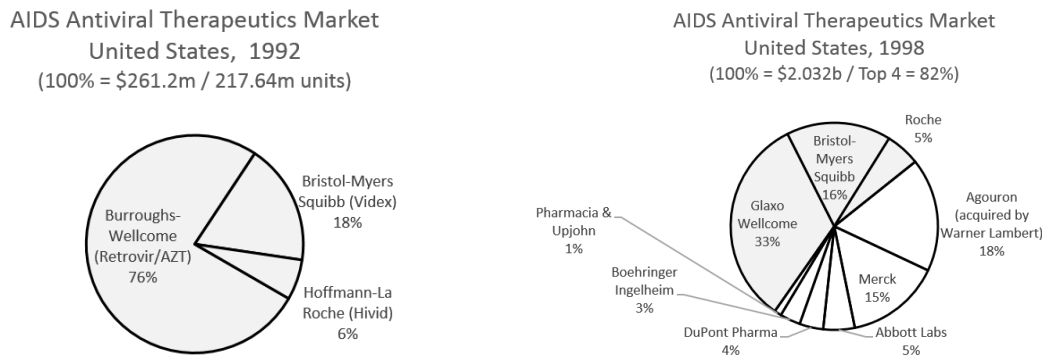
Questions (for reflection and discussion):

Please write down (in less than ten words) which decision, event, or condition you found the most significant in developing AIDS treatments.

- _____

Be prepared to explain why you found this significant.

Figure 8 AIDS Antiviral Therapeutics Market, United States, 1992 and 1998



Source: Frost & Sullivan, (1994 and August 1999)

The Situation in 2000.

Combivir which replaced a complicated eight-pills-per-day regimen with a two-pills-per-day regimen, was the top selling AIDS drug, with revenues of \$453 million. But although considered the "gold standard" in AIDS treatment,⁵⁸ it was not a silver bullet. It did not contain a protease inhibitor, which patients then had to take separately. And it included AZT, which had significant side effects. Many patients also developed resistance to the drugs contained in Combivir. A physician would then have to prescribe other drugs that were not combined into a single pill.

Efforts to develop better individual drugs and combinations continued. Glaxo Wellcome (makers of Combivir) itself developed "Ziagen" as a safer alternative to AZT for use in cases where patients had

developed resistance to AZT or Combivir.⁵⁹ The FDA approved Ziagen in 1998, making it the fifteenth antiretroviral drug approved. The WHO would later include it and Combivir in its “List of Essential Medicines” – the safest and most effective ones needed in a health system.

As before, many promising compounds had failed. For instance, preliminary trials for one of Gilead Sciences’ HIV/AIDS molecules showed efficacy in patients who had developed resistance to other drugs. However, Gilead stopped development in 1999⁶⁰ after large-scale trials revealed risks, such as kidney damage, that the FDA found unacceptable.⁶¹ Efforts to develop vaccines, which had generated great excitement, had also failed to produce effective treatments. The first small-scale trials started in 1987, and large-scale trials did not begin until over ten years later, in 1998, and would not end till 2003.⁶²

Question (for reflection and discussion):

As the CEO of a biotech company developing treatments for AIDS and other diseases, write down (in less than ten words) what is the top change or investment you would want to make in 2000-01.

- _____

Exhibit 1 Founding year and services offered by selected AIDS Organizations

Year	Organization (Location)	Services Provided
1981	Gay Men’s Health Crisis (US)	Information, advice, support, health education resources, prevention, free testing, counseling, advocacy, helpline, legal and financial services, mental health services, meals, job training.
1982	San Francisco AIDS Foundations (US)	Education, testing and counseling (on-site and via a mobile van), housing and financial assistance, needle exchange, referrals to medical and social services.
	Terrence Higgins Trust (UK)	Education, legal services, health services, support.
	AIDS Project Los Angeles (US)	Education, prevention, testing, counseling, referrals, medical and dental care, housing and financial assistance, food bank, support for adherence to antiretroviral therapy regimens. Model for many state-level AIDS Projects in US.
1983	AIDS Resource Centers (US)	State-level programs offering prevention, education, clinical trials, treatment, advocacy, medical and dental clinics.
	AIDS Action Committee of Massachusetts (US)	Education, prevention, testing, counseling, referrals, medical and dental care, housing and financial assistance, needle exchange program, client advocacy, employment training.
	FACES NY (formerly the Minority Task Force on AIDS, US)	Education, testing, counseling, case management, housing and legal assistance, substance abuse counseling, food pantry.
1985	Project Inform (US)	Helpline, education, referrals to health care providers.
	amfAR (The American Foundation for AIDS Research, US)	Research, advocacy.
	NMAC (formerly the National AIDS Minority Council, US)	HIV/AIDS services for communities of color; education, research, training, resources, advocacy.
	AIDS HealthCare Foundation (US)	Free or low-cost healthcare services to HIV/AIDS patients, including testing, counseling, and treatments.
1987	Test Positive Aware Network (US)	Information, education, referrals, support, testing, counseling, needle exchange program, medical clinic, annual guides to available treatments.
	NAM (formerly the National AIDS Manual, UK)	Education and information about testing and treatment.
	Positively Women (UK)	Information, support, health services, and advocacy for children and families with AIDS.
	National AIDS Trust (UK)	Research, advocacy.

Year	Organization (Location)	Services Provided
1988	Elizabeth Glaser Pediatric AIDS Foundation (US)	Research, advocacy, and health programs for children with AIDS.
1989	ACCESS AIDS Care (US)	Health services, including testing and treatment.
	Sister Love Inc. (US)	Prevention, education, support, and advocacy.
1990	AIDS Service Center of NYC (US)	Testing, counseling, outreach, education, training, case management, support for adherence to antiretroviral therapy regimens, collaboration with local hospitals, food and clothing.
	Philadelphia FIGHT (US)	Research, information, education, prevention, primary care
1991	ACRIA (US)	Research and clinical trials, healthcare, treatment, training, and education.
1992	European AIDS Treatment Group (EU)	Improving access to treatment and drug development; offering information, and training.
	Elton John AIDS Foundation (UK and US)	Research, advocacy.
1994	HIV Alliance (US)	Medical and dental care, referrals, free testing and counseling, needle exchange.
1995	National AIDS Treatment Advocacy Project (US)	Information, education, advocacy.
1996	AID for AIDS (INTL)	Education, training, and access to antiretroviral therapies.

Exhibit 2 Organizations and Their Roles in AIDS Drug Development

Organization(s)	Role
The National Institutes of Health (NIH)	Funded basic research on HIV's genetic makeup and life cycle to aid rational development of drugs. Funded R&D of treatments and sponsored clinical trials.
The National Cancer Institute (NCI)	Part of the NIH. Collaborated with companies to test and synthesize potential treatments. Helped to coordinate and run clinical trials. Heavily involved in the research and development of the first three treatments for AIDS.
The Centers for Disease Control and Prevention (CDC)	Set case definition for AIDS. Helped write guidelines for and coordinate distribution of treatments.
The Public Health Service (PHS)	Helped write guidelines for and coordinate the distribution of treatments.
The Food and Drug Administration (FDA)	Reviewed and approved treatments. Established standards of safety and efficacy. Regulated distribution and use of treatments.
Corporations (including startups and large multinationals)	Researched, developed, manufactured, marketed, sold, and distributed treatments. Ran clinical trials independently and in collaboration with the NCI and NIAID.
Activist Groups	A diverse array that included over 600 organizations and advocacy groups, as well as ACT-UP (The AIDS Coalition to Unleash Power) and the Terrence Higgins Trust (in the UK).

Exhibit 3 Phases of Clinical Trials

Typically, drug developers who have found a compound that has potential for treating a disease test it against a “model” of the disease in test tubes (“in vitro”) and in animals such as rats and mice (“in vivo”). After further tests—for instance, to assess potential toxicity and safety in humans, among other things—and determining a potentially suitable dosage and form (tablet, capsule, liquid, etc.), an investigational new drug (IND) application is filed with the FDA, which includes everything that is known about the compound.

If the FDA does not object in thirty days, the IND is approved and human clinical trials begin.

Phase 1 of the trials tests whether the drug is safe and can be tolerated by humans, and Phase 2 tests whether the drug works and in what dosage. Both Phase 1 and Phase 2 are small-scale trials, usually with less than a couple of hundred patients.

Drugs that pass Phase 1 and Phase 2 trials then enter much larger-scale and more comprehensive Phase 3 trials. These can involve several thousand patients and are intended to generate data about the drug’s effectiveness for specific indications, to test for a broad number of potential side-effects, and to identify the best ways to administer and use the drug.

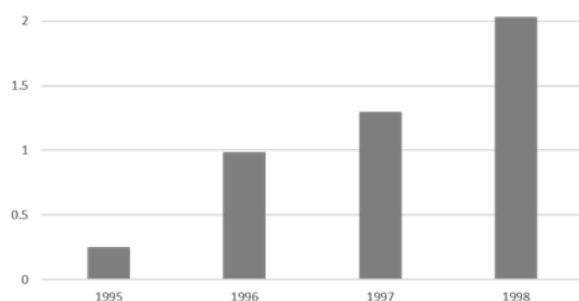
The process involves considerable risk. According to a report of the Congressional Office of Technology Assessment, only five out of 5,000 compounds that go into preclinical testing make it to a Phase 1 human trial, and only about one of those five is ultimately approved by the FDA.

Exhibit 4 Companies developing treatments by 1992.

Company (Location)	Founded	Related Products/Research
SmithKline Beecham (US)	1843	Pharmaceuticals
Schering-Plough Corporation (US)	1851	Pharmaceuticals
Boehringer Ingelheim (GER)	1885	Pharmaceuticals, HIV vaccines
The Upjohn Company (US)	1886	Pharmaceuticals
Bristol-Myers Squibb (US)	1887	Pharmaceuticals, HIV tests, HIV vaccines
Abbott Labs (US)	1888	Pharmaceuticals, diagnostics, HIV tests, experimental drugs to prevent HIV transmission
G.D. Searle (US)	1888	Pharmaceuticals
Hoffmann-La Roche (Roche, CH)	1896	Pharmaceuticals, HIV genetic tests
Merck (US)	1891	Pharmaceuticals, HIV vaccines
Glaxo (UK)	1906	Pharmaceuticals, HIV vaccines
Rhone-Poulenc Rorer (FR) and The Immune Response Corporation (US)	1928/1986	Biotech, Pharmaceuticals, HIV vaccines
Interferon Sciences (US)	1980	Biotech, Pharmaceuticals
Genelabs (US)	1983	Biotech, Pharmaceuticals
Agouron Pharmaceuticals (US)	1984	Biotech, Pharmaceuticals, HIV tests, HIV vaccines

Source: "AIDS Diagnostic, Monitoring, and Therapeutics Markets," Industry Research Report, 1994, Frost & Sullivan, accessed April 2016.

Exhibit 5 HIV/AIDS Therapeutics Revenues, United States, 1995-1998 (\$ billions)



Source: Frost & Sullivan (1999)

Note: Most of the revenues in this chart come from the sales of drugs recommended for use in combination therapies in 1996.

Endnotes

¹ “New Report: Precision Oncology in an Era of Healthcare Reform,” *Economics21*, April 27, 2016, <http://www.economics21.org/html/new-report-precision-oncology-era-healthcare-reform-1781.html>.

² Victoria Angela Harden, *AIDS at 30: A History*, 1st ed. (Washington, DC: Potomac Books, 2012), 20.

³ Harden, *AIDS at 30*.

⁴ Cases had included hemophiliacs and an infant who had contracted the disease after a transfusion from a known donor who also developed AIDS.

⁵ Ibid. 37-38, 83-94; Elizabeth W. Etheridge, *Sentinel for Health: A History of the Centers for Disease Control* (Berkeley: University of California Press, 1992), 331.

⁶ Regulators lifted the ban on Haitians in 1990 and largely allowed for donations from gay and bisexual men after 2015.

⁷ Nonetheless, many individuals refused to work with or care for those suspected of having AIDS.

⁸ However, the data suggests no striking increases in demand for screening tests at these sites occurred. See statistics presented later in our case, as well as research conducted by Tai and Merchant, cited below. Bernard M. Branson et al., “Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings,” *MMWR. Recommendations and Reports: Morbidity and Mortality Weekly Report. Recommendations and reports/Centers for Disease Control* 55, no. RR-14 (2006): 1-17; Frank S. Rhame and Dennis G. Maki, “The Case for Wider Use of Testing for HIV Infection,” *New England Journal of Medicine* 320, no. 19 (May 11, 1989): 1248-54, <https://doi.org/10.1056/NEJM198905113201905>; Miao Tai and Roland C. Merchant, “HIV Testing in US Emergency Departments, Outpatient Ambulatory Medical Departments, and Physician Offices, 1992-2010,” *AIDS Care* 26, no. 9 (September 2, 2014): 1105-8, doi:10.1080/09540121.2013.871220.

⁹ Some of the arguments for and against broader testing are summarized in a 1989 editorial: Rhame and Maki, “The Case for Wider Use of Testing for HIV Infection.” Studies in Europe suggest that the prospect of increased testing has been successful in reducing risky behaviors there. See, for example: T Coenen et al., “Optimal HIV Testing and Earlier Care: The Way Forward in Europe,” *HIV Medicine* 9 (July 1, 2008): 1-5, doi:10.1111/j.1468-1293.2008.00583.x; Jessika Deblonde et al., “HIV Testing in Europe: Mapping Policies,” *Health Policy* 103, no. 2 (2011): 101-110, doi:10.1016/j.healthpol.2011.06.012; Jessika Deblonde et al., “Barriers to HIV Testing in Europe: A Systematic Review,” *European Journal of Public Health* 20, no. 4 (2010): 422-432, doi:10.1093/eurpub/ckp231; Jessika Deblonde, “HIV Testing in Europe: From Policies to Practices” 23, no. 2 (2009): 69-69.

¹⁰ Ron Brookmeyer, “Reconstruction and Future Trends of the AIDS Epidemic in the United States,” *Science* 253, no. 5015 (1991): 37-42; “HIV Surveillance --- United States, 1981-2008,” accessed June 23, 2016, <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6021a2.htm>.

¹¹ Jessika Deblonde, “HIV Testing in Europe: From Policies to Practices” 23, no. 2 (2009): 69-69; Jessika Deblonde et al., “HIV Testing in Europe: Mapping Policies,” *Health Policy* 103, no. 2 (2011): 101-110, <https://doi.org/10.1016/j.healthpol.2011.06.012>; Jessika Deblonde et al., “Barriers to HIV Testing in Europe: A Systematic Review,” *European Journal of Public Health* 20, no. 4 (2010): 422-432, <https://doi.org/10.1093/eurpub/ckp231>.

¹² Rhame and Maki, “The Case for Wider Use of Testing for HIV Infection.”

¹³ “Publications - Hiv-Aids-Surveillance-in-Europe-2014.pdf,” accessed August 11, 2016, http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113d3bb90&ID=1408. While the overall rate of infection in Europe declined, the number of AIDS cases due to blood treatment subsequently rose in France. HIV-infected hemophiliacs and others infected via transfusion there responded with protests and lawsuits seeking damages due to the circulation of tainted blood. Criminal charges of fraud were brought against four French public health officials, three of whom were convicted in 1992. Investigations continued there throughout the 1990s. The French convictions

were overturned in the 2000s. Policy makers faced criminal prosecution in Japan, as well. Government officials and corporate leaders there issued public apologies to victims in 1996. See Harden, *AIDS at 30*.

¹⁴ Harden, *AIDS at 30*; Thomas S. Alexander, "Human Immunodeficiency Virus Diagnostic Testing: 30 Years of Evolution," *Clinical and Vaccine Immunology* 23, no. 4 (April 1, 2016): 249-53, doi:10.1128/CVI.00053-16; "HIV Basics - Testing," accessed June 21, 2016, <http://www.aidsmap.com/hiv-basics/Testing/page/1412439>.

¹⁵ Harden, *AIDS at 30*, 39-53. Harden also discusses the contributions made by Jay Levy's lab at UCSF and others.

¹⁶ Harden, *AIDS at 30*; "The Nobel Prize in Physiology or Medicine 2008"; F. Barre-Sinoussi et al., "Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)," *Science* 220, no. 4599 (May 20, 1983): 868-71, <https://doi.org/10.1126/science.6189183>; Gallo, *Virus Hunting*; Gallo and Montagnier, "The Discovery of HIV as the Cause of AIDS"; Montagnier, "A History of HIV Discovery. (Viewpoint.)"

¹⁷ Harden, *AIDS at 30*; "The Nobel Prize in Physiology or Medicine 2008"; Barre-Sinoussi et al., "Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)"; Gallo, *Virus Hunting*; Gallo and Montagnier, "The Discovery of HIV as the Cause of AIDS"; Montagnier, "A History of HIV Discovery. (Viewpoint.)" One notable study performed later that year in New York and Boston detected the retroviral infection in all of the AIDS patients tested, but in none of the patients in the control group.

¹⁸ The Pasteur team, which had first isolated the retrovirus, was also first to propose a test for detecting two of the antibodies to it. NCI researchers (who were second) proposed tests for different antibodies and a wider range of techniques for detecting infection with a viral extract.

¹⁹ The final agreement stipulated that 80% of royalties be donated to a new AIDS research foundation, and the balance shared between the two parties. There are many popular and scholarly accounts of this dispute. We have relied on the following: Ibid.; Steve Connor, *The Search for the Virus* (London: Penguin, 1989).

²⁰ They gave the virus its official name, HIV, in 1986.

²¹ Harden, *AIDS at 30*, 67-70.

²² Barbara J. Culliton, "Crash Development of AIDS Test Nears Goal," *Science*, New Series, 225, no. 4667 (September 14, 1984): 1129.

²³ HIV-2 was more widespread in Africa.

²⁴ The implications of false positives were a major problem when diagnosing individuals, but less so in screening blood and blood products.

²⁵ Alexander, "Human Immunodeficiency Virus Diagnostic Testing," 249.

²⁶ Alexander, "Human Immunodeficiency Virus Diagnostic Testing," 249-250.

²⁷ Alexander, "Human Immunodeficiency Virus Diagnostic Testing," 250.

²⁸ Western blot shows a range of proteins in sample as lines on a membrane. IFA stains target cells with a dye that can show up under a fluorescent microscope.

²⁹ Alexander, "Human Immunodeficiency Virus Diagnostic Testing," 249-250; "HIV Basics - Testing."

³⁰ Cambridge BioScience's test cost approximately ten times more than the average HIV screening test of the time. Faster and more expensive confirmatory tests (Western blots) were introduced around the same time, as well. The first, from Bio-Rad Laboratories, reduced the time needed for confirmation from 24 to three hours.

³¹ U.S. regulators approved first fully self-administered saliva test for home use in 2012, and lawmakers in the UK made all self-administered at-home tests legal in 2014.

³² Concern about the accuracy of the first Abbott test arose in 1986, however, the American Red Cross chose not to change suppliers. Abbott introduced a more accurate test in January 1987, which the Red Cross adopted immediately.

³³ Between 1986 and 1990, Genetic Systems was owned by Bristol-Myers Squibb.

³⁴ Despite succeeding with a confirmatory test introduced in 1987, DuPont/Biotech dissolved their partnership in 1990 and sold rights to screening and confirmatory tests to Chiron and a division of Johnson & Johnson. Biotech then merged with Cambridge BioScience Corporation, forming Cambridge Biotech.

³⁵ “AIDS Diagnostic, Monitoring, and Therapeutics Markets,” Industry Research Report, 1994, Frost & Sullivan, accessed April 2016.

³⁶ The other two original developers had departed: Electro-Nucleonics was acquired by the Sweden’s Pharmacia Diagnostics in 1988, and Travenol Genentech dissolved their partnership in 1986 after substantial losses.

³⁷ CDC guidelines also encouraged mechanized testing systems as a way to increase the safety of labs by decreasing opportunities for transmission. Advances in robotics and computing were harnessed to expand and improve laboratory automation in late 1980s. However, high costs restricted use to blood banks and similar organizations with large-scale screening programs. Few laboratories bought automated systems until costs declined and system standards developed after 1997.

³⁸ The test was based on techniques and materials invented in the 1980s at the biotech company Cetus Corporation and developed after 1990 by Roche and Chiron Corporation (another biotech company).

³⁹ Direct identification of viral material was also used to identify HIV positive individuals in fourth and fifth generation “screening” tests. These tests reduced the period from infection to detection to less than two weeks, compared to three weeks for the earlier third generation tests that detected antibodies, and became the standard in Europe after 1997. However, in the US, the FDA did not approve the first such test (developed by Abbot) until 2010. And, adoption was slow due to required changes in Confirmatory Protocols, which were finalized in 2014 to include genetic testing. Alexander, “Human Immunodeficiency Virus Diagnostic Testing.”

⁴⁰ For example, in the early 1990s, Roche licensed their viral load test to labs, and then went on to obtain FDA approval in 1996. “AIDS Diagnostic, Monitoring, and Therapeutics Markets,” Industry Research Report, 1994, Frost & Sullivan, accessed April 2016.

⁴¹ Only two groups, Genzyme and Amoco Biotechnology’s GENE-TRAK and Zynaxis, had invested in viral load test R&D by 1992, and Genzyme and Amoco had already decided to terminate their partnership.

⁴² At the time, the rules varied by country. In 1995, the European Union established the European Medicines Agency to regulate devices and medicines within all member states.

⁴³ U.S. regulators approved first fully self-administered saliva test for home use in 2012, and lawmakers in the UK made all self-administered at-home tests legal in 2014.

⁴⁴ Samuel Broder, “The Development of Antiretroviral Therapy and Its Impact on the HIV-1/AIDS Pandemic,” *Antiviral Research*, Twenty-five Years of Antiretroviral Drug Development: Progress and Prospects, 85, no. 1 (January 2010): 1–18, <https://doi.org/10.1016/j.antiviral.2009.10.002>.

⁴⁵ Harden gives an excellent overview of clinical trials in *AIDS at 30*, 134; We have also consulted A Akobeng, “Understanding Randomised Controlled Trials,” *Archives of Disease in Childhood* 90, no. 8 (August 2005): 840–44, doi:10.1136/adc.2004.058222; and “Phases of Clinical Trials,” *Cancer Research UK*, October 21, 2014, <http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/what-clinical-trials-are/phases-of-clinical-trials>.

⁴⁶ “The Inside Story of the AIDS Drug: For the First Time Burroughs Wellcome Tells How It Made Crucial Decisions on AZT That Brought Howls from Congress and Gay Groups. Some of Its Wounds Were Self-Inflicted. - November 5, 1990,” accessed May 6, 2016, http://archive.fortune.com/magazines/fortune/fortune_archive/1990/11/05/74308/index.htm.

⁴⁷ As with other retroviruses, HIV encodes its genetic information in ribonucleic acid (RNA) molecules whereas normal cells encode their genetic information in the deoxyribonucleic acid (DNA) molecules.

⁴⁸ According to the Los Angeles Times, “Agouron Pharmaceuticals Inc. of La Jolla, in collaboration with Cambridge BioScience Corp., has received a \$4.3-million grant from the National Institutes of Health to develop therapeutic drugs, vaccines and diagnostics against the AIDS virus. William Haseltine of the Dana-Farber Cancer Institute at Harvard University will also participate in the research program. Under terms of the agreement, Agouron will have the right to commercialize therapeutic drugs developed through the collaboration, and Cambridge BioScience will have rights to the vaccines and diagnostics.” “Agouron Pharmaceuticals Gets AIDS Research Grant,” Los Angeles Times, September 10, 1987, <https://www.latimes.com/archives/la-xpm-1987-09-10-fi-6897-story.html>.

⁴⁹ Holý had patented the molecule in 1984, but not for treating HIV. Subsequently, Holý and de Clercq had filed a patent to use this molecule to treat HIV. In 1992 they licensed this molecule and some other molecules they had patented to Gilead. Holý and de Clercq would continue licensing more molecules to Gilead through the 1990s.

⁵⁰ Videx, approved by the FDA in 1991, and Zerit, approved in 1994, were licensed to American pharmaceutical company Bristol-Myers Squibb. Hivid, approved in 1992 was licensed to Hoffmann-La Roche.

⁵¹ ACT-UP and other organizations also pressured the government and companies to develop other kinds of AIDS treatments that would be different than AZT, however, a few companies had already put such drug programs into place before ACT-UP was formed.

⁵² Other biotech companies, which included Isis Pharmaceuticals, Chiron Biocine, Synthecell, Selectide, Darwin Molecular Technologies, Ribozyme Pharmaceuticals, and NeXagen, that were developing treatments for secondary infections also formed partnerships with large pharmaceutical companies.

⁵³ Martin Delaney, “History of HAART – the True Story of How Effective Multi-Drug Therapy Was Developed for Treatment of HIV Disease,” *Retrovirology* 3, no. Suppl 1 (2006), doi:10.1186/1742-4690-3-S1-S6; 503.

⁵⁴ Researchers David Ho and George Shaw also presented at the 1996 International AIDS Conference in Vancouver; their research demonstrated that HIV reproduced at such high rates within the body that no single drug would successfully bring it under control.

⁵⁵ Harden, *AIDS at 30*; Jonathan Engel, *The Epidemic: (A Global History of AIDS)* (New York: Smithsonian Books/Collins, 2006); Patrick McGee, “A Quarter Century of Battling HIV/AIDS,” *Drug Discovery & Development* 9, no. 7 (July 2006): 10-12,14-16,18; Alan S. Perelson et al., “HIV-1 Dynamics in Vivo: Virion Clearance Rate, Infected Cell Life-Span, and Viral Generation Time,” *Science* 271, no. 5255 (March 15, 1996): 1582; Angela Pirisi, “Julio Montaner: King of HAART,” *Lancet* 368, no. 9550 (2006): 1863; J. S. Montaner et al., “A Randomized, Double-Blind Trial Comparing Combinations of Nevirapine, Didanosine, and Zidovudine for HIV-Infected Patients: The INCAS Trial. Italy, The Netherlands, Canada and Australia Study,” *JAMA* 279, no. 12 (March 25, 1998): 930-37; Julio SG Montaner, Robert S. Hogg, and Michael V. O’Shaughnessy, “Emerging International Consensus for Use of Antiretroviral Therapy,” *The Lancet* 349, no. 9058 (1997): 1042-1042, [https://doi.org/10.1016/S0140-6736\(05\)62289-1](https://doi.org/10.1016/S0140-6736(05)62289-1); Julio S. G. Montaner and Michael O’Shaughnessy, “Cautious Optimism over New Anti-HIV Agents.(Conference),” *The Lancet* 345, no. 8946 (1995); Julio S. G. Montaner and Martin T. Schechter, “A Year of Transformation in HIV/AIDS.(Supplement to the Lancet: Reviews 1995),” *The Lancet* 346, no. 8991 2 (1995).

⁵⁶ For the data, discussion, and table used here, see: “Health, United States, 2013,” page 25. “hus13.pdf.” Accessed June 27, 2016. <http://www.cdc.gov/nchs/data/hus/hus13.pdf>. See also: Harden, *AIDS at 30*, 149-152; Engel, *The Epidemic*, Chapter 11.

⁵⁷ “United States HIV/AIDS Therapeutics Markets,” Industry Research Report, 5 August 1999, Frost & Sullivan, accessed April 2016.

⁵⁸ Simon D Portsmouth and Christopher J Scott, “The Renaissance of Fixed Dose Combinations: Combivir,” *Therapeutics and Clinical Risk Management* 3, no. 4 (August 2007): 579-83. The National Institute for Health Care Management Research and Educational Foundation. “Prescription Drug Expenditures in 2000: The Upward Trend Continues.” May 2001, page 12.

⁵⁹ Portsmouth and Scott; “FDA Approves First Combination Drug for AIDS News,” AIDSinfo, accessed May 7, 2020, <https://aidsinfo.nih.gov/news/388/fda-approves-first-combination-drug-for-aids>; “FDA Approves Abacavir for HIV-1 Infection News,” AIDSinfo, accessed May 7, 2020, <https://aidsinfo.nih.gov/news/463/fda-approves-abacavir-for-hiv-1-infection>.

⁶⁰ Gilead later repurposed this drug into a successful treatment for hepatitis B.

⁶¹ Wall Street Journal Europe. “Technology Journal: FDA Ruling Is Blow For Gilead Sciences.” 3 November 1999.

⁶² “History of HIV Vaccine Research | NIH: National Institute of Allergy and Infectious Diseases,” accessed May 11, 2020, <http://www.niaid.nih.gov/diseases-conditions/hiv-vaccine-research-history>; “Infographic: Progress Toward an HIV Vaccine | NIH: National Institute of Allergy and Infectious Diseases,” accessed May 12, 2020, <http://www.niaid.nih.gov/diseases-conditions/infographic-hiv-vaccine>.