# What went right: Why is HIV a treatable infection?

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The discovery of an effective treatment for a fatal disease is a major event in human history. In the mid-third of this century treatment discovery occurred with gratifying frequency[1]: hypertension, epilepsy, meningitis, tuberculosis, Hodgkin's disease, hyperthyroidism and a host of other diseases all became treatable, and some even curable. However subsequently, treatment discovery has slowed markedly, and the diseases that killed people in 1965 — such as congestive heart failure, emphysema, most solid cancers, lupus, alcoholism and drug addiction — continue to do so today. Why should AIDS be an exception to this lugubrious rule?

In the past two years, HIV-1-infected patients have been treated with combinations of drugs which inhibit enzymes present in HIV but not in the virus' human host. Most have thereupon become able to forestall or even overcome opportunistic infections, and have exhibited decreased quantities of viral RNA (viral load) and increased numbers of CD4 lymphocytes, another circulating surrogate marker, for at least as long as their treatment continues. Although this treatment is not a cure and its application is unfairly constrained by economic and educational factors, HIV deaths in America actually declined in 1996 (ref. 2) for the first time since AIDS' was recognized as a disease entity in 1981, and this decline is widely attributed to the new treatment. The near-universal pessimism expressed after the 1993 Berlin Meeting about whether AIDS would ever become treatable has been shown to be unfounded, and in retrospect it can be seen that a surprisingly short time, 15 years, elapsed between the recognition of AIDS as a clinical entity and the discovery of a treatment for it.

Our failure to discover similarly effective treatments for most of the diseases that were still fatal thirty years ago has occurred in spite of fourfold real-dollar increases in public and private expenditures for biomedical research, and a vast expansion of our fundamental understanding of biological systems. Although the same period has witnessed a parallel advance in life expectancy, this is attributable to improvements in prevention, diagnosis and surgical management and not to new therapeutic agents[1]. Why has our society apparently been successful in finding a treatment for HIV infection but not, in the last three decades, for most other fatal medical diseases? What went right? Would applying the answer to this question accelerate the discovery of treatments for other diseases?

We previously suggested [1] that the slowdown in treatment discovery resulted in part from a faulty formulation about how the public sector should best organize biomedical research and training in order to maximize its contribution to this process (that is, a primary focus on curiosity-driven, basic-science projects conceptualized by individual scientists, - the formula proposed by Vannevar Bush in his 1945 report: *Science, The Endless Frontier*, - at the expense of programmed 'national missions'). A case study analysis of the origins of present HIV therapy confirms, I believe, the importance of a mission orientation for treatment discovery, and a focus on clinical research and other integrative medical science disciplines. It also demonstrates the importance of realistic regulatory policies in encouraging private pharmaceutical companies to commit resources to the risky business of developing genuinely novel drugs.

### The Origins of 'Triple Therapy'

We now have eleven approved drugs to treat HIV-1 infection (Table 1), each of which inhibits the virus' reverse transcriptase (RT) or protease. HIV infection is apparently treatable because of the availability of these drugs and because we administer them in combinations of two or, preferably, three. Thus any explanation of how AIDS came to be treatable must describe how these drugs came into existence, how physicians learned to administer them in combinations and what needed to be known or done before the drugs could be discovered and combined.

The first anti-HIV drugs were nucleoside analogs (like AZT) whose phosphorylated metabolites compete with natural substrates for incorporation into DNA, thereby terminating DNA synthesis. AZT was initially developed as a treatment for cancer, but was found to have too little efficacy to justify its toxicity. Subsequently AZT, and then the dideoxy compounds (e.g.,ddI; ddC) and 3TC, were shown to impede the replication of retroviruses in cell lines and to inhibit the activity of RT. The RT enzyme was found in HIV soon after the Montagnier and Gallo laboratories identified this retrovirus as the cause of AIDS in 1983-1984 (ref.3,4). A decade later, non-nucleoside RT inhibitors like nevirapine, which bind directly to an allosteric site on the enzyme protein, became available. The first-generation protease inhibitors saquinavir, ritonavir and indinavir were developed and approved for use only recently (Table 1), even though in 1985 HIV was shown by Japanese scientists to contain an aspartyl protease (required for its infectivity[5,6]) and the pharmaceutical industry had previously accumulated abundant experience in searching for inhibitors of aspartyl proteases like renin.

The decision to combine agents for treating HIV had its origins in at least two intellectual traditions: First, Martin Hirsch, Jerome Groopman, Paul Volberding and other practitioners accustomed to treating infectious or neoplastic disease perceived that therapies designed to wipe out populations of rapidly- mutating, 'foreign' cells (like cancer cells or the tubercle bacillus) were far more likely to remain effective if drugs which were metabolized differently and acted at different biochemical loci were administered simultaneously rather than individually and sequentially. Secondly, David Ho, George Shaw and their colleagues obtained direct evidence from kinetic analyses of circulating HIV particles and CD4 cell counts and using knowledge of HIV's *in vivo* mutation rate[7], that only by administering such drugs in combination was it theoretically possible to eradicate the virus from the blood. (Their evidence also reinforced Anthony Fauci's 1993 suggestion that since HIV is not latent prior to the onset of clinical symptoms but is active within lymph glands, therapy should be started early in the course of infection.)

The first studies involving drug combinations - initiated prior to the kinetic analyses - were an *in vitro* study, undertaken by Hirsch's laboratory in 1986 using foscarnet and interferon and *in vivo* studies using AZT plus ddI or ddC. These failed to have an impact on AIDS therapy, either because the drugs used were not sufficiently potent; because their efficacy in combina-

tion was obscured by the inclusion of test subjects already resistant to one of the drugs; or because major delays in their testing and reporting allowed the greater efficacy of 'triple therapy' to be demonstrated first[8]. But had additional effective drugs like 3TC or the protease inhibitors become available in the 1980's, clinical investigators would quickly have tested them in combination with AZT.

The first pharmaceutical companies to search for drugs that inhibit the HIV protease, Abbott, Hoffmann-LaRoche and Merck, all had previously invested considerable resources in an unsuccessful search for a clinically-useful inhibitor of renin, an aspartyl protease, to treat hypertension. When the retroviral proteases were found to belong to this family of enzymes, this suggested a way for recouping that investment. The Abbott program used computer-aided design and biophysical data (NMR spectroscopy; x-ray diffraction) to model the enzyme's active sites and generate inhibitors to occupy those sites. The Roche program was based instead on the more traditional 'transition phase analog analysis', which examines the changes in the protease's conformation that occur when a drug occupies its active site. The Merck program, though not initially structure-driven, did later use knowledge of the enzyme's crystal structure to design its lead drug, indinavir.


In retrospect, it appears that knowing that the HIV enzyme is an aspartyl protease was of major importance in developing therapeutic protease inhibitors. However the subsequent biophysical characterization of the enzyme's active site probably was not. While it helped some companies to accelerate their search for a useful inhibitor, its use also gave rise to false starts, as when knowledge that the enzyme's dimeric structure exhibited symmetry led investigators to search for symmetrical chemicals to inhibit it. Some such compounds turned out to be active, but less so than asymmetric analogs.

Which laboratory discoveries about HIV *per se* and which clinical observations about host responses to the virus made after HIV had been identified as the cause of AIDS in 1983-4 (refs. 3,4), turned out to be essential for treatment discovery? With regard to the virus, only two: The development of cell culture techniques[4] in 1984, that allowed the virus to be grown continuously, and the 1985 demonstration, described above, that retroviral proteases were aspartyl-enzymes[6]. Numerous findings from clinical research did turn out to be important in assessing and reinforcing the use of combination therapy, for example the establishment of 'viral load' as a valid surrogate marker for clinical state[9], and the descriptions of viral and CD4 cell dynamics at various stages of HIV infection. However, once the number of available retroviral drugs increased, investigators began to combine them, even without supporting kinetic data and 'viral load' determinations.

### Political and Economic Factors

If prior experience with aspartyl proteases or a corporate feeling of *noblesse oblige* in favor of ameliorating a societal catastrophe encouraged some drug and biotech companies to initiate the programs that ultimately generated HIV protease inhibitors and non-nucleoside RT inhibitors, it was the political and economic changes of the mid-1980's, particularly those involving FDA regulations, that won these programs the support they needed to be successful.

After five years in which the Reagan-Bush Administration virtually ignored the suffering of people with AIDS (in striking contrast to its responses to, for example, Legionnaire's disease or toxic shock syndrome [20]), its Surgeon General, C. Everett Koop, was finally allowed in 1986 to release a Report to the President on AIDS. Around that time, Congress granted the NIH an additional $60 million for AIDS research, thereby initiating a continuing process by which such funding (as a percent of the total NIH budget)is increased annually.

The Reagan-Bush Administration did not relent on its own: Its prolonged disinterest in AIDS was probably an accurate reflection of the public's at best ambivalence about committing major resources to what it perceived as the special needs of a highly unpopular constituency — gay men — who were confronting a self-inflicted 'Gay Plague'[11]. This view and the Administration's responses to the epidemic began to change when well-known individuals with whom the public could identify — such as Rock Hudson and such 'innocent' heterosexuals as Arthur Ashe, Ryan White and Elizabeth Glaser — contracted AIDS, and when Henry Waxman and Theodore Weiss used the medium of congressional hearings to publicize the rapid spread of the disease and the isolation of many of the patients afflicted with it.

### AIDS Activists and the FDA

But in large measure what caused the public ultimately to support an 'all-out federal war to find a cure for this plague', as proposed by Larry Kramer in March, 1987, and the public's elected officials to implement that war, was the untiring efforts of Kramer and legions of fellow AIDS Activists. Starting with the Gay Men's Health Crisis and its offspring ACT-UP, there came into existence in the mid-1980's an unprecedented array of informed, media-savvy groups organized around a disease. Their members, who were usually but not always gay men, were committed to doing whatever was necessary, including breaking the law, to promote the discovery and dissemination of effective treatments, first for the opportunistic infections associated with HIV-induced immune deficiency and later for the HIV infection itself. The activists also sought to educate patients about their treatment options and their rights; to advise researchers about protocol design; and to enlist volunteers for sometimes-painful studies. Their newsletters - for example, those published by Martin Delaney's Project Inform; the Treatment Action Group's *Tagline*; the National AIDS Treatment Advocacy Project's meeting reports; and John James' *AIDS Treatment News* - mixed articles on political strategies, putative AIDS treatments, and fundamental biomedical research, often attaining a level of scientific sophistication usually associated with mainstream research journals. Lamentably, the AIDS Activists received little or no assistance from established consumer groups concerned with health matters: As Martin Delaney describes, '*Public Citizen* [one such health politics

Table 1 HIV Drugs currently approved by the FDA

| Drug | Mechanism | NDA filed | NDA approved | Manufacturer |
|---|---|---|---|---|
| AZT (Retrovir; zidovudine) | RTI (Nuc) | 12/2/86 | 3/19/87 | Burroughs Wellcome |
| ddI (Videx; didanosine) | RTI (Nuc) | 4/6/91 | 10/9/91 | Bristol-Myers-Squibb |
| ddc (Hivid; zalcitabine) | RTI (Nuc) | 10/31/91 | 6/19/92 | Hoffmann-LaRoche |
| 3TC (Epivir; lamivudine) | RTI (Nuc) | 6/30/95 | 11/20/95 | Biochem. Pharma. |
| d4T (Zerit; stavudine) | RTI (Nuc) | 12/28/93 | 6/24/94 | Bristol-Myers-Squibb |
| Nevirapine (Viramune) | RTI (Non-Nuc) | 2/23/96 | 6/24/96 | Boehringer-Ingelheim |
| Rescriptor (Delavirdine) | RTI (Non-Nuc) | 7/15/96 | 4/4/97 | Upjohn-Pharmacia |
| Saquinavir (Invirase) | PI | 8/8/95 | 12/6/95 | Hoffmann-LaRoche |
| Ritonavir (Norvir) | PI | 12/21/95 | 3/1/96 | Abbott |
| Indinavir (Crixivan) | PI | 1/31/96 | 3/13/96 | Merck |
| Nelfinavir (Viracept) | PI | 12/26/96 | 3/14/97 | Agouron |

RTI: reverse transcriptase inhibitor; Nuc: nucleoside; PI: protease inhibitor

group] weighed in against FDA [The Food and Drug Administration] reform at every step along the way. In many ways *Public Citizen* is the personification of what's wrong with the present system in that it only works one side of the street. It has a concern for safety, but no apparent concern for the harm done when life-saving products are needlessly delayed.'

Indeed the greatest successes of the activists were political: besides creating a broad public constituency for the mission of treating AIDS, their efforts quite literally transformed the FDA[12], changing it from an organization with a traditionally negative role (protector of the public from dangerous drugs like thalidomide), to that of an active collaborator in the treatment discovery process, at least for anti-AIDS drugs. Until 1986 the FDA's involvement in AIDS had largely been restricted to prophylaxis — improving the safety of the national blood supply and monitoring the impermeability of phlebotomist's gloves and condoms — and its only general mechanism for providing AIDS patients with access to not-yet-approved drugs, the Treatment IND (investigational new drug), usually had an effect opposite to that intended, and lengthened the time needed for drug approval[13]. In that year the Burroughs-Wellcome company submitted a New Drug Application (NDA) for the first antiretroviral drug, AZT, and even though that application lacked any Phase III data, the FDA examiner, Ellen Cooper, approved the drug's use in a then-astonishing 107 days (Table I). In the preceding year, the FDA had also authorized AZT's compassionate use by a record 4,800 patients and in 1987 it established an accelerated review mechanism for new AIDS drugs in general (1-AA review priority) and introduced regulations that would provide additional financial incentives and marketing exclusivity to companies that produced such drugs.

The gradual transformation of the FDA to a hotbed of AIDS treatment development may have reflected more than a shift in the public's attitudes towards the disease: It may also have been influenced by the recognition, in Congress and elsewhere, that the agency's prior failure to facilitate the discovery and distribution of treatments was making it irrelevant to these processes, and could ultimately jeopardize its control over drug access in general: Another major function of some activist groups had been to operate 'buyer's groups', which would purchase and resell approved medications at lower costs, and would also provide patients with unapproved compounds. Most such compounds turned out to have no discernible therapeutic value, however on occasion, as with aerosolized pentamidine, the compounds were later sanctioned by the FDA, and distributed through regular commercial channels. In April 1988, at a congressional hearing on the paucity of approved drugs for AIDS, Congresswoman Nancy Pelosi asked Anthony Fauci, probably the senior NIH scientist/administrator researching AIDS, whether, if he were a patient at risk for pneumocystis pneumonia, he would take aerosolized pentamidine to prevent or treat that often-fatal opportunistic infection, even though it lacked FDA approval. Fauci acknowledged that he would indeed take the unapproved drug. This lesson apparently was not lost on Congress nor the FDA, and David Kessler, on becoming the next FDA Commissioner in November, 1990, implemented it by making the development and distribution of anti-AIDS drugs one of his agency's top priorities.

### Making the FDA User-Friendly

Between 1988 and 1992, partly in response to the demands of AIDS activists, the FDA implemented its 'Subpart E' regulations, which provided for close and continuous consultation, sometimes starting at the preclinical phase of drug development, between the agency and companies testing candidate anti-AIDS drugs. It also implemented new and less restrictive mechanisms for importing unapproved AIDS treatments and put into operation the 'Parallel Track' policy that provided test drugs to patients who, for medical or geographic reasons, could not qualify as regular participants in a Phase III study[13]. Passage of the User Fee Act of 1992 further speeded the evaluation of anti-AIDS drugs by allowing the FDA to hire more staff to review NDA's and in 1993, in a major policy change unfortunately not yet generally applied to most other terrible diseases, the FDA, through its 'Accelerated Approval Rule' allowed companies to market new AIDS drugs based on evidence that they improve surrogate markers provided that an FDA-approved clinical-endpoint study was underway. The most effective change in FDA regulations to date has been the Subpart E rule, which for some drugs has significantly shortened the time spent both for acquisition of the clinical data needed for an NDA and for FDA review of that NDA[13]. The net effect of these changes has been to reduce the time the FDA takes to approve an NDA for an AIDS drug often to three months or less (Table 1), and to reduce by years the time spent accumulating the data required for the NDA.

Would patients with other diseases benefit from the universal application of the Subpart E rule to, and acceptance of surrogate markers for, all such diseases? Almost certainly. Although the time required for FDA approval of an NDA (all diseases) decreased from 2.7 to 1.7 years between years 1990-1993 and 1994-1995 (i.e.,before and after passage of the User Fee legislation) the mean periods needed to gather the data

which the FDA demanded in support of those NDA's expanded from 5.5 to 7.2 years. Hence total development time actually increased for most non-AIDS drugs[14].

As described by Richard Gammans, an industrial pharmacologist, companies deciding whether to develop a new anti-AIDS drug or, for comparison, a new antidepressant, started to find financial calculations very much on the side of the AIDS drug. The AIDS drug may get to market in four years or less after the initiation of research, and after total direct outlays of about $ 80 million ($20 million per year for preclinical studies, for two years, and $40 million for one year of clinical studies, plus a year for statistical analysis and FDA evaluation). In contrast, the antidepressant may require seven years or more to reach the market, with double the investment: it will not be fast-tracked; it cannot be marketed based on data using surrogate markers; its NDA will probably have to include two large Phase III studies; and the company will not necessarily enjoy the benefit of frequent consultation with FDA regulators when it is trying to divine what data will be required for its NDA. If one also considers the time value of the monies invested (sometimes calculated at an annual rate of 15% or higher), then subsequent sales of the AIDS drug of $250 million per year, beginning several years sooner, actually become more profitable to the company than sales of $500 million per year for the new antidepressant.

Have such calculations caused wavering companies to fund AIDS Drug Discovery programs? Without transcripts of corporate strategic planning sessions, we cannot know — but it certainly seems likely. Would extension of the FDA's HIV regulations to other terrible diseases accelerate the discovery of treatments for those diseases? Again, the HIV saga certainly suggests so.

### What Went Right for AIDS?

In retrospect, it might be argued that AIDS was an 'easy' disease to treat all along: The paradigm that would and did lead to its therapy had been proposed by Paul Ehrlich more than a century ago, and selective enzyme inhibitors had been used to block cellular functions for at least half that time. It was only necessary to identify target enzymes in the invading organism — soon accomplished once HIV was shown to cause AIDS[3,4] and its enzymes were characterized using classical techniques — and then to apply two-decades-old insights about inhibitors of reverse transciptase and aspartyl protease to identify clinically-acceptable chemicals to block those enzymes. Similarly, it had been recognized for four decades that drug combinations worked better than monotherapy when trying to destroy rapidly-mutating invading cells, and it made sense to try this approach in patients with HIV.

Clearly a critically important factor was the consensus that started to develop in mid-1980's America, that its government should mount a 'War' against AIDS: Thereafter enormous sums were dedicated to AIDS research, the culture of the FDA's AIDS operations was transformed to that of active participant in the treatment-discovery process; and it became easier for individual scientists to disregard the peer consensus against mission-oriented research, and to publicly dedicate their efforts to finding a treatment for AIDS. And the Public's growing commitment convinced many in the pharmaceutical industry, perhaps prematurely, that if they did succeed in developing effective drugs, society would provide patients with the wherewithal to purchase them. Why did America make this commitment to conquering AIDS, but not to emphysema or alcoholism or other fatal diseases? Many factors probably contributed - including the well-publicized spread of AIDS internationally, and to non-gay populations, particularly women. However foremost was the political, educational and media-directed activities of AIDS Activists and their supporters. Other disease constituencies should note that when the AIDS activists were at their most effective, their demand was not for 'more research' but for 'effective treatments'. Perhaps the implicit call for accountability in this demand contributed to its attainment.

Should we now make 'Wars' on other poorly-treated diseases? The 'War on Cancer' enunciated in 1971 is often presented as evidence that 'Wars' against disease must inevitably fail. Although it was supported for too short a period, and involved too few of the institutions that ought to have participated, it did give us taxol and other antineoplastic drugs, as well as AZT and the initial evidence that dideoxy compounds inhibit reverse transcriptase. Of course the 'War on AIDS' is far from won, and must be fought until an effective and inexpensive vaccine becomes available to prevent the disease all over the world. But the battle for a treatment was successful.

But organizing society to accelerate treatment discovery needn't require full-scale 'Wars', - just canonization of such goals as national missions. As with AIDS, such canonization would impart dollars, coordination and accountability to the discovery process. It would also mandate the participation of all of the groups that needed to be involved — including an FDA unambiguously committed to promoting treatment discovery. Should the NIH, with its overriding and enormously successful commitment to fundamental research, also be entrusted with administering such missions? This question requires careful analysis.

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