TAG

FDA REGULATION OF ANTI-HIV DRUGS:

A Historical Perspective

by Spencer Cox

Edited by Mark Harrington & Bruce Schackman

Treatment Action Group
200 East 10th Street #601; New York, NY 10003
Phone:212.873.9044/Fax:212.877.0196

Spencer Cox is the Chair of TAG's Antiviral Drugs Committee, and also serves as the organization's Communications Director. He has also served as Secretary of the Board of Directors of the People With AIDS Coalition (PWAC) in New York, and has done public education work with ACT UP/New York, the Community Research Initiative on AIDS (CRIA), and the American Foundation for AIDS Research (AmFAR).

The Treatment Action Group (TAG) fights to find a cure for AIDS and to ensure that all people living with HIV receive the necessary treatment, care and information they need to save their lives. TAG focuses on the AIDS reseearch effort, both public and private, the drug development process, and our nation's health care delivery systems. We meet with researchers, pharmaceutical companies, and government officials, and resort when necessary to acts of civil disobedience, or to acts of Congress. We strive to develop the scientific and political expertise needed to transform policy. TAG is committed to working for and with all communities affected by HIV.

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This report is dedicated to the memory of

David B Feinberg

✦

The weight of this sad time we must obey:
Speak what we feel, not what we ought to say.
The oldest have borne most; we that are young
Will never see so much, or live so long.

King Lear, V:ii

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EXECUTIVE SUMMARY:

The initial marketing approval of Retrovir brand zidovudine (AZT) was based on one clinical efficacy study, comparing AZT to placebo in patients with AIDS and advanced ARC, which demonstrated that the drug could confer a substantial short-term survival benefit. The indication was later expanded to include asymptomatic patients with less than 500 CD4+ cells/mm^3, based on two studies demonstrating a substantial increase in disease-free survival for patients taking AZT as compared to patients taking placebo.

Videx brand didanosine (ddI), by comparison, was approved, as Mark Harrington noted in his report to ACT UP/New York entitled *"D-day for ddI,"* on the basis of one slide showing a preliminary analysis of ACTG 116b/117, a study which demonstrated that high-dose ddI reduced the slope of CD4+ decline as compared to AZT in one of two tests of significance, and that high- and low-dose ddI increased the number of patients with Normalized Area Under the Curve (NAUC)[1] values of greater than one by two of three significance tests for high-dose ddI, and one of three significance tests for low-dose ddI. The FDA's Antiviral Drugs Advisory Committee recommended that ddI be approved for patients who had experienced significant clinical or immunologic deterioration during AZT treatment.

As follow-up information on ddI, the committee reviewed information from ACTG 116b/117 demonstrating that, after sixteen weeks or more of AZT treatment, patients who switched to ddI had significant reductions in new AIDS defining events, and improved disease-free survival time. On the basis of this data, the committee recommended widening the indication for ddI to include patients who had taken AZT for a significant time, in addition to those who were experiencing clinical or immunologic deterioration during AZT treatment.

The decision to grant accelerated approval to HIVID brand zalcitabine (ddC) was based on a small study intended to evaluate the time to viral resistance in patients taking ddC and AZT together, as compared to patients taking AZT/ddI or AZT alone. The study demonstrated that a greater percentage of patients had a slight increase in CD4+ cells on combination therapy as compared to patients on monotherapy, and that a greater number of patients maintained CD4+ cell counts at or above baseline at 12-20 weeks on combination therapy as compared to monotherapy. Additional data from ACTG 114 demonstrated that AZT was significantly better than ddC in patients without prior antiretroviral therapy in delaying mortality. On the basis of this data, the committee recommended ddC for use in combination with AZT in patients who had experienced significant clinical or immunologic decline.

For follow-up on ddC, the only drug granted accelerated approval whose sponsor subsequently applied for traditional approval, the committee reviewed data from CPCRA 002 demonstrating that, with wide confidence intervals, ddC was roughly comparable to ddI in delaying disease progression or death. In addition, data from ACTG 155 showed that, in patients with less than 300 CD4+ cells and substantial prior use of AZT, combining AZT and ddC conferred no additional clinical benefit. On the basis of this data, the committee recommended withdrawal of the accelerated indication for AZT/ddC combination therapy, and extension of traditional approval for ddC monotherapy in patients experiencing "significant clinical or immunological deterioration during treatment with [AZT]." FDA rejected the committee's recommendation with respect to combination therapy, and granted full approval for the monotherapy indication.

In reviewing the application for accelerated approval of Zerit brand stavudine (d4T), the committee heard data demonstrating that, in patients with less than 500 CD4+ cells and extensive pre- treatment with AZT, d4T could improve CD4+ response using the 10:10, 25:25 and 50:50 analyses[2], as well as increasing the number of patients with NAUC values of greater than one at weeks 12 and 24. The committee recommended the drug for accelerated approval, but did not recommend an indication or dosage. FDA granted accelerated approval at the high dose.

DISCUSSION

Over the period in which FDA has reviewed and regulated anti-HIV therapies, there has been a substantial decline in the quality and quantity of available information regarding the clinical utility of those drugs at the time of their approval. While the experience with accelerated approval remains limited, it seems that the decline in information rapidly increased following the implementation of those regulations. While on the surface this often seems to represent problems in basic trial design methodologies — such as improper controls, early termination, inadequate sample size and post-hoc adjustment and analysis — FDA's willingness to accept fundamentally flawed studies as providing sufficient confirmatory evidence to validate approval may be reducing incentives to properly design and implement post-marketing studies.

Traditionally, regulation has provided incentives and disincentives in order to shape the kinds of safety and efficacy trials performed by pharmaceutical companies in developing new products. By setting "threshold" standards of safety and efficacy, FDA has helped to ensure that studies were designed to answer basic empirical questions about the safety and efficacy of therapies in use. Consequently, efforts to satisfy FDA standards at the end of the process have driven the design of clinical studies much earlier in the process.

In 1989, activists began to articulate the need for a new standard of efficacy, one which "takes account of the uniqueness and potential value of a drug and the urgency of the need for it."[3] In other words, data would be reviewed not based on efforts to answer certain primary questions, but would, in the words of the 1989 "Bush Initiative,"

> consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions, about the risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapies.[4]

Without the knowledge that they would be required to provide specific information about the safety and efficacy of their products, manufacturers began to submit applications for approval based on unrandomized phase I data compared to historical controls, preliminary analyses from studies that were not intended to evaluate treatment effect on the endpoint of interest, and subgroup analyses purporting to demonstrate efficacy in tiny subsets of the original study.

While the FDA's Antiviral Drug Products Advisory Committee has discounted claims based entirely on unrandomized data, it seems ultimately to have settled on an efficacy standard that permits accelerated approval based on one randomized study showing surrogate benefits, even in the presence of conflicting data, as was the case for ddC and d4T[5]. For movement from accelerated approval, the standard is not yet clear. However the case of ddC demonstrates that the standard is not, as was recently suggested by FDA Commissioner David Kessler[6], identical to that imposed by pre-accelerated approval policies.

The concern regarding this flexibility is that it will offer incentives for sponsors to design trials that produce little or no reliable information, because these trials are believed to be faster and less expensive. With accelerated approval virtually guaranteed for antiretroviral drug products sponsored by large, multi-national pharmaceutical companies, the balance of incentives began to shift, producing a "mandate for ignorance": the manufacturer's financial interest is to avoid collecting reliable efficacy data (which would require longer or larger and more expensive trials), and to submit an application for full approval based on little more than time since initiation of product development. If all of the good news comes from small studies of treatment effect on surrogate markers, and all of the bad news comes from large-scale clinical endpoint studies, then industry has financial incentives to avoid the latter.

There is some evidence that such a shift is already occurring: the presumption seems to have favored approval in the absence of data suggesting lack of safety — a concept suggested by conservative policy analysts and some AIDS activists as early as 1988.[7] Consequently, the question about ddC was not, "Is this product safe and effective for the treatment of HIV disease?" but "Can we conduct further studies of this drug, or should we just approve it now?" Given the unwillingness of many patients to enter properly controlled studies following approval, it may be impossible to conduct a simple, empiric evaluation of basic safety and efficacy in post-marketing studies. FDA's Dr. Ellen Cooper warned of such concerns in 1990:

> For drugs to treat serious or life-threatening conditions, the first evidence of efficacy, particularly if it comes from a controlled trial, often makes it very difficult, if not impossible, to conduct additional controlled trials as the world makes up its mind based on the early evidence. Thus, it is very important that the first randomized, controlled trials of new drugs under investigation for the treatment of life-threatening diseases be as well- designed and conducted as possible, with the objective of providing the highest quality results that have adequate power to demonstrate efficacy or lack thereof with reasonable assurance.[8]

Too often, the response of patient advocates to preliminary data suggesting possible efficacy has assumed a greater reliability of such data than may actually be warranted. Such assumptions occur in the best of faith, from a real desire to offer patients hope. As one physician who was himself living with AIDS, noted after the approval of AZT, "We're beginning to bias the process in favor of good news."[9]

Unfortunately, biasing the process in favor of good news is probably the wrong empirical approach: according to the Pharmaceutical and Research Manufacturers of America (PHaRMA), only one drug is approved for every five that enter human testing.[10] In 1990, FDA's Dr. James Bilstad informed the Antiviral Drug Products Advisory Committee that

> Approximately 70 percent of the drugs for which INDs are submitted successfully complete phase-I studies...Approximately one-third of the drugs for which INDs are submitted to the Agency successfully complete phase II testing...There is not much of a drop-off from those that successfully complete phase II to phase III. Approximately 25 to 30 percent of those INDs submitted complete phase III testing.[11]

In other words, the vast majority of drugs entering large-scale human trials will be proven to be unsafe or ineffective. Our presumption must be that new drugs are either unsafe or ineffective until proven otherwise. We must temper our very real desire to rush new treatments to patients at greatest risk with skepticism about "possible" or even "probable" efficacy.

Ultimately, each of the agents currently available presents the very real risk that, measured by the standard of disease and death, risks may outweigh benefits. There are risks to premature approval — risks of acceleration of morbidity and mortality, risks of expenditure of vital health-care resources on therapies of negative or no utility, and risks of utilizing less-than-optimal treatments when more effective agents might be available but poorly characterized. So far, study of antiretroviral agents has been guided by fumbling mistakes, excessive therapeutic optimism and misplaced good intentions.

For example, ddI was considered "validated" by a study comparing two doses of the drug to continued AZT in patients who had already been extensively pre-treated with AZT. However the utility of the "control arm" was unclear given AZT's well- characterized time-limited utility. As Dr. Donald Abrams told the FDA's Antiviral Drug Products Advisory Committee, "I'm not sure if what I'm seeing is a benefit from switching to ddI, or from going off AZT."[12]

And, if the validation of ddI must be regarded as ambiguous at best, then that of ddC, which was based in

a comparison to ddI, must also be called into question. The problems of validation multiply when further controlled studies are regarded as impossible.

One school of regulatory thought has held that

> Clinical studies can only predict how well a given therapy will work for a group of patients, but no matter how positive the outcome, they cannot predict whether it will work for individuals...The best situation is one which permits the patients and their physicians to choose freely among the alternative antiviral therapies, finding the ones which work best for the individual. Clinical trials need only tell patients and physicians that a drug has useful activity, what its side effects are, and the proper dose.[13]

One advocate of this approach has proposed trials

> which do not even try to prove whether a drug is effective...Instead of asking for statistical proof, the important question is whether [a study] provides information useful for making treatment decisions.[14]

Such an approach seems initially attractive and reasonable, because we would all like to share the bias upon which the approach is predicated: we would like to believe that physicians can tell "which [drugs] work best for the individual." Typically, this philosophy has embraced the use of "surrogate markers," such as post-therapeutic changes in absolute CD4+ cell count and various markers of virologic activity, in order to determine whether or not a therapy is "working" in the individual. It is assumed that such changes in surrogate markers must predict rates of continued illness and death.

While the search for useful surrogate markers is rational, our experience both in AIDS and in other diseases suggests that we approach proposed markers with skepticism. The history of failed surrogates in the medical literature, including tumor size for cancer, and rate of arrhythmias in heart disease, is extensive. Dr. Tom Fleming of the University of Seattle recently reviewed data on changes in absolute CD4+ cells as a marker for reduction of AIDS-related morbidity and morality, and concluded that that the direction of surrogate change in previous therapeutic studies has been congruent with the direction of clinical effect approximately 51 percent of the time — in other words, the use of the surrogate for predicting clinical outcome in a population is about as reliable as flipping a coin.[15]

As markers for evaluating clinical effects in individuals, we are forced to use what is available to us. However, clinical confirmation, as required by the accelerated approval regulations, remains integral to the interpretation of individual response. The supposed irrelevance of population-based outcomes to individual outcome is simply untenable. Population-based evaluation is never intended to define the necessary course of treatment for individual patients, but rather to direct bias; a therapy that is helpful "on average" is probably worth trying in the individual (although toxicity concerns may alter that equation).

Ultimately, recent approaches have been predicated on an assumption that it is possible to keep those who are currently desperately ill alive until a cure is found. Unfortunately, this assumption is no longer sustainable. Large treatment effects are easy to discern, but nothing currently in clinical development can be expected to provide miraculous cures. Many of those now ill will die. Barring unexpected advances, many of us who are now infected may be expected to grow ill and to die. However, by careful planning and rigorous evaluation, we can ensure that the available therapeutic arsenal is maximized, to provide persons with HIV/AIDS with the longest healthy survival possible.

When the accelerated approval regulations were established, they were intended to "merely change when some of the studies are done," rather than to "lower the standards for drug approval".[16] As one of the lead-

ing advocates for accelerated approval noted, its success depends on FDA's willingness to:

- Make sure drug companies keep their commitments to doing the long-term studies
- Remove from the market drugs approved in this manner if they later prove unsafe or ineffective
- Decide which drugs warrant expedited approval
- Guarantee adequate staff resources to implement expedited approvals[17]

By building in new mechanisms to ensure that products granted accelerated approval are rigorously evaluated for both surrogate and clinical effects, it will become possible to provide the information needed to meet the access and informational needs of a variety of patients and patient populations.

For too long, activists, scientists and regulators have accepted as dogma that "acceleration comes at a price — less information about drugs, and even the risk that treatments may be useless."[18] We have believed without question that

> statistical proof using clinical endpoints in early HIV disease requires long, large trials. Adding the time required to conduct and analyze the trial itself, the time for recruiting, and the time to build the required commercial and professional momentum to get a large trial going, it is likely to take several years to test each drug or combination. Such trials are not feasible for many reasons.[19]

In cancer and heart disease, clinical research methodologies have been developed that can quickly and efficiently enroll the large numbers of patients needed to reliably answer important questions about the safety and efficacy of therapies.[20] While early versions of these studies were difficult to initiate, subsequent studies utilizing the established networks of researcher/physicians have enrolled massive numbers of patients at lightning speed.[21] Already, randomized expanded access programs have created such a network of physician/researchers in AIDS. We must fully utilize the potential of these networks to provide early, rapid access to the desperately ill, and to rigorously evaluate the effects of treatments in those who are less ill.

In addition, we must ask ourselves on whose behalf we advocate. While advocates are attempting to define access mechanisms for the latest "drug of the month," *pneumocystis carinii* pneumonia, a largely preventable disease, remains the leading cause of AIDS diagnosis, and of AIDS-related morbidity and mortality in New York City, and probably, in the United States. AIDS advocacy that reflects only the treatment priorities of the advocates themselves will be ineffectual at best, and a harmful diversion at worst.

The urgent need to plan for the future has only grown. As the epidemic continues to spread among intravenous drug users, their sexual partners and their children, it has re-emerged as a threat to gay men in the United States. A recent paper from the Multi- Center AIDS Cohort Study (MACS) begins to suggest how high the stakes may be. The authors estimated the lifetime risk of HIV infection for a twenty-year-old gay man today. According to their estimates, "such a man has a 20 percent chance of seroconverting before reaching the age of 25...The overall probability of seroconversion prior to age 55 is about 50, with some seroconversions continuing after that."[22] In other words, the majority of twenty-year-old gay men today can expect to become HIV-infected at some point in their lives, barring unforeseen improvements in prevention technology.

Evaluation of AIDS drugs today does not just affect those who are currently ill; our planning now will determine the quality of HIV treatment for the next generation of people with HIV/AIDS.

If we fail to address the basic question of efficacy standards now — "At what point in the development process do we reliably determine that a treatment can extend health and life?" — then our drug development systems, and our standards of HIV treatment are destined to leave us with substandard therapy for most HIV-infected persons, serious vulnerability to fraudulent claims, and ultimately, to unnecessary sickness and death.

We must and can do better. In continually reviewing and improving our regulatory mechanisms, it may be possible to reconcile the seemingly opposed needs for access to new therapies and reliable information about their efficacy.

POLICY RECOMMENDATIONS

Policy Recommendation 1: FDA should hold periodic public meetings to review the information on surrogate markers currently considered "reasonably likely to predict clinical benefit."

Questions have been raised about the utility of available surrogate markers to evaluate treatment effects in people with AIDS. The accelerated approval regulations require that use of such markers be predicated on a decision that the marker is "reasonably likely to predict clinical efficacy." While there is at present considerable optimism about the utility of new quantitative measures of viral burden in the peripheral blood, it remains unclear to what extent such measures will be "reasonably likely to predict clinical efficacy." As Derek Hodel, now with the Gay Men's Health Crisis has noted, "the degree to which any given surrogate remains non-validated will change."[23] Over time, the use of CD4+ to predict clinical efficacy has changed, and it is to be hoped that continued evaluation of viral burden measures will produce clearer information about their usefulness. It will be necessary over time to submit proposed surrogates to public review and scrutiny, both to ensure that necessary evaluation is being completed, and to review the continued use of the surrogate in the evaluation of new therapies.

Policy Recommendation 2: In order to be eligible for accelerated approval, FDA should require sponsors to submit their development plan to an appropriate advisory committee for evaluation prior to initiation of phase II studies.

The accelerated approval regulations note that studies intended to provide clinical confirmation will usually be underway at the time of accelerated approval. However, too often sponsors have collected the data to meet the surrogate requirement, only to arrive at the advisory committee hearing with development plans that are unlikely to be powerful enough to detect probable modest treatment effects.[24] Public hearings scheduled prior to implementation of phase II studies would allow for evaluation of the development plan to determine its suitability to serve as a confirmation study.

Policy Recommendation 3: FDA should regard parallel track as an important factor in determining the suitability of a product for accelerated approval.

In evaluating the safety of ddI, ddC and d4T, data presented by sponsors on patients enrolled in expanded access programs proved invaluable. Such programs provide a real-world safety database, including information on drug interactions, toxicities at different stages of disease, and on important but infrequent toxicities. FDA should regard safety information from an expanded access as an integral part of an accelerated approval application.

Policy Recommendation 4: In submitting an application for accelerated approval for a product, sponsors should include an analysis explaining why such approval is preferable to other programs, such as treatment IND or parallel track.

When accelerated approval was first advanced, advocates asserted that

> only prescription status — an NDA — brings with it third party coverage for costs associated with the use of the drugs...Anything less than approval as prescription drugs punishes the patient for the failings of the system.[25]

However it remains unclear to what extent accelerated approval has improved access as compared to

expanded access programs. The parallel track program for d4T, for example, enrolled more than 10,000 patients from all fifty states and Puerto Rico. By the time of accelerated approval of 3TC brand lamivudine later this year, more than 40,000 people with AIDS world-wide are expected to have enrolled in expanded access programs. More information is needed on the prescription patterns of therapies on expanded access as opposed to accelerated approval. In assessing an application for accelerated approval, sponsors should submit, and the advisory committee evaluate, an analysis explaining why approval is the preferred means of providing expedited access.

Policy Recommendation 5: FDA should develop incentives for companies to utilize innovative research methodologies, such as the "large, simple trial," and other models.

The "large, simple trial" methodology, first used in heart disease, and later expanded to cancer and AIDS, has been proposed as a means of fulfilling many of the early criticisms leveled by AIDS activists toward standard clinical research methodologies.[26]

By radically simplifying entry criteria and restrictions on concomitant medications, carefully tailoring treatment and data collection to the standards of primary care, and nesting intensive virological and immunological studies, the large, simple trial could provide real-world information on both the surrogate and clinical effects of new therapies as they would be used in typical health care. Such studies may be more cost effective than standard research methodologies[27] while providing more reliable and generalizable information. In addition, large, simple trials can provide easy access to experimental therapies to large numbers of patients at no cost to the patient. A recent study by the Office of Technological Assessment (OTA) of the US Congress strongly recommended the increased use of large, simple trials in assessing the effects of widely-used therapies.[28] A large, simple trial contributed greatly to the approval of d4T.

However, large simple trials are not the only innovative methodology that might be usefully applied to the study of new anti-HIV therapies. FDA should continue to educate industry and consumers about useful methodologies, and, where applicable, should encourage sponsors to utilize those methodologies that maximize both access to and information about new therapies.

Policy Recommendation 6: Community-based treatment advocates and information providers should develop a network to provide ongoing education, technical support, analysis and review of accuracy of the information provided to patients.

As David Barr, also from GMHC, noted before the FDA's antiviral drugs advisory committee, off-the-record comments from investigators and company spokespersons often influence patient perception and demand for products, although the evaluation may be based on little more than personal perception or corporate interests. In addition, AIDS advocates have often fueled demand for access to products with premature assertions about the safety and efficacy of new products. In community newsletters, assertions that ddI was "safer than AZT" were disturbingly frequent prior to the revelation of the pancreatitis deaths. Similarly, assertions about efficacy based on phase I data (or sometimes even just *in vitro* results) are frequent in the community literature, and are rarely accompanied by appropriate disclaimers. As activist John James noted with reference to ddC, "the drug was standard of care accepted by many leading AIDS physicians" following completion of just one phase I study.[29]

In addition, information providers are unregulated, and, while most reputable newsletters have some sort of medical review for general accuracy, there is no systematic peer review system for treatment information newsletters. Treatment information can often unintentionally serve the function of a therapeutic claim, and in fact, some companies have been accused of utilizing their relationships with individual information providers

and information outlets to indirectly make unproven therapeutic claims about their products. When patients rely on information about products to make treatment and policy decisions, the need for accuracy is enormous.

Self-regulation provides a desirable balance between the need to provide accurate information and the need to minimize burdensome requirements for treatment information providers.

Policy Recommendation 7: FDA should time-limit accelerated approvals. Post-marketing agreements should include provisions for a parallel track release in the event of product withdrawal for reasons other than definitive evidence that the product is unsafe or ineffective.

The only mechanism available to FDA to enforce accelerated approval commitments is the expedited product withdrawal provision of the regulations. However, as Harvard's Dr. Deborah Cotton noted during review of ddC's accelerated approval

> I never have felt that we could take back accelerated approval. I thought that was a hopelessly naive point of view. As a physician, I would be the first one at the ramparts saying you can't take away this drug because it is helping my patient here or my patient there. I think it is cruel to have offered this and then take it away. I don't think it can be done, short of proven severe toxicity of one of these agents.[30]

At present, the threat of withdrawal is intended to provide the incentive for clinical evaluation of the therapy; however, clinical evaluation is probably a necessary pre-condition of product withdrawal. In order to assure completion of post-marketing efficacy studies, new incentives are needed.

The concern is not that drugs will be left on the market after the accumulation of evidence demonstrating lack of safety or efficacy, but rather that unvalidated drugs will be left on the market indefinitely. As Antiviral Drug Products Advisory Committee member Dr. Mark Smith commented in 1993,

> I am increasingly unclear on what it means to leave a drug on accelerated approval...it does seem to me that even continuation of the drug as an accelerated approval ought to be linked to some sort of sense of what we ought to know by when.[31]

It must be clear that the completion of agreed-upon studies is insufficient for full marketing approval; those studies must reliably confirm the clinical benefit of the product.

Regulation of new anti-HIV products has never been cut-and-dried; it has always entailed a complicated balancing of risks and benefits. However, without a process to guarantee that our end product is reliable information about the long-term safety and efficacy of new products, we are limiting our own capacity for therapeutic improvement. One such mechanism to address these concerns would include the imposition of a time limit on accelerated approvals — marketing approval would presumptively expire on a certain date unless data were submitted to the agency in the interim which reliably confirm the product's clinical benefit.

Policy Recomendation 8: Congress should pass legislation to encourage manufacturers to continue the evaluation of the safety and efficacy of "breakthrough" technologies after marketing approval.

The Orphan Drug Act, which offered enhanced marketing exclusivity and tax deductions to manufacturers who develope products for the treatment of rare or unprofitable conditions, has been a major success. This act demonstrates the utility of positive incentives in shaping industrial priorities, and provides a model for the development of targeted incentives in other key areas, such as post-marketing evaluation of "breakthrough" products.

As consumers demand broader access to new products earlier in the course of product development, a variety of schemes have been proposed for reducing requirements for pre-marketing evaluation. Such proposals necessarily require assurances that evaluation will be completed. The development of positive incentives, as proposed recently by the National Task Force on AIDS Drug Development, could help to provide such assurance. In particular, extensions of market exclusivity, and targeted tax deductions could help to stimulate vital research on approved products that will enhance the treatment of people with AIDS.

CHAPTER NOTES

1) Comparing the number of patients with CD4+ increases on therapy of 10% or 10 cells, 25% or 25 cells, or 50% or 50 cells

2) NAUC is a method for examining magnitude and longitude of a surrogate response

3) James J, ddI: Compassionate Access Announced, AIDS Treatment News #83, Jul 14 1989

4) Investigational New Drug, Antibiotic and Biological Drug Product Regulations: Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses, Federal Register, Vol 53;No 204, Oct 21 1988

5) Data suggested a survival deficit in antiretroviral-naive patients taking HIVID as compared to those taking Retrovir. In the case of Zerit, no virologic improvement was seen, although some immunologic benefit was measured

6) Speech before the FDA Antiviral Drug Products Advisory Committee, Sep 13 1994

7) The Big Lie Continues: FDA and the Treatment IND, PI Perspective, No. 4, Apr 1988
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10) Statistical Department, Pharmaceutical Research and Manufacturer's Association (PhaRMA), personal communication, Dec 3 1994

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24) c.f. Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, May 20 1994

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28) Office of Technology Assessment of the US Congress, Identifying Health Technologies That Work: Searching for Evidence, US Congressional Printing Office, 1994

29) James J, ddC, AZT Combination Approval Recommended, AIDS Treatment News #150, May 1 1992

30) Cotton D MD in Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, Sep 20 1993

31) Smith M MD in Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, Sep 20 1993

RETROVIR BRAND ZIDOVUDINE (AZT)

We agree that the drug is effective, the drug is toxic, and we have a limited amount of knowledge about how long it is effective, in what populations.

Dr. Douglas Richman
Transcript of a Hearing of the FDA's Anti-infective Drugs Advisory Committee, Jan 16 1987

The real question is how to you make the drug available to those subpopulations of HIV-infected individuals who clearly need it and for whom it clearly has a really beneficial effect, and at the same time, how you restrict its use for those individuals for whom it may actually be toxic or detrimental rather than beneficial.

Dr. Stanley M. Lemon
Transcript of a Hearing of the FDA's Anti-infective Drugs Advisory Committee, Jan 16 1987

On Friday, January 16th, 1987, the FDA's Anti-Infective Drugs Advisory Committee heard evidence regarding the safety and efficacy of Retrovir brand zidovudine. Results of two clinical studies were presented, as well as a variety of pre-clinical data. Two sets of data were presented from an ongoing phase II clinical study,

1) information that had been made available to the study's Data Safety Monitoring Board (DSMB) in September of 1986, when the DSMB recommended that the study be halted, and that patients assigned to placebo be treated with AZT, and
2) more current follow-up data.

Ellen Cooper, a Medical Officer in the Division of Anti-Infective Drug Products, remarked,

I have been involved with the development of this drug since it first came to the attention of the Agency in a pre-IND meeting with Burroughs Wellcome, in April of 1985. A remarkable story in drug development followed, as most of you are aware, and today we are meeting barely a year and a half after the first patient received AZT to discuss whether or not it should be approved for general use, a rapid pace indeed.[1]

Dr. Sandra Nusinoff Lehrman presented preliminary *in vitro* data on AZT, including information on the drug's ability to selectively inhibit reproduction of HTLV-III/LAV, HIV, as well as several other oncogenic and non-transforming mammalian retroviruses, and selective gram-negative bacteria "which may be pathogens in immunocompetent or immunocompromised patients."[2]

Dr. Ken Ayers presented animal studies from rats, monkeys and cats. The most common adverse experiences were non-dose-related leukopenia and thrombocytopenia; in animals treated with high doses of AZT, vomiting with blood and blood in the feces were seen. AZT was "weakly mutagenic" in the mouse lymphoma cell mutagenicity assay, but was negative on the Ames bacterial mutagenicity assay.

Dr. Mary Maha presented clinical results from a phase I study, which enrolled 23 AIDS patients and 12 ARC patients. The highest tolerated oral dose for the longest time was 500mg/q4h.

The most significant toxicities associated with AZT use were

- Probable bone marrow suppression, identified by onset of anemia (38 events in 20 patients), requiring:
  - 3 dose reductions
  - 10 dose interruptions
  - 3 discontinuations

- ✦ 4 transfusions
- ✦ 13 additional patients received one or more transfusions along with dose modification

10/20 patients with anemia also developed leukopenia or neutropenia or both

- Leukopenia (36 events in 20 patients). 3 events required discontinuation of treatment.
- Neutropenia (24 events in 19 patients).
- Occasional thrombocytopenia. (10 events in 7 patients). 1 event required discontinuation of treatment.

Eleven patients (9 AIDS/2 ARC) acquired 15 opportunistic infections (OIs) after three or more weeks of AZT dosing. Three out of twelve ARC patients progressed to AIDS. Eleven patients died. Seven deaths occurred less than one month after discontinuation of AZT or withdrawal.

After an initial 6-8 wks dosing, nine out of twenty-eight patients gained a mean of 4.3 kg. Fourteen out of twenty-nine patients experienced weight gain or maintained weight gain during chronic dosing.

Three out of four patients with neurologic symptoms had improvements including:

- 1 peripheral neuropathy
- 2 improvement in motor coordination
- 3 improvements in dementia

Twenty-three out of twenty-eight patients had increases in CD4+ lymphocyte counts. During chronic administration, ten out of twenty-eight patients had sustained or increased CD4+ counts.

Twenty-five out of twenty-seven patients were anergic at entry. Nine of the twenty-five anergic patients developed a positive skin test to one or more skin test antigens during the course of the study.

Dr. Margaret Fischl presented results from BW02, a large-scale, randomized, double-blinded efficacy study of AZT in relatively late-stage patients.

RESULTS OF BW02[3]

	AZT	PLACEBO	P-VALUE
N	145	137	
ARC	60	62	
AIDS	85	75	
DEATH			
Total	1	19	
ARC	0	7	
AIDS	12	1	
CD4>100	0	4	
CD4<100	1	15	
PROJECTED PROBABILITY OF 24 WK SURVIVAL			
Total	0.98	0.78	<0.001
AIDS	0.96	0.76	<0.001
ARC	1.00	0.81	<0.016
CD4+>100	0.96	0.7	<0.001
CD4+<100	1.00	0.91	0.028
PROJECTED PROBABILITY OF OI IN THE 24 WK STUDY PERIOD			
Total	0.23	0.43	<0.001
AIDS	0.36	0.54	0.004
ARC	0.09	0.30	0.066

DISTRIBUTION OF OPPORTUNISTIC INFECTIONS[4]	AZT	PLACEBO
Total	25	50
PCP	13(52%)	26(52%)
MAC	6(24%)	8(16%)
Dis. CMV	0	3(6%)
Herpes s.	0	2(4%)
Esoph. cand.	0	5(10%)
Cryptosporidium	1(4%)	0
Toxo	2(8%)	4(8%)
Cryptococcosis	2(8%)	2(4%)

Median Karnofsky score at baseline was 89, with significant improvement favoring drug at weeks 8,12, 16, and 20. No significant improvement was seen at week 24.

Significant improvements were seen in CD4+ lymphocyte counts at weeks 4, 8, 12, 16, 20, and 24, with the exception of high CD4+ patients at week 24.

No significance difference was seen between the two groups in anergy conversions.

While efforts were made to find evidence of *in vivo* antiviral activity, no such evidence was found.

In the follow up data presented, which were current up to several days before the advisory committee hearing, there had been some slight changes in the distribution of morbidity and mortality:

FOLLOW UP DATA FROM BW02[5]		
CUMULATIVE MORTALITY	AZT	PLACEBO
Total Deaths	8	32
ARC	1	10
AIDS	7	22
CD4+>100	1	5
CD4+<100	7	27
OPPORTUNISTIC INFECTIONS		
OIs (total)	51	69
# of pts w/ OIs	24	45

Sandra Lehrman presented data on the safety of AZT. Two hundred and twenty-one of 282 participants reported at least 1 adverse event. One hundred and twenty-two AZT patients reported an adverse event, as compared to 99 placebo patients. Nausea, myalgia & insomnia were the only adverse experiences reported statistically more frequently in AZT recipients. Although number of headaches was the same in both groups, AZT patients had significantly increased severity.

However, laboratory toxicities were more severe:

HEMOGLOBIN DECREASES[6]	PLACEBO	AZT
<7.5gHGB	4%	25%

Patients who entered the study with CD4+ counts less than 100/mm^3 had significant evidence of marrow suppression and decreases in neutrophil numbers, often requiring multiple transfusions:

TRANSFUSION REQUIREMENTS IN BW02[7]

	AZT	Placebo
Transfusion	31%	11%
Multiple Transfusions	21%	4%
AIDS/Transfuse	46%	15%
ARC/Transfuse	10%	6%

Only CD4+ lymphocyte count at entry was related to the later development of anemia.

Dr. Christopher King presented data from the Treatment IND, which provided treatment to 3,247 patients between the closing of the trial and the advisory committee hearing. A total of 488 adverse events were reported (376 by mail, 112 by phone), and 97 deaths.

Dr. Cooper then summarized the data:

> I think the major strengths are that there is a highly significant difference in mortality between the two treatment groups, a highly significant difference in the time to first OI between the two treatment groups, and the fact that the efficacy of the drug is also supported by the analyses of lesser clinical efficacy parameters, as you heard, such as weight change, Karnofsky performance status, and some selected immunologic parameters.
>
> The weaknesses include the following points. One is that the optimal dose is not clear. There were many dose changes and temporary discontinuations of therapy in the placebo- controlled study, and also in the Phase I study, but they were not done, necessarily, according to uniform criteria...Secondly, as we all know, the duration of therapy was short in the placebo-controlled trial. It is a disease for which we expect to treat people for life, and so there are some obvious questions: Will the efficacy last? Will toxicity accumulate to intolerable levels with longer exposure?
>
> Thirdly, the range of patients studied in the controlled trial in terms of their stage of disease was narrow. Again, as has been brought up several times, certainly we expect broader use, where there are really no safety and efficacy data.
>
> Fourthly, there is a paucity of animal data, as I referred to earlier, and a lack of virologic confirmation of the *in vivo* efficacy — although, of course, that is a small point, I think, considering the state of the art of culturing persons on therapies for HIV
>
> In conclusion, I would like to remind the committee and everyone present that, once a drug is approved for marketing, it is very difficult to withdraw it. The FDA, in representing the public, has no way of ensuring that needed preclinical and clinical studies are done once approval is granted. The company may agree to perform certain studies prior to approval, but there is no practical way of enforcing these commitments.[8]

Dr. Hughes noted

> I still do not have a grasp of what accounted for the fatalities in these patients. If I read Dr. King right, if 75 percent of these opportunistic infections were due to *Pneumocystis* — if that means 75 percent of the deaths were due to *Pneumocystis*,— then would a drug prophylactic for *Pneumocystis* produce the same effects on morality as we have with this drug? [9]

In general, the Committee agreed with the concerns raised by Dr. Cooper. After voting 10–1 for approval of Retrovir brand zidovudine, they attempted to determine what questions remained for them regarding use of the drug:

- Long-term use
- Dosing
- Resistance
- Risk/benefit in ARC
- Mechanisms of anemia
- Long-term toxicity

CHAPTER NOTES

1: Transcript of a Hearing of the FDA's Anti-infective Drugs Advisory Committee, Jan 16 87

2: ibid

3: ibid

4: ibid

5: ibid

6: ibid

7: ibid

8: ibid

9: ibid

TREATMENT IND & THE BUSH INITIATIVE

On June 22, 1987, the FDA implemented regulations that were designed to allow pre-approval distribution of therapies "intended for treatment of serious or immediately life-threatening conditions in patients for whom no satisfactory alternative therapy or drug exists." The policy was known as the "treatment IND."

Specifically, the policy may be divided into three areas:[1]

1. **Distribution of Investigational Drugs for Treatment Purposes:** The regulations allowed distribution of investigational drugs for the purpose of treatment when six criteria have been met:

   a: The drug is intended for treatment of serious or immediately life-threatening disease. The agency noted that "immediately life-threatening" could be understood to include asymptomatic HIV infection, and would generally apply to "diseases in which premature death is likely without treatment."

   b: There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population.

   c: The drug is under investigation in a controlled clinical trial under an IND or all clinical trials have been completed.

   d: The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with all due diligence.

   e: The FDA Commissioner determines that the drug "may be effective" for its intended use in its intended patient population.

   f: The FDA Commissioner determines that distribution of the drug "would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury."

2. **Cost Recovery for Distribution of Experimental Drugs:** This was the most controversial aspect of the regulations, as it allowed companies to charge patients who received drugs before marketing approval, either through clinical trials or through the treatment IND. Advertising of unapproved products explicitly remained prohibited, as was "charging a price larger than necessary to recover costs of manufacture, research, development and handling of the investigational drug." FDA noted that

   > The agency...should not be put in a position of being a price regulator and has, therefore, drafted the final rule to minimize the degree to which it will have to act in this area...FDA would limit its expenditure of resources by requesting sponsors to include in their requests for prior approval (clinical trial) or prior notifications (treatment IND) a certified statement that, consistent with generally accepted accounting principles, the requested price is not greater than necessary to recover the costs associated with the manufacture, research, development and handling of the investigational drug.[2]

3. **Clinical Holds and Requests for Modification:** A treatment IND or treatment protocol could, according to these regulations, be placed on clinical hold and terminated or modified if any of the criteria for eligibility fail to be met (such as the emergence of a "comparable or satisfactory alternative drug or

other therapy to treat that stage of the disease in the intended patient population"), or if the available scientific evidence "fails to provide a reasonable basis for concluding that the drug may be effective for its intended use."

In general, this policy represented a change in that it allowed for pre-approval distribution of drugs to classes of patients, rather than through individual patient applications to the FDA.

In addition, the policy created a new standard for regulatory review: drugs released under the treatment IND regulations had to show that the available scientific evidence provided the Commissioner with "a reasonable basis...for concluding that the drug may be effective for its intended use in its intended patient population."

Immediate response to the draft regulations was divided: some groups, including the National Gay & Lesbian Task Force (NGLTF) were concerned that the proposal amounted to basic deregulation. Other groups, such as San Francisco's Project Inform, offered moderate support for the regulations:

> Project Inform and other groups find this proposal, although less than perfect in some regards, to be a clear response to the demands gay people have made for improved access to experimental treatments.[3]

Similarly, the American Foundation for AIDS Research (AmFAR) testified before the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS ("The Lasagna committee") that

> While [the safety and efficacy standard imposed by the treatment IND regulations] appears, on its face, to be appropriate, agency interpretation of "effectiveness" needs to be flexible. Agency standards of efficacy for the treatment IND must be significantly less stringent than those applied for general drug approval for marketing purposes for these regulations to fulfill their intended purpose of accelerating the availability of experimental drugs. We believe that once tolerable toxicity levels are established, a less stringent standard of efficacy should be applied taking into account the seriousness of the condition or symptom being treated...Finally, the FDA needs to work closely with drug sponsors to resolve obstacles that have prevented full use of treatment INDs including those related to necessary documentation, cost controls, and potential risks to NDA approval.[4]

However, within a few months the activists were dissatisfied with the implementation of the regulations, calling the treatment IND "little more than a political smokescreen, offering only false hope and empty promises."[5]

> Since June of 1987, the Food and Drug Administration has lied to the media, the Congress, the Presidential AIDS Commission, and people concerned with AIDS. All have been told that a major advance has occurred which is speeding the delivery of experimental drugs to those in need. In fact, AIDS patients are caught in an ever-tightening squeeze by (1) [FDA] Commissioner Young's inability to control his own agency, (2) Dr. Ellen Cooper's misguided consumer protectionism, and the Pharmaceutical Manufacturers Association's jealous defense of the right to do "business as usual."[6]

In particular, the activists were concerned that the efficacy standard relied on the discrimination of the FDA Commissioner. Project Inform proposed that a new standard be imposed for rejecting an application for treatment IND, requiring that "non-efficacy be clearly indicated in the scientific record." In addition, the activists complained, key staff members within FDA were preventing drugs from being released through the treatment IND program.[7]

In response to the activists concerns, on October 21, 1988, FDA announced a new policy, known as "The Bush Initiative," after Vice-President George Bush, to speed approval of new therapies intended to treat

life-threatening and/or severely debilitating illnesses. The new regulations were based on the Agency's successful intensive involvement in the development of AZT.

The policy contained four major points:[8]

1. **Risk/Benefit Analysis:** FDA proposed to evaluate the aggregate data following completion of phase II trials utilizing a "medical risk/benefit analysis" and to invite submission of an NDA when appropriate. This analysis was intended to incorporate information on the severity and probable outcome of the disease, the existence of satisfactory alternative therapy, and the known and potential risks of the drug. FDA would attempt to reach a "scientifically defensible decision based on the results of well-designed phase II controlled clinical trials." Rather than reducing efficacy standards, the policy proposed to reduce (but not eliminate) requirements for reproduction and elaboration of data that would traditionally occur in phase III studies. The agency noted nonetheless that, while in a few cases, the results of a "well-designed multi-center trial" would be accepted as a basis for approval, in general more than one study would be required

2. **Early Consultation:** To ensure that, when appropriate, phase II trials would generate the quality and quantity of data necessary to meet the requirements for approval of an NDA, FDA suggested consultation between relevant agency staff, investigators, and sponsors following completion of phase I studies. This consultation was intended to address key issues related to the design and implementation of phase II trials, to ensure that all necessary questions were answered by the trials. In addition, FDA offered its consultative services regarding the design and implementation of pre-clinical and phase I studies.

3. **Post-marketing Studies:** These regulations also authorized FDA to negotiate with pharmaceutical sponsors, trading earlier approval for a commitment to rigorous post-marketing studies. Examples of data that could be collected after NDA approval included optimal dosing and dosing schedules, chronic use data and new patient populations.

4. **Focused Research on Rate-limiting Aspects of Drug Development:** The policy set out guidelines whereby FDA may conduct "limited, focused research on rate-limiting aspects of the pre-clinical, chemical/manufacturing and clinical phases of drug development and evaluation."

CHAPTER NOTES

1) Federal Register, Vol 52, No 99, May 22 87

2) ibid

3) Major FDA Proposal on Experimental Drugs: Gay Activist Groups Divided in Response, PI Perspective, #1, Apr 1 1987

4) Silverman M, Testimony of the American Foundation for AIDS Research before the National Committee to Review Current Procedures of the Approval of New Drugs for cancer and AIDS, May 2 1989

5) False Hope: Smoke and Mirrors from the FDA, PI Perspective, Oct 1987

6) ibid

7) ibid

8) Federal Register, Vol 53, No 204, Oct 21 1988

MORE INFORMATION ABOUT RETROVIR BRAND ZIDOVUDINE

The delay in submitting additional information makes rapid judgements very difficult, especially in the politically charged atmosphere of AIDS where a single study is frequently perceived as fact in the eyes of the public and the patients. There are innumerable examples in the medical literature where a certain positive finding was then found to be somewhat in disrepute or incorrect on the weight of subsequent evidence.

Steven Gitterman, MD, Medical Officer, Division of Anti-Viral Drugs, US FDA in Transcript of a Hearing of the Antiviral Drug Products Advisory Committee, Jan 19 1990

We have not answered critical questions. We have gone around this before here. We do not know that long-term AZT versus long-term placebo will confer a long-term survival advantage. The chances are we will never know that unless, for whatever reason, some of the placebo studies are allowed to continue. My own guess is that they will not be able to answer the question either ultimately.

Paul Volberding, MD, University of California/San Francisco in Transcript of a Hearing of the Antiviral Drug Product Advisory Committee, Jan 19 1990

On January 29, 1990, the newly-formulated Antiviral Drug Products Advisory Committee of the FDA met to hear new evidence regarding the safety and efficacy of Retrovir brand zidovudine.

Burroughs Wellcome's Dr. Barry opened the presentation with a precautionary note about the data set:

> As in the case of clinical practice throughout the AIDS epidemic, we rarely, if ever, have had as complete a data base as we would have preferred in an ideal world in order to make decisions which were immutably correct. We have had to work in the real world in order to help those patients and, therefore, make decisions which were sometimes half a step ahead of the complete data base in order to gain on an epidemic which has had several years head start on us.[1]

Dr. Kenneth Ayers, a Senior Toxicologist from Burroughs Wellcome Company, made the first presentation regarding possible carcinogenicity of AZT. Animal studies had demonstrated that the drug could induce

> benign and malignant vaginal tumors in mice given the adjusted dose levels of 30 or 40mg/kg/day, and malignant vaginal tumors in rats given an adjusted dose level of 300mg/kg/day.[2]

VAGINAL TUMORS IN RATS AND MICE[3]

	Benign	Malignant	SQC*
Mice			
40mg/kg/day	2	5	0
20mg/kg/day	0	0	1
Rats			
300mg/kg/day	0	0	2

* squamous cell carcinoma

All tumors were non-metastasizing and were detected through microscopic examination of tissues at autopsy.

Ayers noted that vaginal tumors are rare, and mechanisms are not well understood.

> We are still in the very early stages of our thinking with regard to possible mechanisms of pathogenesis of these zidovudine-induced vaginal tumors...We are considering the possibility that chronic local contact with high urine zidovudine concentrations may play a role in tumor formation.[4]

He hypothesized that the mechanism by which AZT induces tumors might be related to high concentrates of zidovudine excrete in the rat and mouse urine as compared to humans, and to the highly replicative epithelial surface in the rat and mouse vagina.

Finally, he noted that "With Retrovir, the unknown risk posed by the rodent carcinogenicity results must be balanced against the known risk of untreated HIV infections."[5]

FDA commented that

> If the toxic effect is related to peak levels, then mice will be predisposed to seeing that toxicity because they have higher peak levels. If the toxicity is related to average exposure or total exposure, then the two species are very similar. It seems that things like myelosuppression are much more closely related to average exposure or total exposure.[6]

On March 31, 1989, a group of researchers had published data in *Science* regarding reduced sensitivity to AZT in HIV isolates from patients who had undergone extensive AZT treatment. Isolates from patients who had been treated for less than six months were virtually indistinguishable from isolates from untreated patients. However, isolates from 5 patients who'd received high-dose AZT treatment showed reductions of sensitivity of 100-fold or more. The authors noted that the reduction in sensitivity did not correlate with deterioration in clinical status.[7]

Dr. Marty St. Clair and Dr. Sandra Lehrman presented data on AZT resistance. In 22 AIDS patients treated with AZT for more than one year, the median IC_{50} (a test of how much drug can to reduce a viral population by 50 percent) was 1.62mcg/ml, or 32-fold higher than the IC_{50} of 0.05mcg/ml found in untreated controls.[8] In six AIDS patients who had received more than one year each of AZT treatment, and who were "no longer responding to therapy and declining rapidly," the median IC_{50} was 2.9mcg/ml, or 59-fold higher than the controls.

In addition, data were presented on asymptomatic patients from the low-CD4+ cell count substudy of ACTG 019, a study of AZT versus placebo in asymptomatic patients.

ACTG 019 RESISTANCE DATA[9]

Treatment	N	Mean AZT (mos)	IC_{50}
Placebo	8	0	0.05mcg/ml
AZT	11	17.5	0.08mcg/ml
500mg/day	5	17.5	0.07mcg/ml
1500mg/day	6	18	0.07mcg/ml

Dr. Lehrman concluded that

> For patients with no symptoms or early symptomatic HIV infection, viruses with altered *in vitro* sensitivity are detected later in the course of treatment and in a much smaller proportion of individuals. When these changes of sensitivity are detected, the magnitude of change is much less.

Dr. Barry noted that no significant cross-resistance had been found between AZT and the other nucleoside analogues, although some minor cross-resistance had been noted between AZT, d4T and AZDU.

Dr. Margaret Fischl of the University of Miami then presented results from ACTG 002, a large-scale study of high-dose versus low-dose AZT in patients with AIDS who had experienced one bout of PCP, and who, with the possible exception of minimal Kaposi's Sarcoma, were presently asymptomatic.

Participants were randomized to receive 1500mg AZT/day or a loading dose of 1200mg AZT/day for one month, followed by 600mg AZT/day. Endpoints were time to first critical event, including death, or a new or recurrent AIDS-defining opportunistic infection or malignancy. Due to the difficulties in diagnosis, dementia and wasting were excluded as endpoints.

OUTCOMES FROM ACTG 002[10]

	High-dose#	Low-dose#
TOTAL ENROLLED	276	276
Lost to follow-up	14	14
N for analysis	262	262
Median follow-up	26.1mos	25.4mos
ENDPOINTS		
Death	169 (72%)	170 (65%)
Malignancy	34 (13%)	49 (19%)
OIs	241 (92%)	234 (89%)
TOXICITY		
Serous anemia	39%	29%
Serious neutropenia	51%	37%
Required dose-modification	87%	33%

Dr. Fischl concluded that

> Low-dose treatment appeared to be as effective as standard treatment as far as survival and occurrence of opportunistic infections were concerned. In fact, there appeared to be a better survival in the low-dose treatment group, most likely related to the ability to give a greater proportion of continuous anti-HIV therapy.[11]

Dr. Fischl then presented results from ACTG 016, a study of AZT versus placebo in patients who were mildly symptomatic.

Participants were required to be HIV-infected, with 200-800 CD4+ cells/mm^3, and or have one or two symptoms including: oral candidiasis, oral hairy leukoplakia, recent zoster, chronic seborrheic dermatitis, chronic pruritic folliculitis, weight loss (10 percent body weight or 10lbs), intermittent diarrhea, documented fatigue with interrupted ability but still able to work.

Endpoints included an AIDS-defining OI or malignancy, or AIDS dementia, or "advanced ARC," which included two consecutive CD4+ cell counts of less than 200 taken at least two weeks apart, and two symptoms of progressive disease, including: recurrent oral candidiasis, oral hairy leukoplakia, recent zoster, profound weight loss, persistent fever, and severe persistent diarrhea.

Patients were randomized to receive 1200mg AZT/day or a placebo. Enrollment was terminated 4 months after completion of enrollment "due to a significantly lower progression rate in the AZT arm."[12]

RESULTS OF ACTG 016[13]			
	AZT	PLACEBO	
TOTAL N	351	360	
<250 CD4+ cells	253	260	
>250 CD4+ cells	98	100	
Median follow-up	11 mos	11 mos	
Median length treatment	9 mos	8 mos	
Loss to follow-up	20	8	
ENDPOINTS:	15	36	
ARC	8	15	
AIDS	5	21	
Death[14]	2	0	
<500 CD4 ENDPOINTS	12	34	
ARC	8	15	
AIDS	3	18	
Death	1	0	
>500 CD4 ENDPOINTS	3	2	
ARC	0	0	
AIDS	2	2	
Death	1	0	
8 mos Event-free survival	91%	81%	
18 mos Event-free survival	90%	76%	
ADVERSE EVENTS			P-VALUE
Malaise or fatigue	275	238	0.012
Nausea	243	162	<0.0001
Vomiting	98	56	<0.001
Bloating	12	3	0.034
Dyspepsia	17	5	0.015
Rectal pain	1	12	0.001
Parasthesias	1	7	0.036
Upper Respiratory tract bleeding	6	16	0.03
Serious anemia	17	0	
Serious neutropenia	15	5	
Myopathy	4	1	

Dr. Fischl noted that

> The number of subjects enrolled in the second stratum [>500 CD4 cells] was small. It was felt that based on the number of patients in the study and the need for long-term follow-up, which probably could not be realized, unfortunately, this study did not have a large enough sample size in this stratum to answer the question of whether zidovudine was effective or not for individuals who had mildly symptomatic disease and greater than 500 cells.[15]

She also observed that

> in the zidovudine group there was an increase in the number of CD4 cells. This occurred early in the study. It persisted through the first 24 weeks of therapy. Then there was a slow decline to baseline by about week 40 or 44. Then there was a decline to below pretreatment values. In the placebo group there was a progressive decline in CD4 cells.[16]

Dr. Paul Volberding of the University of California/San Francisco then presented data from ACTG 019, a study of high-dose AZT versus low-dose AZT versus placebo in asymptomatic HIV-infected patients with less

than 500 CD4+ cells. Endpoints were AIDS, death and advanced ARC, using the same definition as ACTG 016. Initial allocation was 3:2:2 favoring placebo, however the rules were changed to allocate at 1:2:2 during enrollment, resulting in a slightly longer time on therapy for placebo patients.

OUTCOMES FROM ACTG 019[17]

	(Group I) Placebo	(Group II) 1500mg AZT	(Group III) 500mg AZT	(I/II) p-value	(I/III) p-value
N Mean Follow-up Voluntary drop-out Lost to Follow-up	428 61wks 111 41	453 51wks 81 19	457 55wks 73 13		
Endpoints: AIDS ARC	 33 7	 14 6	 11 6		
Events/100 patient years	6.6	3.1	2.3	0.02	0.0001
Median CD4+ change/year	-16	+26	+39		
% p24ag+ pts w/ p24ag reduction <50% at 48wks	20	70	50		
Adverse Events Serious anemia Serious neutropenia SGOT/SGPT elevation Nausea	 1 7 15 1	 29 29 10 23	 5 8 14 14	 0.10 0.78 0.86 0.001	 <0.0001 <0.0001 0.46 <0.001

Dr. Volberding concluded that

> What we have shown is consistent progression in our understanding about this drug and that using it earlier is effective; not as effective as we would like, but it does work..in terms of HIV progression endpoints...To me, that, combined with the resistance information that we have heard which, looking at least at this preliminary point, shows that resistance is much less of a problem in early disease than late, would lead me to recommend prescribing the drug for patients with less than 500 CD4+ cells as an element of early intervention.[18]

However, Dr. John Hamilton, principal investigator of an ongoing Veterans Administration Study of early versus delayed treatment with AZT, noted that his DSMB had reviewed the data from ACTG 016 and ACTG 019, and had declined to terminate his study. He commented that

> The Antiviral Advisory Committee and the Food & Drug Administration may choose to alter the recommendations for the use of AZT in certain groups of patients with early symptomatic or asymptomatic HIV infection. However, we would urge that such recommendations acknowledge the current lack of data concerning the long-term benefits for patients with early versus late or delayed treatment with AZT, and emphasize the need for continuation of studies, such as our own, which are designed to provide this information.[19]

In the FDA review of the data, Dr. Steven Gitterman basically agreed with Drs. Fischl and Volberding's analyses of their results, however he cautioned

> The studies do appear to show a clinical benefit for intervening with drug at earlier stages of disease. Despite this conclusion, which I do believe is real, I would still be less sanguine about directly translating results from these studies to a uniform recommendation that zidovudine is indicated for all patients with CD4 counts greater than 200.

I say this for a few reasons. One is that most obvious is that, in contrast to symptomatic patients — and I am sure this is obvious to the committee — asymptomatic patients are, by definition, feeling well and are now being treated with a drug that does cause adverse reactions...More importantly, we really have very little, if any, idea at this time of what the long-term cumulative toxicities of this drug are...These trials must be considered short-term and they did not evaluate zidovudine use in a manner that will most likely be used in clinical practice, that is, with patients who are symptomatic or patients with low CD4 counts...

We do not have a clear picture of how long AZT is beneficial and whether long-term benefits will actually outweigh toxicity.[20]

In summarizing, Dr. Barry sounded the themes of patient choice that would inform the patient advocacy movement for years to come:

Our discussions have identified a number of other issues for which neither I nor others can provide definitive answers because of uncertainties that have become the watchword of patient management with this disease.

They generally revolve around the issue of whether early treatment will provide benefits to patients three, four, five or even more years from now. The issue really boils down to the decision by both doctor and patient of whether it is better to derive immediate benefits and hope for the future, both clinically and for new therapies, or to await the certainty that can only be obtained by multi-year observation. I believe there are issues impacting on this decision that will vary from patient to patient and from doctor to doctor and that this decision should best be determined by the patient and his or her doctor, based on their knowledge, circumstances and wishes.

...The only way that patients and doctors can truly have such freedom of decision and provide access of AZT, should the patient and physician decide on earlier therapy, is to include that option in the package insert. Not to do so, I believe, will create great inequities in access and some significant degrees of frustration and confusion with patient management and clinical research spheres.[21]

During the committee discussion, a number of questions were raised:

- Would AZT confer a long-term benefit in reduction of opportunistic diseases?
- Could secondary toxicities, such as malaise, nausea and vomiting, be managed?
- What was the clinical meaning of resistance?
- Was there cumulative toxicity, such as cancer, that could change the risk/benefit ratio for asymptomatic patients?
- Would early AZT therapy confer a survival benefit?

In response to this last question, Dr. Barry gave an eloquent speech on ethics and clinical research methodology:

It should be pointed out that these studies which dealt with patients in early stages of infection and disease were never intended to look at survival benefits. I also sincerely hope that we are leaving the days of HIV clinical research when death is an endpoint. It is clear that compassion and necessity have driven surrogate markers to be our guideposts of evaluation. In this respect, AZT does very well.[22]

With the committee's support, the FDA expanded the indication for AZT to include patients with less than 500 CD4+ cells.

CHAPTER NOTES

1) Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, Jan 19-20 1990

2) ibid

3) ibid

4) ibid

5) ibid

6) ibid

7) Larder B et al., Science, Mar 31 1989

8) Transcript, op cit., Jan 19 1990

9) ibid

10) ibid

11) ibid

12) ibid

13) ibid

14) "One patient died from head trauma in an automobile accident. Autopsy did not find any evidence of HIV disease. The second person was in his early 40s and had sudden death. Autopsy showed evidence of massive myocardial infarction. Neither death was believed to be related to HIV infection or treatment." Margaret Fischl in ibid

15) ibid

16) ibid

17) ibid

18) ibid

19) ibid

20) ibid

21) ibid

22) ibid

THE VA STUDY: CONFLICTING INFORMATION ABOUT RETROVIR BRAND ZIDOVUDINE

I think the FDA needs to avoid the temptation, which it would get in such a high-pressure situation, to always think that it has to define the standard of care for HIV disease in this country...FDA should only be licensing drugs as safe and as effective for whatever indication. Then researchers, clinicians and people with HIV can go on and find out what is really the optimal way to use them.

Mark Harrington, ACT UP/New York
Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, Feb 14 1991

I think we all hoped that the VA study would be confirmatory. In HIV disease we are all in a hurry because we want answers, we want treatments, we want perhaps a cure sooner rather than later. But we are approving things in the absence of confirmatory studies. I think I am somewhat disappointed, in fact, that what I was hoping we might see from the study did not come through, and that is a survival advantage.

Donald I. Abrams, MD, University of California/San Francisco
Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, Feb 14 1991

On February 14, 1991, the committee convened to hear information regarding results of VA 298, a study of early versus late treatment with AZT. The entire subject was rife with controversy, as early results of subset analyses had been printed in the media, offering patients the message that AZT harmed patients of color.

FDA's Dr. Paul Beninger opened the meeting with a review of FDA's decision the previous year to license AZT for treatment of patients with less than 500 CD4+ cells/mm^3. At that time, Dr. Beninger observed,

> Major questions concerned the absence of long-term survival data, possible long-term toxicity and the impact of treating large numbers of individuals at a time when the actuarial risk of progression to AIDS was small.[1]

Dr. John Hamilton of the Veterans' Administration (VA) presented results of the study.

BASELINE CHARACTERISTICS OF PATIENTS IN VA 298[2]

CHARACTERISTIC	EARLY THERAPY	LATE THERAPY
N	170	168
200-299 CD4+ cells/mm^3	49 (29%)	45 (27%)
300-500 CD4+ cells/mm^3	121 (71%)	123 (73%)
Race — no. (%) of patients		
Non-Hispanic White	107 (63%)	111 (66%)
Black or Hispanic	63 (37%)	57 (34%)
CD4+ count (/mm^3)	359.7±83.4	348.7±76.9
Serum p24 Antigen — no (%) of patients		
Positive	31 (18%)	32 (19%)
Negative	128 (75%)	130 (77%)

According to Dr. Hamilton

> Early zidovudine delayed progression to AIDS as compared to later treatment, but no benefit for

either treatment arm was detected for survival or the combined clinical endpoints of AIDS and death.[3]

Finally, Dr. Hamilton remarked that, in his study, "Early zidovudine resulted in trends towards benefit in white and neutral or harmful effects in Black/Hispanic patients."[4]

MAJOR CLINICAL END POINTS FROM VA 298[5]

End Point	Early Therapy	Late Therapy	P-Value*	Relative Risk (85% CI) †
DEATH	23	20	0.48	0.81(0.44-1.59)
AIDS-related	13	12		
Non-AIDS-related				
With HIV progression	6	8		
Without HIV progression	4	0		
Progression to AIDS	28	48	0.02	1.75(1.10-2.80)
Other illness ‡	1	3		
AIDS or Death	38	48	0.25	1.29(0.84-1.97)

* By log-rank test
† CI denotes confidence interval
‡ The other illness in the early-therapy group was pneumococcal meningitis; in the late-therapy group it was Hodgkin's disease (one patients) and nephrotic syndrome (two patients).

MAJOR CLINICAL END POINTS ACCORDING TO SUBGROUP IN VA 298

ENDPOINT	EARLY THERAPY # OF PATIENTS	EARLY THERAPY # OF EVENTS	LATE THERAPY # OF PATIENTS	LATE THERAPY # OF EVENTS	P-VALUE*	RELATIVE RISK
DEATH						
CD4+ cells						
200-299/mm^3	46	9	45	11	0.85	1.09
300-500/mm^3	124	14	123	9	0.25	0.62
Serum p24 Antigen†						
Positive	31	7	32	4	0.35	0.54
Negative	128	13	130	13	0.73	0.91
IV Drug Use						
Yes	51	7	41	2	0.1	0.37
No	119	16	127	18	0.97	0.96
Race or ethnic Group						
Hispanic	15	3	16	0	0.07	--
Black	48	6	41	2	0.15	0.36
Non-Hispanic White	107	14	111	18	0.79	1.12
PROGRESSION TO AIDS						
DEATH						
CD4+ cells						
200-299/mm^3	46	9	45	19	0.06	2.13
300-500/mm^3	124	19	123	29	0.12	1.59
Serum p24 Antigen†						
Positive	31	10	32	11	0.98	0.96
Negative	128	14	130	34	<0.01	2.22
IV Drug Use						
Yes	51	11	41	10	0.99	1.00
No	119	17	127	38	0.01	2.5
Race or ethnic Group						
Hispanic	15	4	16	3	0.44	0.66
Black	48	8	41	10	0.7	1.25
Non-Hispanic White	107	16	111	35	0.01	2.33

* By log-rank test
† Only 321 patients were tested for serum p24 antigen

Dr. Hamilton then presented a series of comparisons designed to determine whether the difference in death rates for patients of color was genuine:

> Looking now at progression to AIDS, deaths and combined endpoints, what one sees first in those who were not IV drug abusers is no benefit of one treatment arm versus another in deaths, as we have previously stated; no difference in combined endpoints; and the same highly statistically significant difference in progression to AIDS favoring early therapy. This is what was seen in the group overall and is not a surprise when looked at in those who have potentially no confounding variables.
>
> When one looks at individuals who are IV drug abusers, the differences are somewhat different. Although there are no statistically significant differences between early and late therapy, one sees some disturbing trends, the importance of which has yet to be determined. You see no significant difference in delay in progression to AIDS in patients who are IV drug abusers or have a history of IV drug abuse; no difference in deaths and no difference in the combined endpoints.
>
> Looking again at endpoints...what one sees among white patients is the same benefit in progression to AIDS, a highly statistically significant difference; no significant difference in death or the combined endpoints among white patients..
>
> There were no significant differences in progression to AIDS among black/Hispanic patients, regardless of treatment arm. There were no signficiant differences in the combined endpoints of AIDS or death in black/Hispanic patients. They were marginally significant — by our standards not significant — but I think we would have to admit close differences between early and late therapy but in the opposite direction than you would have expected from the data indicated for the overall population. We see 9 deaths occurring in patients on the early regimen compared to one on the later regimen.
>
> We examined these data again by calculating relative risks. Without belaboring the point unnecessarily, what one sees is essentially the same thing among whites as was seen in the population at large. In the black/Hispanic patients using this parameter, focusing specifically on this relative risk for death, in addition to a very high relative risk reflecting the predominance of deaths, almost to the exclusion of deaths in the other group, what one sees is a very relative risk. But one also sees a very large confidence interval.
>
> These data and the insignificant difference on the p value led us to conclude as time went on that these data may be artifactual and for other reasons not truly the result of a biological effect.[6]

Dr. Steve Lagakos from the ACTG Statistical Center at Harvard, commented on minority subsets in ACTG 019:

> These data say that in 019 — again, this is a subset analysis and carries all the caveats of that, but the overall AZT effect that was observed in 019 is very consistent whether you look at the subset of blacks, hispanics or whites.[7]

Dr. Richard D Moore from the Department of Medicine and Epidemiology at Johns Hopkins then presented data from an observational study of patients from 12 geographically separate clinic sites in Maryland. Participants were required to have less than 250 CD4+ cells and an ARC diagnosis or less than 350 CD4+ cells and an AIDS diagnosis. All patients were taking AZT, and were followed for a maximum of two years.

RACIAL BREAKDOWN FROM JOHNS HOPKINS OBSERVATIONAL STUDY[8]	
No. patients	1044
White	743 (75%)
Black	157 (14%)
Hispanic	144 (10%)

RELATIVE RISK OF DEATH ACCORDING TO SEVERAL SECONDARY FACTORS[9]		
	HAZARD	P-VALUE
CD4+ count of <100 cells/mm^3	1.89	0.001
AIDS diagnosis	1.82	0.001
Total AZT treatment	1.72	0.001
Karnofsky Score	1.51	0.001
IVDU vs. Gay	1.33	0.09
Black vs. White	0.99	NS
Hispanic vs. White	1.1	NS

Dr. Moore noted that

> There is a marginally significant difference — I will stress "marginally" — comparing the white patients with the patients of color. But, as you can see, the difference is small at best.
>
> What we did find, however, when we went back and looked at various baseline enrollment factors, was that black and hispanic patients had significantly lower, on average, CD4 counts. Several other baseline factors that are associated with progression of disease tended also to be somewhat worse in black and Hispanic patients compared to the white patients...Adjusting for those variables, many of which were significant, we found absolutely no differences between whites and blacks or whites and Hispanics in survival in this population from enrollment.[10]

Dr. Julia Hidalgo from the Maryland Department of Health presented data from an observational study of 716 patients (229 white, 485 black) using the National Death Index for long-term follow-up. According to Dr. Hidalgo

> Those persons who were receiving... AZT had experienced substantial survival gains versus those who did not receive the drug. Within racial populations or ethnic groups, we found that among AZT takers there were no signficiant differences in their long-term survival. Among those who were not on the drug we also found no significant differences in survival for those two groups.[11]

Finally, Dr. Terri Creagh-Kirk from the Burroughs Wellcome Company presented long-term follow up on 4,805 patients enrolled in the treatment IND program between October 11, 1986 and March 24, 1987. Dr. Creagh-Kirk's data showed that

> When you look at survival, using as your starting point the time of diagnosis of AIDS, you see that actually Hispanics look slighly better than either blacks or whites. The difference between these three curves is slightly statistically significant.
>
> If you look at categorizing just by whites and people of color, again you see that there was a difference but this time people of color have slighly better survival than whites, again, counting from the time of diagnosis.
>
> If you then take as your starting point the time of starting AZT therapy, you see a little different picture. Again, Hispanics have slightly better survival but there are no statistical differences in these curves.[12]

After extensive discussion, the committee elected to recommend no signficiant change to the labeling of AZT other than the inclusion of this new data.

CHAPTER NOTES

1) Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, Feb 14 1991

2) Hamilton John D MD, A Controlled Trial of Early Versus Late Treatment with Zidovudine in Symptomatic Human Immunodeficiency Virus Infection, NEJM, Vol 326 No 7, Feb 13 1992

3) Transcript, op cit., Feb 14 1991

4) Hamilton J, op cit.

5) Transcript, op cit., Feb 14 1991

6) ibid

7) ibid

8) ibid

9) Engbretson J, Conference Update: FDA Antiviral Drugs Advisory Committee, Feb 14 1991

10) Transcript, op cit., Feb 15 1991

11) ibid

12) ibid

VIDEX BRAND DIDANOSINE (ddI)

I think it's important for everybody to remember that these drugs have to be treated with respect. They have the capacity to produce side effects we can't always predict. This isn't a cure for AIDS.
Samuel Broder, National Cancer Institute
in Chase M, Bristol-Myers Will Supply Its Drug ddI
To AIDS Patients Not Included in Trials, WSJ, Jul 14 1989

It's very good to think about compassionate ways to handle experimental drugs while adhering to the scientific methods needed to find out if they work well...But the only thing that will make a durable imprint is whether we can develop scientific knowledge or not.
Samuel Broder, NCI in Specter M, AIDS Drug
To Be Given At No Cost, Washington Post, Jul 14 1989

Regulators, researchers, drug companies and most AIDS activists all want these trials to get done right. We do not want the market flooded with safe but useless drugs.
Jim Eigo, ACT UP in Specter M, ibid

On July 13th, 1989, the Bristol-Myers Company made an important announcement:

> Bristol-Myers Company is investigating an anti-viral agent, ddI (2'3'-dideoxyinosine), for use against the AIDS virus. Phase I, an initial stage of the drug development process, is nearing completion and inquiries have been received regarding availability of ddI for patients on a compassionate basis before formal drug approval.
>
> Bristol-Myers Company will make ddI available to AIDS patients for whom treatment under an emergency or compassionate drug program would be appropriate: any patient who does not meet the criteria for phase II clinical trials, but for whom ddI is critical, would receive the drug under this plan.[1]

The decision was clearly a political victory for AIDS activists. While a few were cautious about praising the company before it made clear who would be eligible for early access to ddI, others were exuberant: "Hallelujah," ACT UP member Larry Kramer told the *LA Times*, "I pray that Bristol's magnificent example will be duplicated by the manufacturers of numerous other life-saving drugs."[2]

Activists had kept an eye on ddI for some time. In October of 1986, John James had written, "We have heard reports that better forms of AZT, equally effective but much less toxic, have been developed but not yet tested on humans."

In 1989, he wrote:

> The drug appears to be much less toxic than AZT, and the toxicities it does have are different—opening doors to more effective doses, as well as combination therapies.[3]

That same year, ACT UP/New York declared that ddI was "half as effective as AZT, but ten times less toxic."[4]

James did, however, sound a note of caution:

> Persons considering using ddI should realize that not everybody in the AIDS community thinks that this drug is beneficial. There are growing questions and concerns. This history of new drugs suggests caution, as serious side effects of AZT and ddC were not noticed in early trials.

> The best information we are hearing at this time is that ddI may add a year of life to persons who are burned out on AZT.

On July 28, 1989, phase I study results were released (summarized below). AIDS activists were excited:

> Mitchell Speer, the editor of the AIDS/HIV Experimental Treatment Directory, published by the American Foundation for AIDS Research, said ddI was the best new antiviral drug his group had seen. "There is no other drug like it," Mr. Speer said. He added that if ddI "continues to show the kind of clinical results that have been demonstrated so far, the probability is that ddI will be the drug of choice over AZT.[5]

In October, 1989, phase II studies began, and patients started to enroll in the expanded access program.

Patients who had proven intolerant to AZT, or were ineligible for clinical trials, could participate in a Treatment IND protocol. In addition, patients who were failing on AZT and who had AIDS and were ineligible for participation in clinical studies could apply for ddI through a compassionate use protocol.

By March, 1990, more than 700 patients had enrolled in the controlled clinical trials, while about 8,000 patients were participating in the expanded access program.

On March 11th and 12th, 1990, a series of articles ran in leading newspapers about what the *New York Times* called an Odd Surge in Deaths Found in Those Taking AIDS Drug.[6] Two hundred and ninety out of 8,000 patients in the expanded access program had died , reporter Gina Kolata asserted, while only 2 of 700 patients participating in the controlled clinical trials had died.[7] In addition, a number of cases of fatal pancreatitis had been seen. While several patients in the phase I study had experienced pancreatitis, none, according to Kolata, had died.[8]

In response to the information about toxicity, Dr. Thomas Chalmers of the Harvard School of Public Health, called the expanded access program "a disgrace, an absolute disgrace. I think it's a painful way to learn a lesson, but maybe it's the only way they'll learn that, to my mind, they did the wrong thing."[9]

ACT UP's Larry Kramer disagreed:

> We must not forget. This is chemotherapy and people die from chemotherapy, no matter how useful the drug or how controlled the study. The choice still must be the patient's and not the government's, and I hope everyone remembers that.[10]

Dr. Anthony Fauci, Director of the National Institute of Allergy & Infectious Diseases (NIAID) at the National Institutes of Health (NIH), agreed with Kramer:

> Patients have insisted on making the decisions about taking experimental AIDS drugs...We agreed with them that the shift away from doctors telling them what to do was a good one. The side effects are not that surprising. What is surprising is that so many people have died.[11]

Bristol-Myers commented that the patient population in the expanded access program was much sicker than those in the controlled clinical studies, and that, with the exception of five deaths from pancreatitis, most deaths had been attributed to AIDS and its complications.

Response was fast and furious. In a letter to the *New York Times*, one AIDS patient wrote, "I know what I'm doing with my body, I know the risks I'm taking. I'm willing to gamble the next year of my life for another 40."[12]

A group of community leaders wrote

> What alternative does Dr. Thomas Chalmers propose to people who are dying? Would he not fight for any opportunity to prolong the life of his son or daughter? AIDS activists have worked with the National Institutes of Health, the Food and Drug Administration and Bristol- Myers to create an expanded-access program that meets the needs of patients and researchers alike. No one needs good data on these treatments more than those who are living with AIDS.[13]

In an article on the controversy, John James editorialized:

> Despite the new information about the risks of ddI, we still consider ddI to be one of the most important new treatment possibilities. It would be tragic to lose this drug — or to lose the concept of parallel track or early access to treatment — due to hasty decisions not based on careful assessment of all the facts.[14]

In addition to the toxicity concerns, researchers also complained that the large expanded access enrollment had come at the expense of controlled studies. Dr. Howard Liebman, Boston University's principal investigator on the ddI studies, told the *New York Times*

> There is no doubt that it's slowed accrual. I'm aware and many other doctors are aware of patients who would be candidates for the clinical trials who are acquiring the drug through the expanded access program...As a researcher, I think that the expanded access program will slow the approval of ddI. It will be a long time before we have a final answer.[15]

However, some activists were taking steps to ensure that approval would not be slowed. On August 16, 1990, Project Inform's Martin Delaney wrote to the FDA demanding approval of ddI and ddC before the end of 1990.

The drive for early approval of these drugs was not just a slight modification of the application of the regulations, but rather a full-fledged challenge to the Kefauver Amendments of 1962, which required that drugs approved for sale in the United States be proven "safe and efficacious for the use for which [they are] intended in adequate and well-controlled clinical trials." In a letter to FDA officials, Delaney wrote:

> We all agree that it would be best if this approval could be made on the basis of scientific standards. If those standards does (sic) not yield a positive result, for whatever reason, the issue takes on a more political overtone, as the pressure to license will not suddenly go away...The standard or hurdle for approval in general was in fact the product of politics, as there are no scientific absolutes operating here. It is a political decision, made many years ago, which the agency has since interpreted as best it could. The extent to which that interpretation reflects the intent of Congress is uncertain. The challenge before us all is to define or redefine the standard in a way which is neither scientifically irrational nor politically insensitive.[16]

In another letter to ACT UP/New York, Delaney wrote:

> [We need to] bite the bullet and seek to define or redefine the meaning of "sufficient evidence of efficacy." This has been avoided in previous programs and advances. Having agreed this would be better than just forcing the approval politically, we have gone on to argue that the redefinition should not be the FDA's sole decision.[17]

In an article on the effort to approve ddI and ddC, John James wrote:

> In recent years, proof of efficacy may have been taken too far — to the extreme of requiring academically satisfying proof, unrelated to real-world concerns such as balancing cost vs. benefit, or the feasibility of actually carrying out some of the trials which are called for. The

result is a price tag of over $200,000,000 for each new drug approved — money the public pays one way or another in drug prices. The more serious price is paid in lives of patients denied new drugs when no satisfactory alternative treatments are available...

The academic elegance theoretically available from rigidly controlled trials has led to an assumption that all new knowledge about drugs comes from formal trials, and that physicians merely apply that knowledge to patients. In fact, medical progress rests on two legs — scientific studies and also clinical experience — and they must work together for best results.[18]

In general community advocates supported the call for early approval of the drugs. Dr. Donald Abrams of the University of California/San Francisco told the *New York Times* "The FDA's own language says that all the i's don't have to be dotted and the t's crossed before drugs are approved. Why not sooner rather than later?"

Miami physician Paula Sparti commented:

I feel that we have enough experience with ddI and ddC that we should be able to prescribe the drugs for patients who are showing [AZT] intolerance or HIV resistance...If we were dealing with a different disease, we would not have enough information on toxicity with either of the drugs, but you know what, we did not have it with [AZT]. But now more people have HIV and more people are dying, and we don't have another nucleoside analogue in our armory here.[19]

However, there was not complete consensus that the drugs should be licensed. Dr. Neil Schram of the American Association of Physicians for Human Rights noted that

There must be limits at the point where the politicization of the drug approval process must stop. One of the reasons we as a society have dealt well with the epidemic is that recommendations all along the line have been based on the appropriate science.[20]

Brisol-Myers Squibb applied for marketing approval of ddI in March of 1991.

On July 18 and 19, 1991, the Antiviral Drugs Advisory Committee met to review the available information on Videx.

FDA Commissioner David Kessler started the hearing by proposing that the ddI review was not a deviation from the norm in response to remarkable circumstances, but rather that "the intensive and innovative approach to drug development in evidence here today is the paradigm of the future."[21]

Brisol-Myers Squibb presented data from four phase I studies of ddI.[22]

BASELINE CHARACTERISTICS FROM ddI PHASE I STUDIES[23]

On Study	N	Diagnosis AIDS	ARC	CD4>100	p24+	Prior AZT	Median time study (weeks)
NCI	57	32	25	23	28	41	39
BCH	39	21	18	17	22	21	35
ACTG	44	28	16	17	21	36	38
Deaconess	30	8	22	4	19	30	30
TOTAL	170	89	91	61	90	128	135

Data from these studies were compared to information on placebo patients from the first study of AZT, and from three ACTG studies.

BASELINE CHARACTERISTICS & IMMUNOLOGIC IMPROVEMENT DDI PHASE I V. HISTORICAL CONTROLS[23]

	N	% of pts. CD4<100	% with AIDS	% with prior AZT
ddI	170	64	52	75
BW02	137	63	55	0
ACTG 001	89	18	100	0
ACTG 016	344	0	0	0
ACTG 060	60	38	25	25

MEAN CD4 CHANGE (%) AT WEEK 12

TRIAL	N	%CD4+ change	P-VALUE
ddI PHASE 1	147	+14	–
BWO2	108	-27	<0.0001
ACTG 001	63	-17	<0.0007
ACTG 016	288	-5	<0.0013
ACTG 060	45	-20	<0.0007
ddI SUBGROUPS			
PRIOR AZT	112	+12	<0.0001
NO PRIOR AZT	35	-23	<0.0001
<12.5 mg/kg/day ddi	78	+10	
>12.5 mg/kg/day ddi	69	+19	

10:10 RESPONSE (INCREASE OF 10% OR 10 CD4+ CELLS, WHICHEVER IS GREATER)

	Responders R	Responders N	Responders %	ARC Responders %	AIDS Responders %	CD4<100 Responders %	CD4>100 Responders %
NCI	21	57	36	43	28	23	56
ACTG	32	42	51	61	36	40	76
TOTAL ddI PHASE 1	82	164	50			36	73
BWO2			17				
ACTG 001			27				
ACTG 016			31				
ACTG 060			18				

50:50 RESPONSE (50 CELLS OR <50% OF BASELINE, WHICHEVER IS GREATER)[24]	
Total ddI Phase I	22
Range in historical controls	2-12
% Change from Baseline (Week 8)	
Total ddI Phase I	27
Range in Historical Controls	6-24
% with NAUC >1 (weeks 0 to 12)	
ddI Phase I	70
Range in Historical Controls	34-46

VIROLOGIC RESPONSE ddI PHASE I v. HISTORICAL CONTROLS[25]			
p24 RESPONDERS			
ddI	R	N	R (%)
NCI	16	27	59
BCH	9	21	43
ACTG	19	21	90
Deaconess	10	19	53
<12.5mg/day			47
>12.5mg/day			70
Total ddI	54	88	61
Historical Placebo Controls			
BW 02	10	49	20
ACTG 016	3	44	7
ACTG 060	0	48	0

WEIGHT CHANGE AT 12 WEEKS: ddI v. HISTORICAL CONTROLS[26]		
	Responders	Median Weight Gain (lbs)
ddI	151	+2.2
BW02	117	-1.3
ACTG 001	70	-0.3
ACTG 016	270	+0.7

WEIGHT RESPONDERS >2.5KG OVER BASELINE OBSERVED ON AT LEAST 2 OCCASIONS AT LEAST 4 WKS APART[27]			
	R	N	%
NCI	20	55	36
BCH	22	37	59
ACTG	22	43	51
DEACONESS	8	30	27
TOTAL	72	165	44
BW 02			12

For safety comparisons, Brisol-Myers Squibb utilized a series of historic controls from a cohort of patients in the UK taking AZT:

ACTG ddI vs. UK AZT COHORTS[28]		
	ddI	AZT
Total N	42	311
ARC	62%	69%
AIDS	36%	31%
CD4<100	43%	39%
CD4>100	57%	61%
Anemia	10%	9%

Additional data were taken from the US expanded Access program for ddI, and from a French multicenter study.

ddI SAFETY COHORTS[29]

Study	N	Tx duration weeks	Tx duration still on study	Cumulative dose (gm/kg)	Cum. dose still on study
US Phase I	170	37	57	2.3	3.8
St. Stephens UK	105	13	18	1	1.1
French multicenter	103	15	18	0.8	1.0
US Expanded Access	7805	21	32	1.2	1.8
Total	8183				

INCIDENCE OF ddI PANCREATITIS[30]

	Pancreatitis	N	%
Phase I	29	170	17
<12.5mg/kg/day	8	91	9
>12.5mg/kg/day	21	79	27
UK	4	105	4
France	3	103	3
Expanded Access	390	7806	5

Dr. Claude Nicaise, who reported the toxicity data, noted the pancreatitis appeared to be dose-related, and that previous pancreatitis predicted future risk of ddI-related pancreatitis. Dr. Nicaise observed that there had been less follow-up, lower daily doses and lower cumulative doses in the European cohorts than the American cohorts, possibly accounting for the lower rates of pancreatitis seen in those patients.

In addition, 42 percent of patients in the phase I studies, and 16 percent of patients in the US expanded access developed peripheral neuropathy. Neuropathy was dose related, and patients at lower doses experienced reduced rates of neuropathy. A history of neuropathy predicted future ddI-related neuropathy.

The company noted that diarrhea, which had frequently been identified in patients taking ddI, was not dose-related and may have been caused by the citrate-phosphate buffer. However, they had reformulated their product into a chewable tablet, which, they thought would not cause diarrhea.

ddI-ASSOCIATED DIARRHEA[31]

	Diarrhea	Total	Cases requiring Dose Modification
Phase I	44	170	29%
UK	56	105	13%
France	32	103	6%
Expanded Access	1249	7806	4%

ADVERSE REACTION ASSOCIATED DEATHS[32]					
	Phase I	UK	France	Expanded Access	Total
Pancreatitis	—	1	—	28	29
Renal failure	—	—	—	15	15
Cardiac dysfunction	—	—	—	14	14
Liver failure	1	—	3	13	17
Myelosuppression	—	1	—	5	6
Diarrhea	—	—	—	4	4
Hypoglycemia	—	—	—	1	1
Cerebrovascular	—	1	1	—	2
Total	1	3	4	80	88

To supplement their NDA application, Dr. Laurie Smaldone from Bristol-Myers presented data from pediatric studies, concluding that "the entire ddI experience parallels the results seen in adults."[33]

There were two studies available in children, one from the National Cancer Institute and one from the AIDS Clinical Trials Group in collaboration with St. Jude's Children's Research Hospital.

PEDIATRIC ddI STUDIES[34]		
	NCI	ACTG
Total Patients	78	20
Age (median yrs)	6.9	6.3
Prior AZT	41	2
Stage		
AIDS	55	10
CDC Class P1	14	10
CDC Class P2	9	0

Data from these two studies were pooled to provide information on clinical, immunologic and virologic response to ddI.

RESPONSE TO ddI[35]		
	Prior AZT	All patients
N	40	89
10:10 CD4 Response	8/36	31/83
50:50 CD4 Response	5/36	19/83
% CD4 Change/Week 8	+21	+27
p24 Response	10/18%	36/49%
Weight Response	12/36%	32/83%
50:50 CD4 Response+Weight (%)	1	4
p24 Response + Weight (%)	4	9
50:50 CD4 Response +p24 + Weight (%)	1	9
Neuropsych Response*	7/21	12/43

* IQ tests were taken on children at baseline, and at 6 months. For the entire group there was not a statistically significant change, however for patients with a baseline IQ score of < 115 there was a significant difference in the number of children experiencing a rise in IQ score of 10% and 8 points, whichever is greater.

ADVERSE EVENTS IN PEDIATRIC POPULATION[36]		
	<300mg/m²/day ddI	All patients
N	60	98
Abdominal Pain	32%	35%
Diarrhea	82%	81%
Nausea/Vomiting	57%	58%
Pancreatitis	3%	7%

LABORATORY ABNORMALITIES IN PEDIATRIC POPULATION (DOSES <300MG/M²/DAY)[37]		
	Normal Baseline	Abnormal Baseline
Leukopenia	3%	36%
Granulocytopenia	24%	62%
Thrombocytopenia	2%	67%
Anemia	4%	27%
SGPT	3%	25%
SGOT	0%	36%
Bilirubin	2%	0%
Amylase	0%	0%

Dr. Phil Pizzo, a leading specialist in pediatric AIDS, noted that "AZT given in a continuous infusion in similar populations is associated with highly significant improvements in base scores lasting over a year. We have not seen that in ddI...I'm not saying that there's major neurocognitive improvement in children generally, but there is some."[38]

Overall, the sponsor claimed efficacy for ddI based on three different markers:

- CD4+ counts
- p24ag levels
- Weight Gain

FDA's Dr. Rachel Behrman noted that

> The historical controls are incomparable in terms of disease status at baseline. BW 02 is the only one even close to comparable with respect to baseline CD4. ACTG 001 was for people with KS only, whose median CD4 counts were higher. ACTG 016 was for early ARC; median CD4 levels were about 400. ACTG 060 patients also had higher median baseline CD4 levels. These historical trials were conducted between 1986-89, a period when the standards of care were very dynamic, while the ddI trials were conducted between 1988-90.[39]

Dr. Behrman also noted that, using the 50:50 criteria for CD4+ response, and comparing the aggregate data on ddI with the historical controls, "one finds two statistically significant differences supporting placebo, and two supporting ddI."[40]

The committee expressed deep concern over the quality of the data, and the use of historical controls. Dr. Alvin Novick remarked:

> The only strength I can see in the phase I trials was fully expressed one and a half years ago. At that time, we said there was reason to believe that there might be some efficacy. We encouraged the sponsor to do randomized controlled trials. These studies do not push the frontiers of knowledge, they undermine our ability to do clinical trials. We've abandoned randomized controlled trials altogether. This isn't the way to push the frontiers of knowledge. Why would we wish to elevate this to a decisive study? It doesn't meet our criteria at all. Of course I recognize the medical emergency in the affected community. I am from them. I think their needs are

adequately served by the expanded access program for the next few months.[41]

For Dr. Neil Schram, a committee member, the dilemma was even more profound:

> This was a very difficult meeting for me, frankly. I remember back in late 1989, we had people literally hanging by their thumbs waiting for ddI. For many of these patients for at least a limited time ddI saved their lives. But it's frustrating. The data don't show that. It's not a penicillin. It's probably not even an AZT. The data today don't prove to this committee that it works, but it does. The data are not able to accurately reflect the changes I have seen in patients.[42]

Dr. James Bilstad, Director of the FDA's Center for Drug Evaluation, noted that

> If clinical efficacy data later proved inadequate, we could remove ddI from the market by two mechanisms: 1) imminent hazard — if it posed an immediate safety problem — through the Secretary's office; 2) hearing process — a long process — if there is no evidence of clinical efficacy. We used it with an oral hypoglycemia drug which caused lactic acidosis.

Committee member Dr. Paul Meier asked Dr. Bilstad, "How often have these mechanisms been used in the last 10 years?"

Dr. Bilstad responded, "I can't remember any case."[43]

The next morning, investigators presented preliminary data from ACTG 116b/117, an ongoing phase II study of high-dose ddI, low-dose ddI or AZT in patients with less than 300 CD4+ and symptoms, who had already taken AZT. Primary endpoints were time to AIDS and/or death. Patients who reached an endpoint were allowed to cross over to unblinded treatment.

FDA had arranged for data to be presented regarding CD4+ results during the first 24 weeks, with post-crossover data censored. Information on 412 patients was available at the data cutoff point.

ACTG 116B\117: CHANGES IN CD4+ SLOPE[44]

	Group A:	Group B	Group C
	750mg ddI	AZT	500mg ddI
N @ Baseline	141	139	132
N w/ Slope	126	115	111
Mean slope	1.07	0.37	0.34
	A v. B	C v. B	A v. C
p-value (t test)	0.13	0.47	0.44
p-value (rank sum)	0.02	0.21	0.29

ACTG 116B\117: NAUC ANALYSIS[45]

	Group A:	Group B	Group C
	750mg ddI	AZT	500mg ddI
% w/ NAUC >1	58.4	39.7	51.3
Mean NAUC	1.14	0.97	1.14
# NAUC >1	52	29	39
# NAUC <1	89	73	76
Total	141	134	132
	A v. B	C v. B	A v. C
p-value (chi-sq)	0.02	0.16	0.37
p-value (t test)	0.02	0.03	0.97
p-value (rank sum)	0.12	0.30	0.63

In other words, comparisons between high-dose ddI and AZT favored ddI. Comparisons between low-dose ddI and AZT favored ddI. No consistent differences were seen between the two doses of ddI.[46]

The committee was much more enthusiastic about the new data: Dr. Meier commented "This evidence totally dominates the evidence we saw yesterday. I would throw that out and look at this."[47]

However, there was not agreement on what the evidence showed. Dr. Clifford Lane, from the NIH, commented that

> The data do not show that ddI is effective in treating adults. It shows that ddI is effective in raising CD4 cells by ten cells. I don't know what the effect of ten more CD4 cells is...Given the severity of the situation, I would support allowing the drug to be marketed. This is a situation where you should have a conditional approval, waiting for clinical benefit to follow-up the surrogate marker data.[48]

Dr. Meier commented

> We do not have evidence to justify the usual standard. The argument for some kind of approval seems compelling, but we ought not to fudge it: we intend to operate on a lower standard. We shouldn't twist the reasons. Rather than saying we want the whole system to lower standards we should circumscribe it so that it does not become a back door route to approval. Let us take the opportunity to be creative. Conditional approval ought not to be a back door to approval. We ought to set a future date for review under our usual standards. In general our system is too slow to approve, and once approval is granted, too lax in allowing them to be out there without further study.
>
> There are other alternatives. Treatment IND, for example. The sponsor elected not to have cost recovery when requesting its treatment IND in 1989. If conditional approval is impossible, perhaps a treatment IND with cost recovery to support badly needed further studies would be an alternative.[49]

Other committee members concurred on the desirability of a conditional approval, however Dr.Kessler refused that possibility. He told the committee, "I am reluctant to discuss any form of conditional approval in this case unless the committee was not able to reach a decision on full approval."[50]

Finally, the committee voted five to two with one abstention, for approval of ddI limited to symptomatic HIV-positive adults and children who were intolerant of or failing AZT.

The *Wall Street Journal* noted several days later that

> The FDA and the NIH pulled off a deft political feat, enabling release of a second drug for AIDS patients and market approval for Bristol, which made a substantial investment and giveaway program. In the process, it provided an education for drug companies by putting through the painful exercise of watching its uncontrolled trials discredited.[51]

CHAPTER NOTES

1) Statement, Bristol-Myers Company, Jul 13 1989

2) Zonana V, Firm to Offer AIDS Drug Free in Critical Cases, LA Times, Jul 14 1989

3) James J, ddI: Compassionate Access Announced, AIDS Treatment News, Jul 15 1989

4) Harrington M, A National AIDS Treatment Research Agenda, ACT UP/New York, Jun 1989

5) Kolata G, New Drug for AIDS Yields Improvements Without Side Effects, New York Times, Jul 28 1989

6) Cimons M & Steinbrook R, 6 AIDS Patient Deaths May Renew Drug Debate, LA Times, Mar 10 1990
Specter M, Several Deaths Linked to AIDS Drug, Wash Post, Mar 11 1990
Chase M, Six AIDS Patients Die in Trial of ddI, Experimental Drug Being Widely Used, WSJ, Mar 12 1990
Kolata G, Odd Surge in Deaths Found in Those Taking AIDS Drug, NYT, Mar 12 1990

7) In fact, 15/700 had died (Harrington M, Personal Communication, Apr 2 1995)

8) Again, one patient in the phase I study had died of pancreatitis (ibid)

9) Kolata G, op cit., Mar 12 1990

10) Cimons & Steinbrook, op cit., Mar 10 1990

11) Specter M, op cit., Mar 11 1990

12) Lopez D, Don't Blame Drug Program for AIDS Deaths, NYT, Mar 28 1990

13) Barr D et al., Too Quick to Criticize, NYT, Mar 28 1990

14) James J, ddI Risks: Perspective and Precautions, AIDS Treatment News, Mar 16 1990

15) Kolata G, Interest Grows in Licensing Shortcut for 2 AIDS Drugs, New York Times, 25 Sep 1989

16) Delaney M, letter to Dr. Ellen Cooper & Dr. Paul Beninger, dated Nov 2 1990

17) Delaney M, letter to Peter Staley, Nov 6 1990

18) James J, ddI and ddC: The Call for Early Approval, AIDS Treatment News, No. 112, Oct 5 1990

19) ibid

20) ibid

21) Transcript, Meeting of the FDA's Antiviral Drugs Advisory Committee, Jul 18 1991

22) Summary information from Harrington M, D-Day for ddI, Jul 22 1991. Harrington also notes that "the studies used different dosing regimens. The NCI [National Cancer Institute], BCH [Boston City Hospital], and ACTG [AIDS Clinical Trials Group] studies escalated doses; the earliest participants took the lowest doses and the later ones took higher doses. The NCI and ACTG studies gave ddI twice daily, the BCH study gave it once daily. NCI doses ranged from 0.8-51.2 mg/kg/day; BCH from 1.6-30.4; ACTG from 1.6-86.0; and Deaconess 750-1500 mg/day. Only the first 4 Deaconess participants dose escalated; the others took fixed doses (derived from previous studies) twice daily. Jul 18 & 19 1990, Harrington M D-Day for ddI, op cit. , and package insert, Videx brand didanosine, July 1 1990

23) ibid

24) ibid

25) ibid

26) ibid

27) ibid

28) ibid

29) ibid

30) ibid

31) ibid

32) ibid

33) Transcript op cit., Jul 18-19 1991

34) ibid, and Package Insert op cit.

35) ibid

36) ibid

37) ibid

38) Transcript, op cit., Jul 18-19 1991

39) ibid

40) ibid

41) ibid

42) ibid

43) exchange from ibid

44) ibid

45) ibid

46) ibid

47) ibid

48) ibid

49) ibid

50) ibid

51) Chase M, ddI Decision Heralds a New FDA Activism, Wall Street Journal, Jul 22 1991

MORE INFORMATION ABOUT VIDEX BRAND DIDANOSINE

Little toxicity was observed with the lower doses used during the first eight months or so of clinical testing of ddI, and by the spring of 1989, the drug had earned the label "AZT without tears" from the patient community,

Dr. Eileen Leonard, Medical Officer, FDA,
Transcript of a Hearing of the Antiviral Drug Product Advisory Committee,
Jan 19 1990

Yet, those moments when I am not in complete despair, I am almost hopeful. There is an array of anti-HIV drugs now in clinical trials and the exciting article in last month's New England Journal of Medicine raises at least the possibility of a direct measure of the effectiveness of anti-HIV drugs, or, at the very least, of the nucleoside analogs and the attendant prospect of shorter trials.

Jim Eigo, ACT UP/New York,
Transcript of a Hearing of the Antiviral Drug Product Advisory Committee,
Jan 19 1990

The committee convened again on April 20th, 1991, to review new information regarding the efficacy of Videx brand didanosine. The committee, had recommended approval, but expressed serious reservations and the approval letter contained a mandate to return to the committee and present to the committee the clinical endpoints as soon as they became available.

In support of ddI, Dr. James Kahn of the University of California/San Francisco and Dr. Steven Lagakos of Harvard presented clinical results from ACTG study 116b/117, a trial comparing AZT to high-dose and low-dose ddI in patients who had already been treated with AZT for more than four months.

Participants were required to have symptomatic AIDS/ARC and less than 300 CD4+ cells/mm^3, or to be asymptomatic with less than 200 CD4+ cells. Study endpoints included time to death or to previously undiagnosed AIDS- related event, excluding Kaposi's Sarcoma.

BASELINE CHARACTERISTICS OF STUDY SUBJECTS IN ACTG 116B/117[1]

	750mg ddI	AZT	500mg ddI	All
N	311	304	298	913
DIAGNOSIS (%)				
AIDS	30	31	2	30
ARC	62	58	61	60
PREVIOUS AZT				
(mean mos)	14.2	13.6	13.5	13.9
CD4+ COUNT				
median (cells/mm^3)	97	84	98	95
<50 (%	31	33	2	31
>200 (%	19	18	18	19
DISCONTINUED STUDY DRUG	106	124	86	316
LOST TO FOLLOW-UP (mos)	12	18	18	48
AVERAGE FOLLOW-UP (mos)	55	55	55	55

ENDPOINTS IN ACTG 116B/117[2]

	GROUP I	GROUP II	GROUP III	I v.II	II v. III
	750mg ddI	AZT	500mg	ddI p-value	p-value
Primary clinical end point	115	125	94	0.045	0.015
New AIDS Diagnosis	86	104	71	0.06	0.035
Death	29	21	23		
Death	57	54	49	0.49	0.99
New or recurrent AIDS Diagnosis or death	118	132	101	0.25	0.02

The researchers concluded that

> There is a significant difference between the low-dose ddI arm and the zidovudine arm both in terms of new AIDS diagnosis or death, or in new or recurrent AIDS diagnosis or death. There was no difference between either high-dose ddI and low-dose ddI, or between high- dose ddI and zidovudine.
>
> In addition, there was a significant reduction in the probability of a new, non-recurrent AIDS-defining event or death favoring low-dose ddI over zidovudine. There was no difference between either high-dose ddI and low-dose ddI, or between high-dose ddI and zidovudine.[3]

However, they also observed that there was no difference in time to death between any of the three treatment arms, nor a significant difference in time to first opportunistic infection or death.

Immunologic and virologic benefits were also seen with ddI therapy:

CD4+ CELL COUNTS AND HIV P24 ANTIGEN RESPONSES[4]

STUDY	750MG ddI		AZT		500MG ddI	
Week	Median CD4 change since Baseline	p24 Response	Median CD4 change since Baseline	p24 response	Median change since Baseline	p24 response
2	+5 (284)	19% (96)	-6 (271)	6% (83)	+2 (274)	17% (89)
8	+3 (255)	29% (79)	-10 (261)	12% (86)	+2 (243)	27% (85)
12	0 (253)	26% (81)	-14 (238)	8% (79)	0 (246)	29% (82)
16	-3 (245	31% (72)	-15 (221)	17% (63)	-1 (236)	22% (79)
24	-10 (228)	32% (66)	-23 (193)	21% (63)	-10 (225)	21% (76)
P-value compared w/ AZT	<0.001	0.005	—	—	<0.001	0.03

LABORATORY AND CLINICAL TOXIC EFFECTS OF THE STUDY DRUGS[5]

	Group I 750mg ddI	Group II AZT	Group III 500mg ddI	I v. II p-value	II v. III p-value
Pancreatitis	31 (13%)	6 (13%)	17 (7%)	0.001	0.09
Peripheral Neuropathy	30 (14%)	26 (14%)	33 (13%)	0.79	0.95
Amylase >1.3x upper limit of normal	68 (30%)	16 (6%)	45 (20%)	<0.001	0.001
Hematologic Toxicity	66 (24%)	91 (36%)	70 (31%)	0.004	0.008
Leukocytes <2.0x109/L	41 (14%)	67 (26%)	49 (22%)	0.001	0.01
Granulocytes <0.75x109/L	26 (12%)	45 (19%)	25 (11%)	0.007	0.004
Platelets <50x109/L	6 (3%)	8 (4%)	6 (4%)	0.49	0.45
Hemoglobin <8g/dl	6 (3%)	16 (7%)	8 (3%)	0.04	0.06

Hematologic toxicity was more common with AZT therapy compared with ddI. Pancreatitits was more likely in those subjects receiving ddI and significantly more frequent in those patients receiving 750mg daily dosage.

Dr. Lagakos then commented on the correlation between CD4+ cell counts and clinical outcomes.

> There was a CD4 effect in both the high-dose and the low-dose ddI arms and an improvement relative to AZT. For the high-dose ddI arm, though, there was not a corresponding clinical benefit in terms of new OI or death. There was in the low-dose ddI arm.
>
> The two CD4 effects - benefits of the two ddI arms — were very similar, yet one of them manifested a clinical effect and the other didn't. Neither showed an effect on death.
>
> If you just look at AIDS patients, as I mentioned a few minutes ago, both treatments showed a significantly beneficial effect relative to AZT, both ddI arms, but neither showed a clinical effect or a death effect.
>
> If you just look at ARC and asymptomatic patients, there was a CD4 effect in both the ddI arms relative to AZT. Both showed an effect on new OI or death, but neither showed a survival effect.
>
> So, just looking at those outcomes without looking at the correlation in terms of, to what extent does the CD4+ effect predict the clinical effect, you can see it is a rather mixed bag.[6]

However, Dr. Sheiner, a San Francisco pharmacologist, disagreed:

> I am rather heartened that the CD4 marker data seems to have gone along rather nicely with the efficacy, marred as it may be by the drop-outs, but nevertheless the picture emerges that the groups that have the change in CD4 also seemed to have a beneficial effect.[7]

The meaning of the differences between CD4 effect and clinical effect were a subject of much concern to the committee, prompting Dr. Lagakos to comment

> When I see a lack of a survival benefit, it worries me when the message seems to be that these treatments don't affect survival when, indeed, the power to detect a survival difference may be extremely low because we may be comparing like with like.[8]

Dr. Paul Meier from the University of Chicago, took issue with the study's endpoints:

> If we were to take the coronary arrhythmia studies and count, as they did, events which are serious arrhythmias which did not result in death and they combined those as an endpoint with those that did result in death. If one were to look at the serious arrhythmias that did not result in death alone, I have no idea what we might have seen, but I would expect that the anti- arrhythmic drugs would have looked good in that measure. The thing that happened is that death intervened.
>
> And the result is that the interpretation of endpoints, which is a segment out of this continuum, generally speaking is going to be totally confusing. I think here it is totally confusing. It gives one the appearance of the two doses of ddI looking better than AZT. That, I say, is a chimera, and we would be better to put that aside.[9]

Finally, the committee agreed that the data it had seen ratified its earlier decision to recommend approval for ddI. The FDA altered the drug's indication to include not just patients who were "experiencing clinical or immunologic decline" during treatment with AZT therapy, but also patients who had been treated with AZT for a significant period of time.

CHAPTER NOTES

1) Chart from Kahn MD J, A controlled Trial Comparing Continued Zidovudine with Didanosine in Human Immunodeficiency Virus Infection NEJM 327:9, Aug 27 1992

2) Chart from Kahn MD J, ibid, Aug 27 1992

3) Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, Apr 20 1992. In other words,endpoints were analyzed using four different measures of outcome: 1) a new opportunistic infection never before experienced by the patient, including death, 2) a new or recurrent opportunistic infection or death, 3) death, or 4) time to first OI or death. Outcome indicators 1 and 2 were significant favoring low-dose ddI, while outcome indicators 3 and 4 were not significant in any analysis

4) Kahn op cit.

5) ibid

6) Transcript, op cit., Apr 20 1992

7) ibid

8) ibid

9) ibid

PARALLEL TRACK & ACCELERATED APPROVAL

People talk about the possibility of losing lives due to toxicity, but nobody is counting the lives lost due to delays in drug development.

Martin Delaney in Zonana V, Firm to Offer AIDS Drug Free in Critical Cases, LA Times, Jun 14 1989

As somebody who works on AIDS policy and treatment, I am just as concerned as anybody else, maybe more than anybody else, about treatments becoming fashionable before we have information. I am deeply committed to the idea of patient autonomy, but patients can only truly have autonomy when we have information by which to make decisions.

David Barr in Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, Sep 20 1993

The issue of which mechanism might be used to allow access is less important to the quietly desperate people with HIV infection than how the limits to access are defined.

Nancy Pelosi in Hearings on the Parallel Track Proposal for Drug Development, Jul 19 1989

In mid-June, 1989, Dr. Anthony Fauci, the Director of the NIH's National Institute of Allergy & Infectious Diseases (NIAID) spoke before a community forum on HIV treatment in San Francisco, and proposed that experimental drugs be distributed before FDA approval to patients "who cannot participate in clinical trials."[1] Such a program would, Fauci proposed, be conducted as a "parallel track" to the ongoing clinical research process, and would exclude patients who qualified for formal studies.

Patient advocates had grown frustrated and angry regarding the FDA's implementation of the treatment IND guidelines. In 1989, members of ACT UP/New York wrote:

> [The treatment IND regulations] aroused and subsequently dashed the hopes of those affected by AIDS. Too few treatments were made available to too few subjects under too stringent restrictions.
>
> Perhaps the most notorious AIDS-related treatment IND was that for trimetrexate, a treatment for *pneumocystis*. An initial study conducted by the National Cancer Institute (NCI) showed trimetrexate to be a viable second-line intervention against PCP, yet the treatment IND restricted trimetrexate to those who had adverse reactions to both other treatments. It excluded subjects who had merely failed to respond to them. This left many people with no therapeutic options and an often fatal disease. Although the criteria have since been expanded, trimetrexate is still not approved. There are persistent reports that its sponsor is considering dropping the IND altogether.
>
> In other cases, treatment IND has been implemented as a bridge between submission of final New Drug Application (NDA) data and full marketing approval by the FDA. This "bridge to NDA" approach was virtually codified in the FDA's revised Investigational New Drug (IND) regulations of October, 1988. This provided useful access 6 months before NDA approval for some people who needed aerosolized pentamidine or DHPG. But it usually occurs too late in the approval process to provide access to experimental treatments for many whose need is most urgent.[2]

Dr. Mathilde Krim, a co-founder of the American Foundation for AIDS Research (AmFAR) pronounced Dr. Fauci's proposal "a great step forward. It represents a new consensus on how to handle drug development for AIDS and life-threatening diseases in general."[3]

Others, including Jeff Levi, then the Executive Director of the National Gay & Lesbian Task Force, and Rep. Henry Waxman, the Chair of the House Subcommittee on Health and the Environment, were more measured in their response. Rep. Waxman, in hearings on the parallel track idea, said

> This is an important proposal. It could change ground rules on research, clinical care, markets, and insurance. It could also provide access to drugs — the good ones and the worthless ones — long before data are available. If it works it could revolutionize drug development. If it fails it could cripple AIDS research for some time.[4]

Mr. Levi called the proposal "a very interesting approach," but asked,

> Where is the money going to come from? Who is going to pay for the drugs and the associated care? Will it be the NIH? The drug companies? Third-party payers? Or is this going to be of value only to those wealthy enough to pay for the drugs?[5]

The Pharmaceutical Manufacturers' Association (PMA)[6] endorsed the plan, but sounded a note that would be heard again and again when they observed that

> Ultimately the single most important element in making safe and effective drugs available to all of the people who need them is the rapid development and approval of new medicines. To meet that objective, there are a number of issues such as the use of surrogate markers for demonstrating efficacy which need resolution.
>
> We strongly support the view that endpoints other than survival rates are meaningful both in a medical sense to the treating physician and in a personal sense to the patient. Surrogate markers should therefore be sufficient to warrant approval of a new drug...Our common goal is to get new drugs that work onto the market in the shortest possible time. We must therefore take every opportunity to reduce unnecessary delays and to expedite the process.[7]

As Bristol-Myers began to design its pre-approval distribution program for ddI, the company used existing regulations to shape the new parallel track regulations: by combining a compassionate use protocol for AIDS patients who had failed on AZT, and who were ineligible for study participation, with a treatment IND for patients who had demonstrated intolerance to the drug, they developed a program that closely resembled the activists' parallel track. Unlike a normal compassionate use protocol, which would be targeted to an individual patient, their program was designed to reach classes of patients; unlike a normal treatment IND, their program was being implemented concurrent with, rather than following, the phase II studies.

In fact, the program was so successful that one AIDS activist called it

> the best working relationship to date of industry, FDA, AIDS activists and community doctors. What we have tried to do is create a balance whereby those patients who need the drug now are identified and treated, without interfering with the trial enrollment and without caving into the pressure of rumor and fashion that often surrounds AIDS treatments.[8]

Still the formal parallel track program remained just a name with no policy attached to it. The Public Health Service referred the concept to the Anti-Infective Drug Products Advisory Committee, and asked them to review the proposal. A group of sixteen non-profit AIDS organizations, including ACT UP/New York, Project Inform, and the National Gay & Lesbian Task Force, assembled a consensus document outlining their vision of parallel track. In particular, they emphasized the need for broad inclusion criteria, including people who were intolerant or failing on AZT, who did not qualify for study participation, or who lived too far from the trial site to participate. In addition, they emphasized simplicity in data collection, and treatment through primary-care physicians and clinics.[9]

The activists emphasized that

Sponsors would benefit from parallel track which, unlike compassionate use, would give them data for every dollar they spend. Sponsors should realize that adjunct data from the parallel track may well mean fewer, or shorter clinical trials to prove a drug's efficacy. This should be a major economic incentive for parallel track.

Finally, parallel track will also be a good market strategy. There is already in AZT an accepted antiretroviral. Nothing could more quickly gain a new, effective, less toxic antiretroviral a foothold in the marketplace than its acceptance by many, widely disseminated community members. Designation of a treatment to go on parallel track will be seen as a certification of a treatment's potential efficacy. Short term economic outlays will translate into long term gain — short trials, clean data, good community relations and free publicity — for any effective drug.[10]

The advisory committee endorsed the consensus document, and referred the final drafting of the regulations to a Public Health Service working group.

The policy was finally published on April 15th, 1992, with a notation that

PHS intends to evaluate the parallel track experiences specifically to determine whether worthwhile benefits are provided in addition to those available under mechanisms such as the treatment IND or Group C approaches. The evaluation would also include a consideration of whether parallel track has had detrimental effects on individuals or on the ability to determine the safety and effectiveness of promising therapies.[11]

The policy detailed provisions for sponsors to submit applications for parallel track either through FDA directly, or through the AIDS Research Advisory Committee (ARAC) of the NIH, which would then make a recommendation to the Commissioner of the FDA. This allowed for external review, unhampered by the perceived unwillingness of the regulatory agency to allow significant numbers of patients to have access to therapies early in the development process.

Patients eligible for parallel track protocols would include those who

1) had "clinically significant HIV-related illness," or were at "imminent health risk due to HIV-related immunodeficiency."
2) could not participate in controlled clinical trials because:
   A) they did not meet entry criteria,
   B) they were too ill to participate,
   C) participation would impose "undue hardship," or
   D) the studies are fully enrolled.
3) could not take standard treatment because of contraindication, failure or intolerance.

In addition, the policy required the following information to be submitted as part of an application for approval of a parallel track protocol:

1) Sufficient evidence showing:
   A) promising evidence of efficacy...
   B) that the investigational drug is reasonably safe...
   C) an appropriate starting dose.
2) Preliminary pharmacokinetic and dose-response data, and, ideally, data about interactions with other drugs commonly used in the intended patient population.
3) Evidence of a lack of satisfactory alternative therapy for defined patient populations.
4) A description of the patient population to receive the drug under expanded access.
5) Assurance that the manufacturer is willing and able to produce sufficient amounts of the drug product for both the controlled clinical trials and the proposed expanded availability study.

6) A statement of the status of the controlled clinical trial protocols.
7) An assessment of the impact that the parallel track study may have on patient enrollment for the controlled clinical trials and a proposed plan for monitoring progress of the controlled trials.
8) Information describing the informational, educational and informed consent efforts that will be undertaken to ensure that participating physicians and potential recipients have sufficient knowledge of the potential risks and benefits of the investigational agent being studied in the parallel track process.

The policy also detailed criteria for removing a drug from parallel track:
1) Evidence that subjects are being exposed to unreasonable and significant risks.
2) Evidence that the parallel track study is interfering with the successful enrollment in, and completion of, adequate and well-controlled studies of this or other investigational drugs.
3) Evidence that the sponsor is not in active pursuit of marketing approval.
4) Evidence from in an adequately controlled clinical trial that strongly suggests lack of effectiveness.
5) Another product approved or under investigation for the same indication in the same population demonstrates a better potential balance of risks and benefits.
6) The drug receives marketing approval for the same indication in the same patient population.
7) Insufficient product exists to conduct both the parallel track protocols and the controlled clinical trials.
8) The Commissioner of Food and Drugs determines that, in the interests of the public health, the parallel track study should not be continued.

Finally, the policy included guidelines for collection of adverse event reports and provisions for a national IRB to approve parallel track protocols, and specified that each protocol include a Data Safety Monitoring Board to review information from the program.

The publication of the parallel track policy represented the culmination of years of AIDS activists' work. Since before the approval of AZT, they had fought for broad and early access to drugs perceived to be promising, and the parallel track policy fully met that goal. However, the consensus that had governed AIDS activism had already begun to break down.

During the massive expanded access program for ddI, statisticians Paul Meier and Thomas Chalmers had commented that

> The ratio of patients entering controlled to unrandomized trials should be sharply reversed. If a patient is to receive one of the new drugs, the only excuse for not randomizing is totally insurmountable geographic isolation. With proper communication, any physician with an AIDS patient can be part of a proper trial.[12]

During an early advisory committee discussion about the ddI expanded access program, Dr. Meier commented that

> The failure to have any concurrent control at all means, in my opinion, that the resources and efforts that may be poured into these 6000 and their successors are taken away from much more fruitful effort that could be put into that part of the study which is controlled. I cannot forbear to ask once again if we have these patients regularly seeing their physicians, if the physicians are dedicated and prepared to fill out forms and so on, could we not at least have a high-dose/low-dose randomization of those patients? I see nothing in what has been said to preclude it and we would immediately now have an internally controlled study, to be sure, with much lower precision per unit that what we have in the standard controlled study, but we would have something.[13]

Later that year, ACT UP/New York released the *AIDS Treatment Research Agenda* at the VI International Conference on AIDS in San Francisco, calling for the implementation of a "middle track." The activists proposed that

> people enrolling [in parallel track programs] at sites capable of collecting more detailed — but still minimal — efficacy data could participate in a randomized form of parallel track which would compare various doses of the parallel track drug, and generate rapid efficacy data...Sites appropriate for middle track would include community-based clinical trials groups and qualified physicians' offices and public health clinics.[14]

The activists noted that "middle Track would, like parallel track, be primarily a distribution program, with a secondary goal of gathering minimal efficacy data. The endpoints could be similar to those used in large, simple trials."[15]

In 1989, a group of leading statisticians, led by the late Dr. David Byar from the NCI with the assistance of ACT UP/New York member Rebecca Smith, began to meet to discuss some of the activists' proposals regarding study design. In November of 1990, they published an article in the *New England Journal of Medicine* advocating substantial changes in clinical trial design:

> Broadening eligibility criteria would provide many more patients with easier access to experimental treatments within randomized trials. Simplifying trial protocols and limiting data collection would allow more physicians to collaborate, provided that appropriate mechanisms were created to manage such trials. Then, even patients and physicians who live a long way from the academic hospitals where trials are traditionally conducted could participate. Collaborating physicians would need to provide only essential base-line data and then submit brief follow-up forms periodically with information on drug dose, toxicity and survival status. In such clinical trials, more extensive data could be collected for some subgroups of patients, such as those at academic centers, whereas only limited data on the main outcomes would be collected for a much larger number of patients.[16]

Activists from ACT UP/New York's Treatment and Data Committee, who would later break off to form the Treatment Action Group (TAG), began working collaboratively with the statisticians to improve both availability to and information on new AIDS drugs.

At the same time, some activists from San Francisco were growing increasingly unhappy with the expanded access model of activism. When Bristol Myers-Squibb's d4T became the first drug to be released under the Parallel Track policy, John James commented that

> The new parallel-track program for d4T seems to be as good as we can hope for at this time. However, we believe a better policy would be to allow urgently-needed drugs which are ready for parallel track to be marketed instead, under conditional approval, and reimbursed by public or private insurance like other approved drugs. Such a system would (1) give more control of medical decisions to physicians and patients, (2) allow earlier access to drugs like peptide T which do not have a major developer able to afford parallel track, (3) be at least as equitable across social classes as "free" distribution which requires physician time and laboratory tests commonly paid for out of the patient's pocket — or the physician's; (4) allow faster learning about new treatments under conditions of practical use, and (5) permit small companies to bring out the most important new advances ... when big companies are not aggressive or not effective in doing so.[17]

Similarly, San Francisco activist James Driscoll argued that

> The expanded access, no matter how good it is, is not going to give the full choice we need because of the levels of sophistication of the patients. We have many patients in small towns, in the ghettos, conservative patients with conservative doctors, who are afraid to try anything that is not approved

by FDA, or who may not even know about things which aren't approved by FDA [18]

Using their proposal for expedited approval of ddI and ddC, these activists began to argue for a policy that would allow "conditional approval" of drugs shown to improve surrogate markers. Such a plan would, advocates assured, "not lower the standards for drug approval "but would" merely changes when some of the studies are done."[19]

As New York activists began efforts to extract more data from the pre-approval process, San Francisco activists began to demand less data before approval:

> When a drug is known to be safe, and known to show antiviral activity in humans, then it should be made available as an option to physicians and patients, without waiting for a large phase III trial to get definitive proof of clinical benefit. In testing treatments for an infectious disease, control of the causative organism is not a "surrogate marker" which must itself be validated by years-long clinical trials before it can be used. It is instead, the central goal of therapy.[20]

FDA Commissioner Dr. David Kessler was listening. He instructed his staff to prepare regulations governing the "accelerated approval" of new drugs intended for the treatment of "serious or life-threatening conditions."

> The regulations, which became effective in April 1992, allow drugs and biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments" to be approved "on the basis of adequate and well-controlled trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely...to predict clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.[21]

> In such cases, the regulations noted that
> approval will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway...The applicant shall carry out any such studies with due diligence.[22]

In addition, where the treatment demonstrates specific safety concerns, FDA may restrict distribution "to certain facilities or physicians with special training or experience, or...conditioned on the performance of a specified medical procedure."[23]

Finally, the regulation allows for accelerated withdrawal of products granted accelerated approval, with appropriate due process guarantees, if:

1) A postmarketing clinical study fails to verify clinical benefit,
2) The applicant fails to perform the required postmarketing study with due diligence,
3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the product,
4) The applicant fails to adhere to the postmarketing restrictions agreed upon,
5) The promotional materials are false or misleading, or
6) Other evidence demonstrates that the product is not shown to be safe or effective under its conditions of use.[24]

CHAPTER NOTES

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3) Kolata G, AIDS Studies Head Seeks Wide Access to Drugs in Tests, NYT, Jun 26 1989

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7) Pettriciani J in ibid

8) Barr D in Transcript of a Hearing of the Antiviral Drug Products, Jul 18 1991

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HIVID BRAND ZALCITABINE (ddC)

I would just like to congratulate you for being the first company to do a randomized expanded access program. I think it was extremely useful. I would just like to suggest in the future — it looked like there was a trend and maybe if there had been more people in it, it would have really yielded a definitive answer.

Mark Harrington, Treatment Action Group
Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, Apr 20 1992

There was a lot of talk about choice this morning by people in the activist community; choice. Give the patients a choice. Well, I am here to say on behalf of a lot of people who don't have the time and money to get here, that choice isn't always meaningful if is isn't supplemented by some information that makes the choice meaningful....What are people going to do? There are a million people in this country who are asymptomatically infected with HIV. What are they going to do? How are they going to figure out how to use these drugs? How are their doctors going to do it? And this is about choice.

Rebecca Smith, ACT UP/New York
Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, Apr 20 1992

I think to say that one needs the drug and at the same time one doesn't know that it is efficacious is a contradiction. It is a perception that you need the drug. And, obviously, with denying the drug, that means we are denying it because we know it is efficacious. If we do not know that it is efficacious, then we are not denying it to anybody.

Monto Ho, MD
Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, Apr 20 1992

On April 20th, 1992, after a long, long day of hearings, including the follow-up presentation regarding ddI, a discussion of the use of absolute CD4+ cell counts as a marker of clinical efficacy, and a lecture from the Commissioner regarding the new accelerated approval regulations, the Antiviral Drug Products Advisory Committee heard the available evidence regarding Hoffmann-LaRoche's HIVID brand zalcitabine (ddC).

The application sought approval for use of ddC both as monotherapy and in combination with AZT.

For the monotherapy indication, the company proposed that the drug be labeled for use in "those patients, who in the opinion of treating physicians are not candidates for AZT monotherapy."

For the combination indication, the company proposed that ddC be suggested "for the management of HIV-infected adult patients, with AIDS or advanced ARC and CD4+ counts of less than 300."

The first ddC clinical study was actually initiated by the National Cancer Institute (NCI) before the drug was licensed to Hoffmann-LaRoche. At the doses used in this study, almost all the patients who received more than six weeks of therapy developed severe, dose-dependent peripheral neuropathy requiring discontinuation of therapy. However, NCI researchers noted transient increases of CD4 cells and reductions of p24.[1]

Hoffmann-LaRoche's Dr. Whaijen Soo presented results from ACTG 114, a study of 0.75mg ddC versus 1200mg AZT in patients with less than 90 days of AZT therapy (the dose of AZT was lowered when ACTG 002

released). The study was terminated early when the DSMB determined that the death rate in the AZT arm was significantly lower than that in the ddC arm.

RESULTS OF ACTG 114[2]		
	ddC	AZT
N	320	315
Median Tx	44 wks	53 wks
Drop-out	187	142
Deaths	101	73
% Alive after 1 year	85%	92.5%

The time to the first critical event, including death, or an AIDS-defining opportunistic infection or malignancy, was statistically significant favoring the AZT group in all patients. The CD4 analysis clearly favored AZT through week 20: after that time, however, there was no difference between the two treatment groups. In the sicker subpopulation, there was "essentially no increase in CD4 in the ddC treatment group."

Dr. Soo then presented results from ACTG 119, a study comparing 600mg AZT/day to 0.75mg ddC/day in patients who had already been treated with AZT. While the study had intended to enroll 320 patients, only 111 were actually recruited.

RESULTS FROM ACTG 119[3]			
	600mg AZT	0.75mg ddC	p-value
N	52	59	
Median Tx duration	21 wks	34 wks	
Drop out	34	22	
Death	13	10	non-significant
AIDS or death as 1st critical event	17	19	1.0
12-mo. AIDS-free survival probability	66%	69%	>0.2

Having seen no difference in terms of clinical improvement between the treatment groups, the researchers presented analyses of surrogate response.

"From about week 28 on," Dr. Soo noted, "there was at least a 20 cell difference between the two treatment groups."

In addition, the researchers analyzed the average slopes of CD4+ cell decline. The difference between the two treatment groups, in terms of slope analysis, significantly favored ddC (p=.05). This was, as Dr. Soo remarked, not seen in the sicker patients, but in patients "with the CD4 over 100 at baseline, beyond week 20 there was at least a 30 cell difference consistently across the remaining of the study period." No effect was seen on p24 antigen levels.

While there was no significant difference between the two groups in terms of changing Karnofsky scores, Dr. Soo observed that, here too, "there is a trend that seemed to favor ddC which was not clear in the sicker subpopulation, but in the less sick subpopulation the trend, again, seemed to favor the ddC treatment group." ddC induced a similar response with weight gain .[4]

Finally, Dr. Soo noted,

> The number of patients are (sic) very small and, again, it is unfortunate that we could not enroll up to full accrual and no conclusion can be really drawn based on statistical analysis, probably due to the small number of patients.[5]

In addition, Dr. Soo presented data on patients enrolled in Hoffmann-LaRoche's expanded access program.

EXPANDED ACCESS[6]		
	0.75mg Q8h	0.325mg Q8h
N	1735	1721
Median Tx duration	16 wks	16 wks
Deaths	260	296

There was no significant difference in either number of deaths or time to death between the two treatment groups. However, there was a smaller decrease and slower decrease in CD4 cell counts in the standard dose group as compared to the low-dose group.

The committee then heard data from Dr. Margaret Fischl from ACTG 106, a multi-arm, multi-dose, multi-treatment study designed to evaluate the safety of combination therapy, as well as immunologic and virologic markers of efficacy and development of resistance. Patients were treated with one of four doses of ddC in combination with AZT.

EFFICACY PARAMETERS FROM ACTG 106[7]				
CHARACTERISTICS	DOSE OF ddC			
	0.06 mg/kg	0.03 mg/kg	0.01 mg/kg	0.005 mg/kg
Average number of patient-weeks on therapy (range)	6.5 (1.1-11.9)	8.5 (2.6-13.6)	11.2 (5.0-14.0)	16.8 (6.6-26.7)
Average change in Karnofsky Score	-15.8 (18)	-5.0 (17)	0.0 (11)	-11.4 (14)
Change in weight, *kg*	-0.5 (18)	0.9 (17)	3.0 (11)	3.8 (14)
Changes in total number of enlarged lymph nodes†	-4.8 (15)	-3.6 (15)	-0.1 (11)	-2.6 (14)
Appearance of:				
Thrush	0.22,0.33 (18)	0.24,0.29 (16)	0.09,0.09 (11)	0.29,0.29 (14)
Hairy Leukoplakia	0.22,0.11 (18)	0.29,0.29 (16)	0.18,0.27 (11)	0.50,0.50 (14)
Other OIs	5	1	1	4
Kaposi's Sarcoma or Other Tumors	1	1	0	0
Median percent reduction in p24 from baseline value◊	78.5 (15)	81.9 (16)	50.3 + (11)	56.1 + (14)
Median percent change in CD4+ levels x 10^6/L	9 (15)	23 (15)	-14 (11)	-6 (14)

Dr. Fischl commented that

> Initially if one looks at the zidovudine alone arm — this is 50mg every 8 hours — one can see that there was indeed a minimal increase in CD4 with a rapid decrease to below pre-treatment values by week 12.
>
> If one then look at 50mg every eight hours of zidovudine with low-dose ddC, one can see, in comparison to monotherapy with zidovudine, that the magnitude of increase in CD4 cells appears to be greater, that the rate of decrease in CD4 cell counts appears to be slower, that patients with this combination appeared to remain with a mean change above pre-treatment for a longer period of time and this suggested to us that at this dose of zidovudine that the addition of ddC indeed had enhanced activity as far as CD4 cells are concerned.
>
> Now, if one looked at the remainder of the combinations, I think in general, looking at this, we can see that there was a prompt increase in CD4 cells with all the combinations somewhere between 80 and 110 CD4 cells, and that there was a slow decline in CD4 cells so that the majority of the combination regimens, the mean value, went below pre-treatment somewhere around a year and that the mean value on a few of these regimens did not go below pre-treatment beyond one year.[8]

Dr. Fischl then compared these patients to the treatment-naive patients in the AZT arm of ACTG 114 whose CD4 cells dropped below baseline at 24 or 26 weeks. She remarked that

> if you look at the comparison with these two studies, it indeed suggests that the magnitude of CD4 cell response and the durability of the response appears to be different with the combination therapy arm.[9]

In addition, comparing the ACTG 106 patients with patients in the AZT arm of ACTG 114, a greater percentage of combination therapy patients had NAUC values of greater than one, and a greater percentage of combination therapy patients had CD4+ responses of 25/25, 50/50, or 75/75.

Dr. Mark Smith asked, "If I understand, at a year we are talking about like two patients in each of these groups, two or three patients; right?"

Dr. Fischl responded

> Yes, when we are looking at long-term follow-up of patients yes, the number of patients that we are looking at are about 10 or 15 patients altogether...If you look at 48 weeks of follow- up in regimen A, there were 4 patients. In regimen B there were 6, in regimen C there were 5; in regimen D there were 6; in regimen E there were 7; and in regimen F there were 6.[10]

Patients in ACTG 106 with positive baseline p24 measurements had, "a prompt suppression of p24 antigen...that was maintained through follow-up of these patients." Dr. Fischl noted that the drift upwards of p24 values that had been noted with AZT monotherapy was not seen in this study.

Combination therapy also produced weight gain, according to Dr. Fischl, that was sustained. Weight gain in patients taking AZT in ACTG 114 occurred near the beginning of treatment and then drifted downward.

Dr. Robert Schooley presented data from BW 45,225:02, an ongoing study of nucleoside resistance. Patients had less than 300 CD4 cells, Karnofsky scores of over 60, and less than 4wks prior AZT. They were randomly assigned to receive 600mg AZT or. 600mg AZT in combination with 200mg ddI or 2.25mg ddC/day. Patients entering this study had a mean CD4 cell count of slightly under 150 on both arms. Fifty people were randomized per arm.

CD4+ cell counts of people on combination therapy peaked at about eight weeks, at about 225 CD4 cells. People on the single arm peaked slightly later but slightly lower, starting from a slightly higher baseline. The peak rise in people on combination therapy was 90 cells, for people on AZT alone, about half that.[11]

During the open public comment section of the hearing, some advocates expressed dismay. GMHC's David Barr commented that

> I have to say that after sitting through the data that we saw yesterday...there wasn't much that was very promising. It seems that with ddC, what people have always looked for is a window. Is there a window at which this drug is effective, but not too toxic? And that window is clearly very, very narrow and who knows if it is even there. We certainly didn't see much of it there yesterday and I have to say that it is depressing. I wish that the data was better. I wish there was more of it...There isn't much there for us to make our decisions on. There isn't much for my doctor to make decisions with and it becomes an increasingly frustrated situation for us.[12]

Derek Link, from New York's People with AIDS Health Group, pointed out that

> some very powerful researchers, primarily from Miami and San Diego, have been on a road show for the last year talking about the benefits of combination therapy with really the slightest of data. Many, many community activists have joined on to this. It has almost become a mantra for people in the community to talk about the benefits of combination therapy with really the slimmest of data. I don't know if this drug should be approved, but I am afraid that people have been lied to thus far. I would like to know where the data is to support adding this therapy to your AZT when the only effect that has been clearly demonstrated thus far is peripheral neuropathy and potentially deadly pancreatitis.[13]

Others, however, were concerned that the committee was backpedaling on its commitment to speedy approval based on short-term surrogate marker changes. Project Inform's Joel Thomas told the committee

> That I am having to defend CD4s as a marker is an affront to PWAs and their physicians. You tell me how many HIV-infected individuals have died with an abundance of CD4s. Just let me know. I don't think very many. I don't give a damn if you ever scientifically find linkage between CD4s and survivability. I look around me and at my own CD4 count and know that it is real.[14]

Project Inform's Delaney echoed the point:

> I am struck as so many other people were yesterday, with the revisitation of surrogate markers...It seems to me you made the right decision on ddI. You validated the surrogate markers. The data came back in support of it...CD4 may not be a perfect marker for survival in this disease, but as best we can tell, it is the primary organ of dysfunction in the disease. It is the primary target of the virus in the disease. How we can, you know, wring our hands to any extent is amazing to me.[15]

In FDA's review of the application, it acknowledged the poverty of the data set, in particular as pertained to the proposed monotherapy indication. In addition, FDA noted that approval of the application would represent something of a policy change with respect to the application of accelerated approval.

> This is the first potential approval based on surrogate markers for an indiction where currently approved therapy exists. In this respect, it is different than the ddI submission.[16]

Finally, FDA observed that, in proportion to the limited surrogate benefits of the treatment, the rate and magnitude of the observed toxicities presented great concern:

> It should be recognized that, although overall toxicity may be similar to zidovudine, as for all the drugs, any toxicity is relative to benefit. Being equivalent to zidovudine for toxicity, which itself is toxic to many body systems, is certainly no badge of honor for any new chemical entity.[17]

Finally, FDA noted that the combination regimen seemed to offer little improvement over monotherapy.

> The present regimen lacks some of the theoretical benefits of combinations, i.e., it is again there should not be less toxicity *a priori* and there doesn't appear to be delay of resistance, which appears to be the primary *raison d'etre* for the — or one of the *raison d'etres* for the study.[18]

Dr. Carla Petinelli from the NIH's Division of AIDS, presented a summary of ongoing follow-up studies of ddC.

PLANNED FOLLOW-UP STUDIES OF ddC[19]

Study	N	Patients	Treatments	Endpoints
ACTG 155	1001	<200 CD4 asx or <300 CD4 sx	AZT v. AZT+ddC v. ddC	OI or death
ACTG 175	2000	200-500 CD4	AZT v. ddI v. AZT+ddI v. AZT+ddC	OI or death, 50% CD4 decline
CPCRA 002	460	<300 CD4+, AZT failure, intolerant	ddI v. ddC	OI or death
CPCRA 007	1200	<200 CD4+	AZT v. AZT+ddI v. AZT+ddC	OI or death
ACTG 193	700	<50 CD4	Conc. AZT+ddI v. Conc AZT+ddc v. Alt. AZT+ddI v. Alt. AZT+ddC	Death

In evaluating the data supporting the proposed indications, Dr. Mark Smith began to express concern about the use of surrogate markers:

> In this hearing, we have already heard the beginning of some selective use of CD4s, when it seems to show an effect, and ignoring some other aspects when they don't...Let me say that it seems to me we are supposed to decide if this drug is safe and effective. Is it safe? Not particularly. Is it effective? I don't know. Not much, if it is. You know, I am not — I am frankly underwhelmed by bumps and blips and 10 cells at 24 weeks. That doesn't move me much.[20]

Dr. Donald Abrams of the University of California/San Francisco, advanced another critique of the surrogate effects:

> I think I am getting somewhat confused and discouraged. I agree with everybody, who said in the clinical world that certainly our patients like to have more and we like it when our patients have more CD4 cells than less, as well. I am relieved...that our July decision to recommend approval of ddI on the basis of that blip we saw in 117, while we were still blinded, was translated into some clinical benefit.
>
> Where I become discouraged and saddened again is in the lack of a translation into survival benefit...There have been a number of studies that have demonstrated that there is not a correlation between that bump, transient often as it is, and prolonged survival. And I guess maybe it is a personal thing, too, and I — you know, people live in New York. I live in San Francisco. It is a terrible epidemic. When I look at my friends, I can't see their CD4 counts through them. I don't see their normalized area under the curve. I see my friends dying.[21]

One substantive area of agreement among the committee members was the need for reliable post-marketing validation of surrogate effects. Dr. Meier told the committee

> I feel very strongly that the committee cannot, must not ignore the legal and moral responsibility that it has to inquire into the valuation of evidence of clinical benefit....If the surrogate markers do not, in fact, match up with clinical benefit, then we are simply not doing our job if we turn to them alone.

Worse yet, we teach a lesson. A fair number of comments from industry-related people after our ddI decision were along the lines, we don't need the long-term follow-up studies any more. All we have to do is show benefit in CD4 counts and that is what we are going to do. You did it for ddI. So you have got to do it for us...

It would be, in my opinion, terribly irresponsible to take the surrogate as enough without the insistence on follow-up of clinical end point studies that even if the patients are not kept on the original treatments, studies that follow those patients for at least a couple of years to see what the clinical effect of having been placed on one drug or another may be.

I think the main response needs to be more efficient clinical trials, more efficient design, more efficient analysis.[22]

Finally the committee voted against approval of the monotherapy indication, and for accelerated approval of the combination indicaton.

New York University's Dr. Fred Valentine sounded the final warning note

It is critical that these accelerated approvals not compromise our ability to get the definitive data because otherwise we will be swimming in a sea of anecdotal medicine. We must not compromise our ability to learn how to use these drugs properly and to get proper data...I would also like to ask Dr. Kessler for an interpretation of the withdrawal process. The summary statement that we were given says that if a postmarketing study fails to verify clinical benefit. Now that could occur because the study was done and it did not verify clinical benefit or the same net effect would happen if the study could not be done. If the study could not be done, how would that fit into the failure of a study to provide clinical benefit? [23]

Dr. Kessler responded:

As I interpret the whole concept, as we intend it, there would remain an — the burden would remain on the manufacturer to come forward and show a positive clinical benefit. The absence of showing a clinical benefit in a reasonable period of time, I think, would be tantamount to almost no clinical benefit. You have to keep — you just have to keep the incentive in the direction of getting more data and that is the reason why we have to keep the burden on the manufacturer.[24]

Ultimately, FDA granted accelerated approval to the combination therapy indication, but rejected the proposed monotherapy indication.

CHAPTER NOTES

1) Soo W MD in Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, Apr 20 1992

2) Chart derived from Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, April 20-21 1992

3) Chart derived from ibid

4) FDA would later note that weight gain is not a reliable surrogate marker for more significant outcomes, such as survival. In fact, in ACTG 114, Dr. Gitterman observed that "The patients with the most impressive weight gain were the ones with the highest mortality."

5) Transcript, op cit., Apr 20 1992

6) Chart derived ibid

7) Fischl M, et al., A Phase I/II Study of Combination 2',3'-dideoxycytidine and Zidovudine in Patients with Acquired Immunodeficiency Syndrome (AIDS) and Advanced AIDS-related Complex, Am J Med

8) Transcript, op. cit., Apr 20 1992

9) ibid

10) ibid

11) ibid

12) ibid

13) ibid

14) ibid

15) ibid

16) Gitterman S MD in ibid

17) ibid

18) ibid

19) Compiled from Pettinelli C MD, in Transcript, op cit., Apr 20 1992

20) ibid

21) ibid

22) ibid

23) ibid

24) ibid

25) ibid

Although this debate is sometimes framed as patients just wanting drugs and the researchers are concerned about the data, that is really not the case and it has never been the case. I am not changing my argument from 1988. It has always been my argument. Nobody is concerned at the table about good data more than I am. Because I am the one who puts it in my mouth.

David Barr in Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, Sep 20 1993

This, to me, is in some sense no easier than if we simply said there exist three drugs for AIDS. These are their toxicities. They might or might not have benefit for some or all patients in some or all clinical or laboratory subgroups. We are talking art here, not science, as far as I can see.

I truly do believe that we have set things back, and I have said that before. But I think nothing that I have heard in the last six months has made me feel any differently. I think we would be further ahead now if we had stayed with the 1987 standard of two controlled trials. But we did not. And here we are, and it is 1993, and what are we going to do?...

I think my inclination would be to leave things alone. I think we have made things bad enough. I don't want to see us make them worse. And to try to finally, I hope, come together and say that we have to start going back to basics and doing these trials in essentially the traditional way — no more amendments; no more unbalanced randomizations. We need to go back to basics. If we know what the result is going to be we shouldn't be doing the trial. If we don't, let's do the trial the way we have worked out over approximately 40 years of methodologic research. To me, there is just no way around that. So I would leave things alone.

Debbie Cotton in Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, Sep 20 1993

On September 20, 1993, the Committee again met to review an application for an extension of indication for HIVID brand zalcitabine (ddC). In particular, Hoffmann-LaRoche was requesting that FDA grant full approval for its combination regimen, as well as approval for a monotherapy indication.

FDA's Dr. David Feigal began the meeting by clearly prohibiting discussion about the clinical relevance of small changes in absolute CD4+ count:

> It is clear, based on these new studies that they have a bearing on the use of this drug and on the labeling of this drug, and that is the agenda for today. We have primarily focused on studies with clinical endpoints and will not be revisiting in any detail the issues of what the surrogate markers show.[1]

The company chose to identify indications that the committee would later criticize as downright bizarre:

> In terms of a proposed monotherapy indication, we are proposing that HIVID is indicated for the treatment of adult patients with advanced HIV infection with demonstrated intolerance or significant clinical or immunologic deterioration during AZT therapy.
>
> In combination with ZDV or AZT, we are proposing that HIVID is indicated for the treatment of adult patients with advanced HIV infection, CD4 cell counts of 100-300, who have demonstrated signs of clinical or immunologic progression.[2]

As the presentation involved large amounts of data from four trials, information was summarized first by trial, and then by indication. Dr. Anne Goldman began the presentation with a summary of CPCRA 002, a study comparing ddI to ddC in patients with less than 300 CD4+ cells and/or AIDS. Endpoints included time to

death and/or a new AIDS-defining opportunistic infection. Patients reaching a morbidity endpoint were allowed to switch to the other therapy open-label.

BASELINE CHARACTERISTICS OF PATIENTS IN CPCRA 002[3]

	ddI	ddC
N	230	237
AZT Response (%)		
Failure	36.5	38.4
Intolerant	63.5	61.6
Duration of prior AZT (mos)	17.4+11.6	17.5+10.3
Failure	22.6+11.3	23.1+9.2
n	84	91
Intolerant	14.4+10.6	14.0+9.3
n	146	146
Karnofsky Scores	87.2+11.9	85.3+11.9
CD4+ counts (cells/mm3)		
Mean	75.1+86.2	71.1+84.3
Median	40	34
AIDS (%)	64.8	66.7
Switchovers	43	26

Dr. Goldman observed that

> It appears to divide into sort of 3 phases, an initial phase where there is no difference at all and then a short phase where ddI actually seems to be somewhat better, and then another phase where ddC seems to be somewhat better. But trying to interpret this crossover is probably an over-interpretation of the data.
>
> As far as survival is concerned, there was somewhat more difference between the two drugs, with ddC appearing somewhat better.[4]

CLINICAL ENDPOINTS FROM CPCRA 002[5]

	ddI N=230		ddC N=237		Relative Risk (ddC:ddI)			
	No. of Patients	Rate	No. of Patients	Rate	Unadjusted Risk (95%) CI	p value	Adjusted Risk (95% CI)	p value
Disease Progression or death	157	93.3	152	87.7	0.93 (0.74-1.18)	0.56	0.84 (0.67-1.06)	0.2
Disease Progression only	120	71.9	115	66.4	0.92 (0.70-1.20)	0.52	0.87 (0.67-1.13)	0.3
Death only	100	42.8	88	35.1	0.78 (0.58-1.04)	0.094	0.63 (0.46-0.85)	0.03

While no significant differences were noted between the treatments in terms of their ability to delay morbidity and mortality, when adjustments were made for small baseline differences in Karnofsky score, CD4+ count and prior AIDS diagnosis, the data suggest a substantial survival benefit for ddC.

Dr. Goldman commented on these adjustments

> I think that is partly due to the small imbalances at baseline, but, more importantly, due to the heterogeneity and the dramatic effect of these prognostic variables, which are far larger than the differences between the two study groups.[6]

People on ddI had an initial increase in CD4+ cells, however people on ddC had no such increase. At eight weeks, the difference was significant, with an average 8.6 cell increase for ddI versus an average drop of 6 cells on ddC.

Dr. Goldman noted that "ddC was at least as efficacious as ddI in delaying disease progression and...the patients in the ddC group had improved survival." She added an observation that "we are not trying to show efficacy; we are just trying to show relative efficacy."

Dr. Margaret Fischl then presented results from ACTG 155, a randomized, double-blinded study of AZT v. ddC versus. AZT plus ddC in patients that had prior AZT therapy. Participants were required to have symptomatic HIV disease and an absolute CD4+ cell count of less than or equal to 300, or asymptomatic HIV disease with a maximum absolute CD4+ count of 200. In addition, participants were required to have undergone at least six months prior treatment with AZT. Endpoints included time to AIDS or death.

In a striking deviation from standard practice, patients were randomized disproportionately (2:2:3), with the plurality of participants receiving combination therapy.

Midway through the study, researchers added an option allowing patients to crossover to combination therapy after development of primary study endpoint. In addition, the study team added a stratification by CD4+ cells, dividing patients into groups of less than 50 CD4+ cells, 50 to 150 cells, or more than 150 cells.

BASELINE PATIENT CHARACTERISTICS & PRIMARY ENDPOINTS FROM ACTG 155[7]

	AZT	ddC	Combo
N	283	285	423
Duration prior AZT	18mos	18mos	18mos
Follow-up	17.5mos	17.5mos	17.5mos
Median duration tx	10.5	12.2	11.9
Discontinuation	45%	33%	38%
Loss to follow-up	10%	8%	7%
Cross-over	27	22	36
CD4+ cell count			
Median	127	117	112
<50	71	85	113
50-150	94	89	153
>150	118	111	157
HIV p24ag >25pg/mL	26	27	29
Death	43	51	78

Overall, there was no difference between the three treatment groups suggesting, as Dr. Fischl pointed out, that there" appeared to be no additional or increased benefit by switching to ddC or by adding ddC to the regimen of these patients with advanced HIV disease."

However, Dr. Fischl observed,

> You can see, looking by the three [CD4] subgroups that as the pretreatment CD4 cells increased one could see a benefit favoring combination therapy. In fact, when one looked at the greater than 150 subgroup, one can see that the relative risk was 0.5, which means the difference between combination and zidovudine was actually quite large in this group.
>
> Time to first event or time to the primary endpoint, which was a first AIDS-defining event or death...there was a significant difference between the combination and zidovudine but not between the combination and ddC [in the high CD4 subgroup]. If one looks at the 50-150, there were no

significant differences between the groups...Finally, with the less than 50, the curves are overlapping and there were no differences at all between these groups.[8]

There were no differences between the subgroups in rates of survival.

ADVERSE EVENTS FROM ACTG 155[9]

Toxic Effect (#/%)	AZT (n=283)	ddC (n=285)	Combo (n=243)	P-Value
Neutropenia	49(17)	26(9)	82(19)	0.0005
Anemia	14(5)	13(5)	35(8)	0.09
Hepatic	24(8)	16(6)	25(6)	>0.1
Neuropathy	12(4)	18(6)	25(6)	>0.1
Fever	23(8)	12(4)	17(4)	0.05
Fatigue	7(2)	5(2)	19(4)	0.10
Headache	5(2)	5(2)	10(2)	>0.1
Nausea or vomiting	7(2)	4(1)	4(1)	>0.1
Pancreatitis	4(1)	9(3)	8(2)	>0.1
Stomatitis	2(1)	11(4)	4(1)	0.01
Rash	4(1)	6(2)	6(1)	>0.1

KEY ADVERSE EVENTS FROM ACTG 155 STRATIFIED BY CD4+ CELL COUNT[10]

Toxic Effects	AZT (n=283)	ddC (n=285)	Combination (n=423)
Neutropenia (<750 cells/mm³) (#/%)			
>150 CD4 cells/mm³	**9(8)**	**3(3)**	**14(9)**
50-150 CD4 cells/mm³	**11(12)**	**8(9)**	**28(18)**
<50 CD4 cells/mm³	**29(41)***	**15(18)***	**40(35)***
Anemia (hemoglobin level <79 g/L) (#/%)			
>150 CD4 cells/mm³	6(5)	1(1)	8(5)
50-150 CD4 cells/mm³	2(2)	4(4)*	10(7)*
<50 CD4 cells/mm³	6(8)	8(9)	17(15)
Severe or worse peripheral neuropathy (#/%)			
>150 CD4 cells/mm³	**2(2)**	**4(4)**	**7(4)**
50-150 CD4 cells/mm³	**6(6)**	**7(8)**	**10(7)**
<50 CD4 cells/mm³	**4(6)**	**7(8)**	**8(7)**
Moderate or worse peripheral neuropathy (#/%)			
>150 CD4 cells/mm³	11(9)	18(16)	33(21)†
50-150 CD4 cells/mm³	13(14)	25(28)	32(21)
<50 CD4 cells/mm³)	14(20)*	23(27)	26(23)

* P<0.05 for the comparison of the CD4 cell count subgroups within a treatment using an exact test for ordinal data.
† P<0.05 for the comparison of the three treatments overall using the Fisher exact test.

The decision to add the CD4+ subgroup analyses after randomization had been controversial for some time. At the IX International Conference on AIDS in Berlin, during the summer of 1993, Dr. Fischl had presented

the subgroup analyses without noting the overall finding of the primary randomization, that no benefit was found in patients taking combination therapy versus patients taking monotherapy. Activists had termed the analysis "Intention to Cheat," and the NIAID had withdrawn a press release that touted the subgroup analysis without commenting on the primary analysis.[11]

Although Dr. Fischl had presented the results of the primary analysis to the committee, the post-hoc subgroup analyses continued to trouble the interpretation of the data. Dr. Cotton observed that

> I do think that we have to realize that in many ways it seems that there were certain assumptions made in the design of this study that the combination was going to be better. For one thing, the randomization was not balanced. More people were randomized to combination therapy. The approach to reaching an endpoint was to crossover specifically to combination therapy. You were not randomized to crossover to something you hadn't been on; you were put on combination therapy. So I think there was certainly the hope, if not the presumption, that combination therapy was going to be better.
>
> Therefore, I think we have to be extraordinarily cautious, because, human nature being what it is, it is very hard to see things through a particular lens when you truly believe, on very scientific grounds, on very good laboratory grounds, that the combination therapy is going to be better...
>
> The particular arguments that are being made may be driven in the results we see by stratification. But I am not convinced that we wouldn't be coming up with another set of arguments, and I think we have to be very, very careful about that, given everybody's hope that combination is better.[12]

Dr. Ken Stanley, the protocol team statistician, stepped in to explain the subset analyses:

> [The CD4 subset analyses] were predetermined and we made a decision as the protocol team not to modify the protocol. They were not there when the protocol was initially designed.
>
> Let me just run you through the time line here. Patient entry began in the study in December 1990. Patient entry ended with a flourish in August 1991...
>
> In February 1992, there were a number of presentations at the ACTG meetings which indicated that baseline CD4s might be quite influential with respect to influencing studies. Based on that, the study chairs specified the analysis into these particular cut-offs, and the analysis plan at that point in time was revised to state an analysis by these 3 cut-offs...
>
> There was a DSMB in February of 1992. They looked at what at that point in time was only 25 percent of the failures. There was clearly nothing going on at that point. There was another DMSB in August of 1992 when the study was half mature. There was nothing going on at that point overall. In January of 1993 the study was stopped. The endpoints were reviewed in a blinded fashion by the study chair and co-chair. So they did not know any of this up to that point in time. As a matter of fact, it wasn't until the day after they stopped the blinded review that they even knew any of the study results.
>
> So they had made this determination with respect to cut-offs and their analysis plan 8 months prior to knowing anything with respect to the analysis results. In fact, the particular subgroup analyses were not even done until August of 1992. So there was no way it could have influenced that particular decision in June of 1992.[13]

David Barr echoed the concerns about patient and investigator bias in the design and implementation of ACTG 155:

> I can't help myself, this is from a transcript of a meeting with Hoffmann-LaRoche that ACT UP had in August of 1990...
>
> This was said by Dr. Soo. "I would like to confide a comment of Dr. Fischl's. The difference she sees among people on the ddC-AZT combination in ACTG 106 is a big difference, like the difference between people on AZT versus placebo in the original trial. She can almost tell them apart by

looking at their behavior. It is only anecdotal, but it is very promising."...

Now the patient demand for combination therapy comes from statements like that at this meeting, knowing full well that I am going to go back to my community and give the reports of the anecdotal evidence that I heard. So, yes, there was a tremendous demand for combination therapy but how was that fueled, and how did it then impact on the design of the future trials?[14]

Dr. Sheiner disagreed with the concerns about the effect of possible investigator bias on the subset analyses:

I honestly do not know why I should focus on the fact that before the data were ever looked at, but not before the study began, this was decided to be a stratified analysis. If there had been imbalance, if, in fact, because they were not randomized to the different strata of this particular variable and there had been a large imbalance, that would have presented a problem with power to find differences between the subgroups. It would not, in fact, have caused a spurious difference between subgroups to arise.

As far as I can see, the only harm done by not specifying when the study begins relative to before looking at the data is that you might lose power, not that you will get false conclusions.[15]

FDA's Dr. Kazempour explained the concerns:

The main reason for the problem that we will have if we do post-stratification — there are two. One might conduct too many tests on too many subgroups [increasing the probability of a false positive result]. That is one. The other one is that the data may not be randomized properly with known or unknown factors. They may be unevenly distributed among treatment groups. Some of the factors that we know and we have looked at, like age, was properly well distributed. But some others, like ethnicity, were not well distributed among different treatments.[16]

Dr. Robert Schooley then presented long-term results from his study of resistance to antiretroviral therapies in patients with absolute CD4+ cell counts of less than or equal to 300. The study compared patients taking AZT to patients taking AZT with ddC or ddI. One hundred and eighty patients had been randomized, and immunologic and some clinical data were collected.

Dr. Schooley explained that combination therapy had been significantly better than monotherapy by a number of measures:[17]

- Combination therapy produced sustained increases in CD4+ cell counts to one and a half years
- Combination therapy produced improvements in the median CD4+ cell counts
- Combination therapy produced a better responses using the 10:10, 50:50 and 75:75 measures
- Combination therapy produced greater NAUC values compared to monotherapy

Dr. Schooley concluded that, looking only at the surrogate response, "there is a substantial benefit for combination therapy over monotherapy."[18]

Dr. Miklos Salgo from Hoffmann LaRoche then summarized the data by indication, beginning with monotherapy:

CPCRA 002, as previously described, showed that ddC was at least as efficacious as ddI in that study, whether adjusted or unadjusted. With the adjusted analysis there was a benefit on survival favoring ddC.

With the [ACTG] 114, as you know, AZT was found to be superior to that and that study was terminated. However, I would point out that that was basically an AZT-naive patient population that we are not discussing in the indication today.

[ACTG 119], as we mentioned last year in presenting this, we were not able to fully accrue this study because of difficulty accruing — competing things, including expanded access, but we did

have about 115 patients and we did do a follow-up looking at survival alone...through January of this year. We did find that there were somewhat fewer deaths overall on ddC compared to AZT in patients who had at least a year of prior AZT. We looked at the OIs. It was at a different time point, last summer. It was not statistically significant between the two treatments.

The monotherapy arm for 155 — here we can see that for both deaths and death or OI there were slightly fewer on AZT compared to ddC but the difference was not significant for either comparison.

In conclusion, in advanced patients who were AZT intolerant or AZT failures, in other words, very specifically the entry criteria for CPCRA 002, ddC is at least equivalent to ddI in terms of progression of disease or death and provides a survival advantage, which in the adjusted analysis had a p value of 0.002. In patients with prolonged prior AZT there is no statistically significant difference between ddC and AZT and, indeed, in those and other studies there is surrogate marker evidence of activity of ddC.[19]

Dr. Salgos then pointed to the post-hoc subset analysis from ACTG 155, indicating improvement in patients with less than 150 CD4+ cells, to support the following combination indication:

ddC is indicated in combination with AZT in patients who have advanced HIV infection, with CD4 counts of 100-300, who have demonstrated signs of clinical and immunological progression.[20]

In another post-hoc subset analysis, Dr. Salgo analyzed the data from ACTG 155 by CD4 greater than or less than 100 CD4+ cells. Using that analysis, in the healthier patients, with 130/405 clinical endpoint events, 19 percent progressed on combination while 30 percent progressed on AZT alone (p=0.01).

Dr. Salgo then summarized the available toxicity data:

The incidence of peripheral neuropathy possibly or probably related to ddC of moderate severity is about 23-28 percent.

Looking now at pancreatitis across all studies — pancreatitis is obviously serious but, fortunately, a rare occurrence with ddC. In our monotherapy controlled trials, 1.3%; combination, 0.6%; overall, about 1 percent. I would point out that in the Roche trials, including the expanded access...we reviewed especially the expanded access data and if a patient had increased amylase at the same time that they had abdominal pain, that was classified as pancreatitis.[21]

Dr. Salgo then presented information on concerns about lymphoma associated with ddC use:

An animal study, by the National Institute of Environmental Health Sciences, in female mice that showed that mice given a large dose of ddC, 1000 mg/kg, had a high rate of thymic lymphomas. I would point out that the importance of this is unclear. These are thymic lymphomas, not the B-cell lymphomas seen in AIDS patients. The doses were very high, about 1000-fold higher than the plasma concentrations seen in humans, and this particular strain of mice had a high strain of neoplasms...

155 did have a significantly higher rate of lymphomas on the ddC-containing arm, a total of 18, none on AZT, 5 and 13, and this was statistically significant at 0.03...

I would also point out that in expanded access we had a large patient population, about 4000 patients and there was no dose response. The occurrence of lymphomas was roughly the same in high-dose or low-dose.[22]

In the FDA's summary of the information regarding combination therapy, Dr. Gitterman observed that

The number of endpoints is small for the specific indication that the sponsor is seeking...For the group greater than 100 we have 44 deaths in the combo group, 36 in the ddC group and 50 in the AZT group. Obviously the denominator is different. Obviously [they differ in time-to- death], which is why they come close to statistical significance. But again, in absolute terms this is not a

large number of patients on which you are making decisions that may affect substantially more patients than is reflected in the study...

I would also mention, as also was brought up, that it is clear the study was under-powered for detecting a difference in survival for the indication the sponsor is seeking, even if one existed.

The endpoint may not be the most appropriate for the disease, by which I mean the primary endpoint for the study. You know, in almost all studies with nucleoside analogs as monotherapy, to date, drug efficacy has been shown to be time limited. Because of this, the endpoint of "time to first OI" may be flawed. This parameter may not predict survival or it may not even predict the frequency of subsequent OIs. There are several explanations for this — viral resistance, phenotype changes, cellular factors — but again, it may be a flawed endpoint at this point when you are just looking at the first event.

Percentage-wise, and we can't push this too far because it is talking about percentages on the one hand, Kaplan-Meiers on the other and risk ratios, but percentage-wise, the difference in neuropathy probably is greater percentage-wise than the therapeutic benefit you're looking at.[23]

During the open community comment session of the hearing, activists were uniformly opposed to any change in the regulatory status of ddC. Derek Link argued that

Full approval of the questions before you would both abuse the intent of the accelerated approval regulations and allow unacceptably low approval standards for new AIDS drugs. Fully approving ddC combination therapy would sanction the type of data analysis you see in 155. It would also mean that all of the other studies Roche is required to perform for full approval, studies that could still answer important clinical questions, may never be done.[24]

Link warned that

Efficacy studies for the protease inhibitors are being designed today with the methods and mistakes of yesterday.[25]

Mark Harrington, from TAG, echoed this concern

Some of us believe that, if the committee today approves these new indications for full marketing of mono and combination therapy, we may never again see compelling or definitive evidence of clinical efficacy for any antiretroviral drug in a disease that is very hard to study, in which progress is frustratingly slow.

Thus, for AIDS drugs, the 1962 Kefauver amendments would effectively have been abrogated by regulatory fiat. Though this might please the industry, it would be a disaster for people with HIV, and it is something we have never sought.[26]

Project Inform's Brenda Lein and Joel Thomas concurred:

[when the committee recommended accelerated approval of ddC] many people in this room felt uncomfortable about the decision, feeling that the limited data available pushed hard the flexibility and spirit of the new regulatory reforms.[27]

Committee members agreed with the activists' concern about the meaning of continued accelerated approval for ddC. Dr. Smith observed that

I am increasingly unclear on what it means to leave a drug on accelerated approval. It has been accelerated for a year now. I guess at some point we need to talk about by when we ought to have something else, by which time accelerated approval ought to be either traditional or withdrawn. That would be my own view. I guess we had said there ought to be an opportunity for the company to respond to what studies are under way and what we might reasonably expect them to

demonstrate. But it does seem to me that even continuation of the drug as an accelerated approval ought to be linked to some sort of sense of what we ought to know by when.[28]

Almost immediately, the committee reached agreement that "we do not feel that the data presented support a change from accelerated to traditional approval for any of the indications."[29]

Deciding what to do, however, proved to be somewhat harder. The committee, having rejected full approval for combination therapy, seemed inclined to maintain the drug's current regulatory status:

I guess I agree that leaving the label alone is probably the best of a bad set of choices...On the other hand, I don't agree with the statement that the data for accelerated approval stay on the table for ever. I think they are decaying rapidly. The question is have they decayed enough to change the label in the interim period? And that may be too short a period with the demanding kind of clinical evidence that this Committee seems to be asking for in the form of randomized trials. On the other hand, three years from now I would have a very different judgement about whether or not that evidence was sufficient to allow the drug to be on the market.[30]

One committee member expressed their concern: "I would hate to think that this committee will be going through the same kind of agony year after year with other products."[31]

Finally, Dr. Cotton proposed the solution that would carry the day:

I think we have seen equivalence, at least in some patient populations. It is tough clinically because in naive patients it would appear that ddC is inferior to AZT as monotherapy. But in patients who have been on AZT for a reasonable period of time, they look perhaps equivalent; maybe an advantage to ddC. In people who are in the CPCRA group, intolerant of AZT, ddI and ddC appear roughly equivalent, with different kinds of toxicities...Right now I don't want to say for sure how I feel, but I am leaning toward approval for monotherapy. I don't believe in accelerated approval. I think we either approve it traditionally or we don't approve it, but I wouldn't get involved in accelerated approval for, among other reasons, look at what we are dealing with now with accelerated approval for combination.[32]

Other committee members concurred half-heartedly:

I think we can say...that in the person who is AZT intolerant, that ddI and ddC are at least equivalent. Whether they are better than placebo is something that we will never probably be able to know. In my heart I hope they are a little better than placebo but they are at least as good as each other and, therefore, that part of the approval I think is appropriate.[33]

Finally, after much soul-searching, the committee voted to rescind the accelerated approval indication for combination therapy, and to recommend full approval for monotherapy in patients who had experienced significant clinical or immunological deterioration on AZT therapy.

David Barr summarized the afternoon:

You approved this drug for accelerated approval and the follow-up has not yet been done. You already said that when we did the first go-around. You will now make it much more difficult for us to get any of those answers. As long as nobody is hurt by not approving the monotherapy indication, then I don't see why you would want to do that. It seems in conflict with everything else that you have said around here.[34]

In August of 1994, the FDA approved ddC as monotherapy, while maintaining the accelerated indication for combination therapy. The specter of this decision haunts FDA to this day.

CHAPTER NOTES

1) Feigal D in Transcript of a Hearing of the FDA's Antiviral Drug Products Advisory Committee, Sep 20 1993

2) Perkins G Ph.D. in ibid

3) Abrams DI, A Comparative Trial of Didanosine or Zalcitabine after Treatment with Zidovudine in Patients with Human Immunodeficiency Virus Infection, NEJM, 330:657 62, Mar 10 1994

4) Transcript, op cit., Sep 20 1993

5) Abrams DI, op cit.

6) Transcript, op cit., Sep 20 1993

7) Fischl M MD et al., Combination and Monotherapy with Zidovudine and Zalcitabine in Patients with Advanced HIV Disease, Ann Intern Med, Jan 1 1995

8) Transcript, op cit., Sep 20 1993

9) Fischl M, op cit., Jan 1 1995

10) ibid

11) Link D, in Letter to Dr. Anthony Fauci, MD, dated Sep 14 1993

12) Transcript, op cit., Sep 20 1993

13) ibid

14) ibid

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16) ibid

17) ibid

18) ibid

19) Salgo M MD in ibid

20) ibid

21) ibid

22) ibid

23) ibid

24) ibid

25) ibid

26) ibid

27) ibid

28) ibid

29) Masur H MD in ibid

30) Feinberg J MD in ibid

31) Tsoukas C MD in ibid

32) ibid

33) Horsburghe MD in ibid

34) ibid

ZERIT BRAND STAVUDINE (d4T)

On Friday, May 20, 1994, the Committee met to review data regarding Bristol-Myers Squibb's Zerit brand stavudine (d4T).

Dr. Feigal began the meeting with a summary of the accelerated approval regulations. In particular, the committee expressed confusion regarding the requirement that there be a population for whom this therapy provides meaningful therapeutic benefit over existing treatment. Asked to clarify the phrase "meaningful therapeutic benefit over existing treatment," Dr. Feigal replied that he meant an improved surrogate marker response in patients for whom no useful therapy existed, or who had failed or proved intolerant to standard therapy.

With respect to the requirement that drugs considered for accelerated approval must demonstrate improvements in a surrogate marker that is "reasonably likely to predict clinical efficacy," Dr. Feigal noted that there had been criticisms of the use of CD4+ changes, however he also noted that FDA remained firmly committed to approvals based on small changes in CD4+ counts. "After all," he noted, "If surrogate markers were perfect, we wouldn't be using them as surrogate markers."[1]

The company had conducted three major phase I studies of d4T in people with AIDS/ARC: AI455- 002, AI455-003, and AI455-004/5. Studies 004/5 were conducted in AZT intolerant patients. All studies were non-randomized dose ranging (0.5-12.0 mg/kg/day), and were intended to define the maximum tolerated dose, and then to de-escalate to determine the minimum active dose.

NUMBER OF PATIENTS BY STUDY AND DOSE IN PHASE I STUDIES OF d4T[2]

	Dose (in mg/kg/day)				
0.5	1.0	2.0	4.0	12.0	All
002	5	8	7	21	41
003	6	5	10	22	43
004/5	10	13	—	—	23
Total	21	26	17	43	107

BASELINE PATIENT CHARACTERISTICS FROM d4T PHASE I STUDIES[3]

N	107
HIV Diagnosis (%):	
ARC:	67
AIDS:	33
Prior AZT (%):	68
CD4 count (cells/mm³):	
Median:	110
Range	4-598

The maximum tolerated dose was 2.0 mg/kg/day. Neuropathy was dose-limiting and dose-related. No minimum active dose was seen. CD4+ and p24 effects were dose-responsive.

The company then presented results from AI455-006, a phase II study in HIV+ patients. The study began with 45 patients, and then expanded to 152 patients.

PATIENT CHARACTERISTICS FROM AI455-006

	Dose (in mg/kg/day)		
	0.1	0.5	2.0
N	51	53	45
HIV diagnosis (%):			
Asymptomatic:	10	8	13
ARC:	65	70	73
AIDS:	25	23	15
Prior AZT (%):	82	74	63
CD4+ count (cells/mm^3):			
Median:	280	212	270
Range	2-486	2-596	8-491

Three doses were compared to determine effects on CD4+ counts, p24 response, quantitative HIV in PBMC, and weight. Median time on treatment was 1.5 years. CD4+ counts rose at all doses. Prior AZT treatment did not influence the CD4 response.

PBMC VIRAL TITRES (IU/100 PBMC) FROM AI455-006

	Dose (in mg/kg/day)		
	0.1	0.5	2.0
Baseline:	21.3	26.2	49.1
10 weeks:	38.6	25.8	10.5
% change	+81	-2	-79

Body weight rose at all doses, with no dose-response.

SERIOUS ADVERSE EVENTS

	Dose (in mg/kg/day)		
	0.1	0.5	2.0
N	51	53	45
Neuropathy	6	17	31
Other PN sx	10	9	8
Depression	2	6	10
Asthenia	4	8	4
Headache	4	8	2
Chills/Fever	4	6	4

Bristol-Myers Squibb's Dr. Lisa Dunkle presented AI455-019, the company's pivotal efficacy study, which compared 80mg d4T daily to 600mg AZT, and was stratified by site and baseline CD4+ count (<100, 101-300, >300). Primary endpoints included death, new or recurrent AIDS-defining OI, or drop to less than 50 percent of baseline CD4+ cell count. Primary endpoints remained blinded at the time of this analysis.

BASELINE PATIENT CHARACTERISTICS IN AI455-019		
	d4T	**AZT**
N	172	265
HIV Diagnosis (%)		
Asymptomatic	45	36
Symptomatic (non-AIDS)	45	55
AIDS	10	9
Median length of prior AZT	81 wks	89 wks
Baseline CD4 Distribution		
Median (cells/mm^3):	238	215
<100	17%	13%
100-300	49%	49%
>300	34%	34%
Baseline p24ag Status		
p24+ (%)	42	40
Median (pg/ml)	117	159
Baseline HIV cultures:		
Culture + (n)	24	27
Mean titer (IU/10^6 PBMC)	18.7	10

Dr. Dunkle observed that differences in p24ag response between d4T and AZT were not significant.

Subjects on d4T had an average increase of 20-25 CD4+ cells compared to subjects on AZT, and that increase was sustained for more than 20 weeks.

HIV VIRAL TITERS (IU/10^6 PBMC) IN AI455-019[3]				
	N	**BASELINE**	**WK 12**	**% CHANGE**
d4T	23	16.5	7.7	-53
AZT	27	10	11.2	+11

CD4+ RESPONSE IN AI455-019			
Analysis	**d4T**	**AZT**	**P-VALUE**
10:10	40	21	0.0002
25:25	23	7	0.0001
50:50	6	1	0.02
NAUC 12 >1	70	42	<0.0001
NAUC 24 >1	62	31	0.0001

ADVERSE EVENTS IN AI455-019

	d4T	AZT	P-VALUE
Total	172	185	
Headache	42	40	NS
Other PN sx	30	27	NS
Cough	26	25	NS
Diarrhea	26	30	NS
Myalgia	22	21	NS
Nausea/Vomiting	17	30	0.005
Chills/Fever	17	30	0.009
Insomnia	15	12	0.06
Asthenia	13	21	0.09
Rash	17	18	0.05
Malaise	12	11	NS
Arthralgia	11	10	NS
Pain	19	12	NS
Anorexia	3	12	0.001
Neuropathy	6	2	0.1

HEMATOLOGIC/CHEMISTRY ABNORMALITIES

	d4T	AZT	P-VALUE
Chemistry:			
Total	172	185	
Hgb < 11gm/dl	5	11	0.01
WBC < 4000/cmm	62	76	0.0001
PMN < 1500/cmm	29	48	0.0001
Plt < 100,000/cmm	5	4	NS
Chemistry abnormalities:			
Total	172	185	
SGOT > 1.25 x ULN	52	44	0.05
SGPT > 1.25 x ULN	59	44	0.0001
Alk Phos > 1.25 x ULN	5	6	NS
Bilirubin > 1.0 mg/dL	6	10	NS
Amylase > 1.0 x ULN	10	12	NS

Three quality of life instruments (MOS SF36, Karnofsky, and Spitzer QOL) were administered. MOS SF36 produces results in 8 domains of daily living, each of which receives a score of 0-100. At week 12, one domain showed a statistically significant difference between treatment arms favoring d4T. No other statistically significant differences were seen, and MOS SF36 showed no differences at weeks 8 and 16.[4]

Dr. Dunkle also showed an updated analysis, with median follow-up of 60 wks. There was an average difference of 50 CD4+ cells between the two treatment groups at 40 weeks, which had gone down to 40 cells at week 75. No statistically significant difference in p24ag was seen. 12% of patients experienced neuropathy.

Dr. Laurie Smaldone from Bristol-Myers Squibb then presented data from the randomized US parallel track program, which Bristol termed a "large, simple trial." Patients were randomized to receive 20mg twice daily, or 40mg twice daily, came from all 50 states and Puerto Rico. Data were presented on 3,786/10,438 patients from the parallel track.

BASELINE PATIENT CHARACTERISTICS FROM THE PARALLEL TRACK	
N	10,438
CD4+ count (cells/mm³):	
Median	41
Range	0-426
CD4+ distribution (%):	
<50	53
50-100	19
101-300	26
>300	<1
Previous Antiretroviral Therapy	
AZT	10,350
Median time (wks)	91
ddI	10,167
Median Time (wks)	22
ddC	5,241
Median Time (wks)	26

No significant survival difference was seen.

SERIOUS ADVERSE EVENTS FROM THE PARALLEL TRACK			
	40MG	20MG	P-VALUE
N	4623	4603	
Infection (%)	24	26	0.11
Neuropathy (%)	21	15	<0.001
Other PN sx (%)	5	6	NS
Death (%)	5	5	NS
Neoplasm (%)	4	4	NS
Chills/Fever (%)	4	4	NS
Pneumonia (%)	3	4	0.06
Nausea/Vomiting (%)	3	2	NS
Abdominal Pain (%)	2	3	NS

NEUROPATHY SEVERITY (%)		
N	4623	4503
Any grade	21	15
Grade 1	11	9
Grade 2	7	4
Grade 3-4	3	2

Bristol-Myers Squibb also noted that AI455-019 would continue through December of 1994, and expressed their hope that the study would accrue enough clinical endpoints to confirm clinical efficacy.

Additionally, the company noted that it is conducting study AI455-020 in Europe, another double-blind randomized comparison of two doses of d4T in a population similar to that of study 019.

The company concluded that "Stavudine should be recommended for the treatment of HIV infected adults with advanced disease in whom approved anti-HIV therapies are no longer indicated."

The Committee was again confused by what seemed to be conflicting information. Dr. Scott Hammer of New England Deaconess Hospital, noted that, "while there is clearly a need for new drugs, it was unclear whether there was a need for this drug." Dr. Hammer also noted that, because neuropathy rates on the high dose in the Parallel Track program were 20 percent, but the only efficacy data were in healthier patients with the high dose, he felt unable to recommend a specific dose for a specific patient population.

Dr. Joseph L. Fleiss off Columbia University's Division of Biostatistics came somewhat more to the point:

> Accelerated approval is a horror, and the person who thought of it should be shot. surrogate markers are a horror. Phase IV is a horror. It's just a euphemism for uncontrolled data.[5]

Dr. Fred Valentine also echoed the comments about the difficulty of defining a target patient base. He remarked that because patient management can have a significant impact on "hard" clinical endpoints, such as morbidity and mortality, they are "crummy surrogates for underlying disease." He noted that he was "very frustrated by the lack of surrogate markers."[6]

Dr. Mark Smith noted that the drug has "acceptable toxicity" in the group targeted by the application — the parallel track group. "The company," he said, "is asking us to find efficacy in one group, with unacceptable toxicity, and safety in another."[7]

At this point, Dr. David Feigal stepped in to save the day for d4T.

Questions initially submitted for consideration by the committee were:

1) Does there exist a population for whom stavudine will provide meaningful therapeutic benefit over existing therapies?

2) Has the applicant provided evidence from adequate and well-controlled clinical trials establishing that stavudine has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit?

Dr. Feigal re-worded question number one to read "for whom stavudine will likely provide..." As the committee agreed generally that the answer to both questions was "yes," but for different patient populations, Dr. Feigal proposed that extrapolation was available to the committee — in other words, they could decide that the surrogate marker effect in the healthier 019 patients also applied to the sicker parallel track population.[8]

Dr. Cotton asked, "Is evidence of this required?"
Dr. Feigal: "No."
Dr. Cotton: "Evidence is not required?"
Dr. Feigal. "No."
Dr. Cotton: "Is evidence permitted?"[9]

Ultimately, the committee voted as follows:

	YES	NO	ABSTENTION
QUESTION 1:	4	1	2
QUESTION 2:	5	1	1

After the hearing, Derek Link asked Dr. Cotton, the committee chair if the committee had approved the drug, and if so, at what dose. "I don't know," she answered.

On June 27th,1994, the FDA granted accelerated approval to d4T at a dose of 40mg/day for the treatment of patients who had failed or proven intolerant to all other available antiretroviral drugs.

Commissioner Kessler commented "Stavudine is an important drug because it gives people with AIDS — and their doctors — another treatment option, when currently available drugs become less effective."

CHAPTER NOTES

1) Cox S, Send in the Clowns, May 20 1994

2) All charts derived from ibid

3) Discrepancy between number of positive baseline HIV viral titres, and mean titer at baseline on previous page, and the figures offered here may be explained by exclusion of one d4T patient from analysis. B-MS offered no comment on this

4) It is confusing, therefore, that Bristol-Myers Squibb concluded that d4T therapy produces "consistent and pronounced improvements" in "Quality of life and performance status."

5) Cox S, op cit., May 20 1994, May 20 1994

6) ibid

7) ibid

8) ibid

9) ibid

APPENDIX

TIMELINE OF ANTI-HIV DRUG DEVELOPMENT

February, 1986
BW02 opens to enrollment

October, 1986
DSMB Recommends that BW02 be halted

January 16, 1987
FDA Advisory Committee recommends approval of AZT for late-stage patients

July 23, 1987
Publication: The Efficacy of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-related Complex," NEJM, 317:4 (BW02)

February, 1988
Publication: Human Immunodeficiency Virus (HIV) Antigenemia (p24) in the Acquired Immunodeficiency Syndrome (AIDS) and the Effect of Treatment With Zidovudine, Ann Intern Med

June 23, 1989
Dr. Anthony Fauci proposes "parallel track" program to release experimental drugs prior to FDA approval

July 13, 1989
Bristol-Myers Company announces that they will release their Videx brand didanosine (ddI) through expanded access programs concurrent with clinical trials

July 28, 1989
Publication: In vivo activity against HIV and favorable toxicity profile of 2',3'-dideoxyinosine, Science

November 3, 1989
Publication: Prolonged Zidovudine Therapy in Patients with AIDS and Advanced AIDS-related Complex, JAMA (BW-02 follow-up)

March 10, 1990
New York Times runs Odd Surge of Deaths Found in Those Taking AIDS Drug

April 5, 1990
Publication: Zidovudine in Asymptomatic Human Immunodeficiency Virus Infection, NEJM 322:14 (ACTG-019)

May 15, 1990
Publication: The Safety and Efficacy of Zidovudine (AZT) in the Treatment of Subjects with Mildly Symptomatic Human Immunodeficiency Virus Type 1 (HIV) Infection, Ann Intern Med (ACTG-016)

May 21, 1990
Publication: A Phase I/II Study of Combination 2',3'-dideoxycytidine and Zidovudine in Patients with Acquired Immunodeficiency Syndrome (AIDS) and Advanced AIDS-related Complex, Am J Med

August 16, 1990
Martin Delaney writes to FDA demanding early approval of ddI and ddC

October 11, 1990
Publication:A Randomized Controlled Trial of a Reduced Daily Dose of Zidovudine in Patients with the Acquired Immunodeficiency Syndrome, NEJM (ACTG-002)

September 20, 1990
Publication: Aerosolized Pentamidine for Prophylaxis Against Pneumocystis carinii Pneumonia, NEJM

July 19, 1991
FDA Antiviral Drug Products Advisory Committee recommends approval of ddI

October 10, 1991
Videx brand didanosine is approved

October 11, 1991
Publication: A Pilot Study of Low-Dose Zidovudine in Human Immunodeficiency Virus Infection, NEJM

February 13, 1992
Publication: A Controlled Trial of Early Versus Late Treatment with Zidovudine in Symptomatic Human Immunodeficiency Virus Infection, NEJM (VA Study)

April 20, 1992
FDA Antiviral Drugs Advisory Committee recommends expansion of ddI labeling. In addition, the committee recommends accelerated approval for ddc in combination with AZT for the treatment of patients who had failed on AZT monotherapy

August 27, 1992
Publication: A Controlled Trial Comparing Continued Zidovudine with Didanosine in Human Immunodeficiency Virus Infection, NEJM (ACTG116b/117)

October 13, 1992
Bristol-Myers Squibb opens enrollment on parallel track program for Zerit brand stavudine (d4)

April 3, 1993
Publication: Preliminary Analysis of the Concorde Trial, Lancet

July 29, 1993
Publication: Zidovudine in Persons with Aymptomatic HIV infection and CD4+ Cell Counts Greater than 400 per Cubic Millimeter, NEJM (European/Australian Collaborative Study)

September 20, 1993
FDA Antiviral Drug Products Advisory Committee recommends termination of accelerated approval for ddc in combination with AZT, and full approval for ddc as monotherapy

May 20, 1994
FDA Antiviral Drug Products Advisory Committee recommends accelerated approval of Zerit brand stavudine