RESCUING ACCELERATED APPROVAL:

Moving Beyond the Status Quo

A Report to the FDA
Antiviral Drugs Advisory Committee

by

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"We are not against all drug regulation of any sort. We don't want ourselves or our friends to die from taking unsafe drugs and we disagree with the radical deregulators of the right who would abolish all efficacy requirements, and risk flooding the market with safe, but ineffective, AIDS drugs..."

-- Jim Eigo
ACT UP/New York
Lasagna Committee, May 2, 1989[2]

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[2] Quoted in Jim Eigo, Iris Long and Mark Harrington, *AIDS Drugs Now: Interim Report to the National Committee to Review Current Procedures for New Drugs for Cancer and AIDS*, Treatment + Data Committee, ACT UP/New York, May 2, 1989, and in the transcript of that day's hearing.

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Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

FDA may grant marketing approval for a new drug product on the basis of **adequate and well-controlled** clinical trials establishing that the drug product has an effect on a surrogate endpoint that is **reasonably likely**, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, **to predict clinical benefit** or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section 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**. When required to be conducted, such studies must be **adequate and well-controlled**. The applicant shall carry out any such studies with **due diligence.**

Moving Beyond the Status Quo
A Statement of Principles on AIDS Drug Development
Gregg Gonsalves, TAG

We believe that the development of a new class of antiretroviral agents, the protease inhibitors, offers a unique opportunity to improve the way we study drugs for HIV infection, incorporating lessons learned from the development of the nucleoside analogues AZT, ddI, ddC and d4T. We firmly support the right to earlier and broader access to experimental therapies for HIV infection that has been achieve through the use of novel regulatory mechanisms, including parallel track and accelerated approval. We also support the right of people with HIV infection to have access to the information they need to make well-informed treatment decisions about the drugs available to them.

People with HIV have a right to the earliest possible access to new therapies shown to be safe and which show a reasonable measure of antiviral activity in human subjects. However, the status quo has been unable to provide reliable evidence of the clinical efficacy of antiretroviral agents forcing people with HIV infection to make treatment decisions in the dark. While maintaining early access to new therapies through parallel track and accelerated approval, we believe we must supplement these mechanisms to give people with HIV the answers they need about the drugs they put into their bodies.

Accelerated approval allows the marketing of experimental drugs for HIV infection based on a suggestion of efficacy by salutary changes in surrogate markers. However, the accelerated approval regulations require pharmaceutical companies to conduct studies to reliably confirm the clinical benefit of the drugs approved under this mechanism. Unfortunately, the agents granted accelerated approval by the Food and Drug Administration have not demonstrated clinical benefits for the indication for which they were licensed nor have the pharmaceutical sponsors of these agents initiated studies to resolve the unanswered questions about their use. There is currently no viable mechanism in place to compel pharmaceutical companies to demonstrate the clinical benefits of their agents as required by the accelerated approval regulations.

We must build upon our successes with expanded access and accelerated approval and finally offer people with HIV early access to new antiretroviral therapies and answers to the fundamental unresolved questions about these agents: is taking these drugs likely to be more helpful or more harmful than taking nothing at all? The Food and Drug Administration must insure that people with HIV will have these basic questions answered while maintaining early access to experimental therapies.

Right now, there is little credible scientific evidence on the clinical benefits of the currently approved antiretroviral therapies. Four drugs that no one knows how to use. The vast majority of people with HIV in the United States, if they receive medical care at all, are treated at public clinics, emergency rooms or in private practices with little experience in HIV disease. Primary-care providers in these settings are wary of prescribing drugs with unknown therapeutic effects and known toxicities. Only with credible information on their clinical benefits will these agents be offered to people with HIV from communities under-served by the medical profession, especially women and people of color, who are not connected with primary-care providers who have large

HIV case loads and are willing to experiment with these new agents at their own discretion or at their patient's request.

Clinical research on anti-HIV drugs has not served people with HIV well in the past. Major questions remain unresolved after over five years of research on the currently approved antiretroviral therapies. Will these drugs keep me healthier and alive for longer than taking nothing at all? If they will, what agents are best to start with and when? When do you switch from one drug or drug combination to another? The list goes on. If we are to give people with HIV the information they need to keep them healthy and living longer, we are going to have to take a hard look at how we do clinical research. We cannot afford to continue to make the mistakes we have made in the past with the protease inhibitors and any other new classes of drugs that will enter the pipeline in the coming years.

Past studies of antiretroviral agents were designed to look for "home-run" or "magic bullet" drugs, with enormous effects. We were wishing and hoping for a penicillin for AIDS. We still are. However, the drugs developed for HIV infection have not been "home-runs," but they may be "singles" or "doubles." We have been unable to find out if the drugs we have may have small to moderate benefits (or on the other hand, small to moderate harmful effects) because the trials were designed only to look for something bigger and better. However, major effects may come incrementally: one moderate effect on top of another as four singles together get you to home base.

We can do better. Several proposals have been made. One series of proposals is for large, simple trials to evaluate antiretroviral therapies, including those from the Treatment Action Group (TAG) in New York City and the American Foundation for AIDS Research (AmFAR). What these have in common is that they are trying to give us answers about drugs with small to moderate effects. Preliminary results on the protease inhibitors do not indicate that they are "home-run" drugs. We need to be prepared to find out what benefits they can offer so we will not have several protease inhibitors on the market in several years without any information on their clinical usefulness.

Such trials also offer a way to validate new viral surrogate markers now in development. To show that a surrogate marker is a useful predictor of the clinical benefit of a drug, you need to conduct a trial that can show a drug can slow progression of disease or extend survival in which these markers are used. These markers cannot be scientifically and reliably validated in any other way. Once the new viral markers are credibly validated, it will be possible to further speed the development and approval of new drugs.

We can keep AIDS drug development as it is now and pretend nothing is wrong with the status quo. Those with vested interests would be happy to see no changes, even if they are changes for the better. Or we can move beyond the status quo and try to speed the development of and access to new experimental therapies for HIV infection while we also finally offer people with HIV accurate and reliable information that can save their lives.

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TAG Position Statements

1. *What is TAG's position on Expanded Access?*

TAG supports the routine deployment by drug companies of expanded access programs for new treatments against HIV and its complications. After phase I data have demonstrated the preliminary safety profile and microbiological or immunological activity, TAG believes sponsors should make experimental treatments available through expanded access programs in the following circumstances: 1) in conditions where no approved treatment exists, to patients with that condition who are unable to enroll in controlled trials; and 2) in patients for whom standard therapy is not working, or who have become intolerant to standard therapy, for those patients unable to enroll in controlled trials. Depending on the condition, its standard of care, and the magnitude of patient need, TAG believes expanded access programs should encompass the spectrum from compassionate use/single patient IND to treatment IND and parallel track. In the latter cases, TAG believes useful efficacy information can be gathered by randomizing patients to different doses of the experimental drug, as was done with the Clarithromycin, ddC and d4T programs. *TAG also believes sponsors applying for accelerated approval must have conducted expanded access programs, to develop real-world safety data on the heterogeneous populations not studied in controlled trials, which will use the treatment after its approval.*

> **TAG believes that protease inhibitor developers should immediately begin planning and scaling-up production for an expanded access program for their compounds, which would open when they enter phase II/III studies. By sharing the burden between sponsors, each individual sponsor would have to contribute less than if only one sponsor were to provide expanded access, as Bristol-Myers did with ddI in 1989, giving Roche an opportunity to delay and deny meaningful expanded access. *Industry must not deny expanded access to people with CD4<50, intolerant or failing approved therapies, as a gambit to whip up hysteria in the community for immediate accelerated approval.***

2. *What is TAG's position on Accelerated Approval?*

TAG supports the Accelerated Approval regulations as written, but does not believe they have been fully implemented. FDA has not insisted on adequate and well-controlled confirmatory studies, and industry has not provided sufficient post-marketing information on whether accelerated-approved drugs actually work. In order to ensure that industry fulfills its commitments to FDA, and to people with HIV who are taking approved but still unproved therapies, TAG believes the following steps must be taken: 1) FDA must have a public, pre-phase-II/III meeting to discuss any sponsor's development plan for a drug for which it envisions

applying for accelerated approval; these meetings should provide an opportunity for the committee to assess whether the projected trials are likely to provide clear evidence of clinical benefit and to define what magnitude and duration of marker response(s) appeared likely, based on the most current data, to be associated with clinical benefit; 2) the sponsor must provide an expanded access program in the interim, for the reasons discussed above; and 3) the sponsor must have, underway at the time accelerated approval is granted, studies which are likely to demonstrate whether the drug prolongs health or life.

3. What is TAG's position on Surrogate Markers?

TAG believes that statistically significant changes in surrogate markers, developed from adequate and well-controlled studies, are acceptable indices for accelerated approval, provided that the conditions stated above are met, and that a study measuring clinical benefit is well underway at the time of approval and likely to provide a clear answer. TAG also believes that clinical efficacy studies are critical for validating and improving the use of surrogate markers, both for studying new drugs and, perhaps, eventually, using them to guide treatment strategies in primary care settings. Unless, however, clinical efficacy studies are conducted to validate and confirm surrogate marker effects, we believe that using surrogate markers alone to evaluate drugs relies on a plausible, but unproven hypothesis that equates activity with efficacy.

4. What kind of evidence does TAG believe is necessary for FDA to approve protease inhibitors for treating HIV infection?

As soon as protease inhibitors are proved, by adequate and well-controlled studies, to prolong disease-free time or life better than either 1) nothing at all, or 2) today's standard of care, we believe they should be fully approved. *If studies likely to prove this are well underway*, and adequate and well-controlled studies show a favorable combination of changes in CD4 levels and viral load, the latter preferably measured using new, more sensitive assays, we believe that a protease inhibitor could be considered for accelerated approval, provided that the spectrum of safety and toxicity is as well characterized as it was in the ddI, ddC and d4T expanded access programs. The safety data should include long-term observation of people with symptomatic disease on concomitant medications, in sufficient numbers to observe potential rarer side effects, like the pancreatitis seen with ddI and ddC. This again emphasizes the importance of the sponsor's having conducted a pre-approval expanded access program. Because of the potential for synergy between therapies targeting different viral proteins, we believe that protease inhibitors should be studied both as monotherapy and in combination with nucleoside analogues. If a protease inhibitor proved "equivalence" with an approved nucleoside analogue, for example, ddC, we would not know whether that was, in fact, better than nothing at all. Whether AZT/Saquinavir is, in fact, equivalent to AZT/ddC, for example, is not a question which we think is worth asking, or easy answering. Therefore, we are most interested in the question: does a protease inhibitor, added to the best current therapeutic strategy, which is the standard-of-care outlined in the 1993 state-of-the-art (SOTA) guidelines, improve outcomes when compared with standard-of-care alone?

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TESTIMONY BEFORE THE FDA ANTIVIRAL DRUGS ADVISORY COMMITTEE REGARDING ACCELERATED APPROVAL OF STAVUDINE (D4T)

By Spencer Cox, Member, Treatment Action Group (TAG)
Delivered on May 20, 1994

My name is Spencer Cox, and I'm a member of the Treatment Action Group (TAG). I'd like to start by thanking the Committee for the opportunity to present my thoughts on this application for Accelerated Approval.

As has been noted at previous meetings of this Committee, there are significant problems with the way in which we are evaluating new drugs, and many of these problems may be attributable to key regulatory changes that have altered the criteria by which therapeutic efficacy is measured.

The initial approval of Zidovudine, for example, was based on substantial demonstrated clinical benefit: nineteen patients in the placebo group had died at the end of twenty-four study weeks, versus one patient in the treatment group. Critics have subsequently noted difficulties with the interpretation of this data, including concern about the biasing effect of premature termination of the trial. Such criticisms are legitimate, but nonetheless we must note that the approval was based on the measured ability of the drug to delay mortality in people with AIDS.

By contrast, full marketing approval for Didanosine (dideoxcyinosine, ddI) was based on a difference of about ten CD4+ cells between the treatment and control groups. Zalcidabine (dideoxecytidine, ddC) was conditionally approved for use in combination with Zidovudine based on a similar CD4+ cell response in even fewer subjects, and has been recommended for full approval based on a study suggesting equivalence to Didanosine.

The approval of therapies based on inadequate, ambiguous, uninterpretable or incomplete data offers severe and possibly insurmountable difficulties in the future evaluation of new treatments. This is the deck with which the current therapeutic house of cards was built.

In an effort to resolve perceived conflicts between the need for adequate information on new therapies and the need to expedite approval of new drugs, FDA offered regulations governing "Accelerated," or "Conditional Approval." Under these regulations, a drug may be considered for accelerated approval before the establishment of clinical efficacy, based on changes in "a surrogate endpoint that reasonably suggests clinical efficacy." The regulations explicitly do not apply to validated surrogate endpoints; they state, "Products used to treat serious or life-threatening illnesses, for which approval is based on a surrogate endpoint that is recognized as validated by definitive studies, will be considered for approval under the traditional process."

When Hoffmann-LaRoche was granted Accelerated Approval for Zalcidabine, they agreed to conduct a large, simple trial to measure the effects of treatment on morbidity and mortality. They did not even begin this study, nor did they present compelling evidence of treatment effect on clinical markers, nor did they present comparing Zalcidabine therapy to no treatment, or to a treatment of demonstrated clinical efficacy. However, this committee chose to recommend full approval. While FDA has not yet responded to the committee's recommendation, I believe that this experience raises serious questions about the available mechanisms for enforcing Accelerated Approval agreements, and questions about the political will to do so.

Essentially, we have two mechanisms for enforcing agreements for post-approval studies: we may withhold full approval, which conveys only symbolic benefits to the manufacturer as compared to Accelerated Approval, or we may remove the drug from the market. I believe that, in the absence of data suggesting *lack* of efficacy, revocation of approval is widely recognized as both politically impossible and cruel to patients who are taking the drug. In other words, following an Accelerated Approval, the burden of evidential responsibility is shifted from the manufacturer to the FDA.

Given the minimal requirements of the Accelerated Approval regulations for evidence of therapeutic efficacy, the implications of this shift of evidential responsibility are profound: the balance of financial incentives of FDA regulations, as now applied, favor the production of data that do not disprove efficacy, rather than data that clearly indicate clinical efficacy. In other words, FDA has developed incentives for industry to produce ambiguous data.

In application, this has meant a drastic reduction in the amounts of useful information available following full marketing approval of a new drug. Physicians and patients working together to make the treatment decisions on which a brief but important portion of our lives may depend have little, if any data on which to base rational decisions.

To borrow a metaphor from Mr. Gonsalves, each of us -- regulators and scientists, activists and industry -- has contributed to the stock of good intentions with which this road has been paved. However, it's high time we noticed in which direction we're headed.

In recent days, members of this Committee have cited the need for consistent application of standards as their rationale for key regulatory actions. This is a prime example of the old adage that two wrongs don't make a right. The consistent application of clearly defined standards of approval is obviously a desirable goal -- unless those standards fail to do what we need them to do, in which case their consistent application becomes a hindrance to your important task.

What is that task? An Accelerated Approval requires that two standards be met.

First, you must decide if the data contained in this application "reasonably suggest clinical efficacy." If not, then you are both legally and morally obligated to recommend against Accelerated Approval. I believe that, based on the secondary clinical data, such as weight gain, rather than on the surrogate data, a case could be made that this application demonstrates efficacy under the minimal standards of the Accelerated Approval regulations. Unfortunately, the wisdom of setting such low standards is not under discussion today.

Second, the sponsor must also present a credible plan for confirming the therapy's clinical benefit. Examination of the statistical analysis of study AI455-019 suggests that the study may well lack the statistical power to detect probable magnitudes of clinical effect. In assessing the credibility of B-MS's post-marketing plan, you must address the effect of an Accelerated Approval -- in the context of real-world medical, scientific and political concerns -- on our future ability to collect data on the clinical effects of stavudine treatment, on our ability to appropriately evaluate the clinical effects of other anti-HIV treatments, and on the patients throughout the US struggling to make to make important treatment decisions in the virtual absence of data. I believe that application of these criteria recommends against Accelerated Approval for Stavudine.

I'd like to end on a personal note. I am an HIV-infected patient, and I have sat through excruciating discussions with my physicians about how we should use available antiretroviral therapies. I see two physicians, who disagree with each other about optimal use of these drugs, and who both acknowledge significant uncertainty about their own practice. I urge you to consider the effect on patients on patients like me, who are taking these drugs daily -- often enduring nausea and neuropathy, pancreatitis, anemia -- without knowing whether these drugs are doing anything to preserve our health and our lives. In fact, because no long-term clinical data is available, we are often unsure whether or not long-term use of these treatments is harmful. The information on how or whether to use treatments is as important as their availability.

Should you choose to recommend approval, I urge you now to decide how you will respond if AI455-019 fails to produce compelling evidence of clinical efficacy. Please also remember that your reccomendation today will determine the quality of data you will consider in future applications. The 3TC application is unlikely to contain more data than is required for approval of stavudine.

I thank you again for allowing me to share my thoughts with you.

"We are in an evidence-free zone."
– Gregg Gonsalves, Treatment Action Group
Ad hoc Community Consultant, D4T Hearings
Antiviral Drugs Advisory Committee
Food and Drug Administration
Rockville, MD
20 May 1994

"Evidence may not be required, but is it permitted?"
--Deborah Cotton, M.D., Harvard Medical School
Chairwoman, Antiviral Drugs Advisory Committee

The Mood
Despite the untimely and tragic death of Jacqueline Bouvier Kennedy Onassis late on 19 May, the Antiviral Drugs Advisory Committee of the FDA still met as scheduled early on Friday 20 May to consider the approval of D4T (Zerit™ brand stavudine), an anti-HIV nucleoside analog that is chemically and microbiologically similar to AZT, ddI, ddC, etc.

From its start at 7:30AM in the basement conference room of the FDA's Parklawn office complex, a decaying but fine example of 1960's suburban architecture, the mood of the committee was eerily upbeat. Unlike its September 1993 meeting, where the committee caused a stir when it rejected the approval application of AZT/ddC combination therapy, this time the committee, resigning itself to jejune data, approached the D4T application with a chirpy sense of *fait accompli.*

The Antiviral Advisory Committee, which evaluates most AIDS drug approval applications, is one of many FDA advisory committees. [Other disease and drug products have their own committees.] Advisory committees are composed of outside experts and "consumer" representatives (that's us, the consumers!). Advisory committees are charged with making recommendations to the FDA on drug approval applications. The advisory committee do not themselves approve drugs. They only make recommendations to the FDA. The FDA is the only agency which can approve new drugs. Although advisory committee decisions carry no legal or regulatory weight, they are almost always implemented by FDA.

Ten community representatives, including myself, spoke to the committee during the public hearing portion of the meeting. Most representatives, including those from TAG, Project Inform, and AIDS Action Baltimore, argued for the immediate approval of D4T. But all community voices did not echo the same theme. Spencer Cox, a TAG member and person with HIV, exhorted the committee not "to do him any favors" by approving the drug. I diplomatically (or perhaps spinelessly) avoided the topic of approval altogether and instead described the dilemma doctors and patients face when drugs are approved with little or no clinical data. (Please see attached 21 May NYT article where my quote is accurate but my name misspelt.)

The Decision
After nine grueling hours, the committee was asked to vote on five questions.

1. Is there a medical need for D4T? If so, which patients are most likely to benefit?
2. Are the surrogate responses in the application "reasonably likely" to predict clinical benefit?
3. Are there enough safety data on the drug?
4. Is there an adequate plan with timelines for additional studies on the drug?
5. What should additional studies address?

The committee voted on only the first two questions that (a) there is a medical need for new therapies and (b) the surrogate data in the D4T application are "reasonably predictive" of clinical outcome. The committee was unable to decide which patients should take D4T, how it can be safely used, and what additional studies ought to be conducted with the drug. The committee left the last three questions undecided.

Unlike previous hearings, the committee was not asked directly to recommend approval. (Usually there is an explicit question like "Should this drug be recommended for approval?") At the end of the hearing, I approached the Chair and asked her what had just happened.

> **Link:** "Debbie, did you approve the drug?"
> **Cotton:** "I'm not sure. I think so."

I then approached Dave Feigal, Director of the Antiviral Division at the FDA.

> **Link:** "So what just happened? Is the drug approved?"
> **Feigal:** "Yeah. We just broke out the question into its component parts."

The Data
Since there are no clinical data in the D4T application (i.e. do patients live or stay healthy longer), the decision to approve the drug rests on indirect measurements of benefit, such as laboratory tests and "soft" endpoints.

There are two important studies:

AI455-019: Compared D4T to AZT in patients who had used AZT for at least 6 months. (The main study)
The Parallel Track: Compared two doses of D4T in more advanced patients.

The case for approval rests on the following five main arguments:

•Perhaps the most absurd argument for approval was the **"medical need"** for new therapies. The committee was asked to determine if there is a medical need for new AIDS treatments. While no one disputes that people with HIV have extremely limited treatment options, this does not necessarily mean that D4T can fill these real medical needs. In other words, whether or not D4T works is secondary to the fact that it is available.

•D4T produced a **CD4 effect** of approximately 20 more cells in participants in the main clinical study, AI455-019. This CD4 effect was the lowest level of response defined in the protocol. The CD4 cells increased by approximately 20 cells and fell back to baseline by 20 weeks. The problem, of course, is that other studies have cast significant doubt on the predictive use of CD4 responses of this magnitude and duration. Another large D4T (the parallel track) study failed to show a dose-related survival or CD4 cell response, which might be expected with an active therapeutic agent.

•**Weight gain** is clearly an important "soft" clinical endpoint. Patients who lose weight are at increased risk for disease and death. Patients on D4T in the main study had an average weight increase of approximately 1.5 kilograms compared to patients who received AZT. This finding would normally be viewed with substantial interest; however, in this case, correlation and causation are difficult to sort out. Patients who received AZT reported significantly more nausea, vomiting, and anorexia, which are all common side-effects of AZT treatment and which may impact on weight status. Did patients gain weight because D4T had a therapeutic impact or did patients who continued AZT lose more weight due to that drug's unique side-effects? Did this study find that patients should take D4T or stop taking AZT?

•**Quality of life measurements** are increasingly used in antiretroviral studies. Quality of life refers to an individual's subjective assessment of his/her own welfare, functioning, and health. D4T was evaluated using three quality of life instruments. Only one instrument demonstrated a statistically significant difference between AZT and D4T. This difference was marginal and could only be demonstrated at one point in time (12 weeks), opening up the real possibility that it represents a statistical aberration. (As the number of measurements increases, so does the possibility that any one particular measurement is a result of chance alone.)

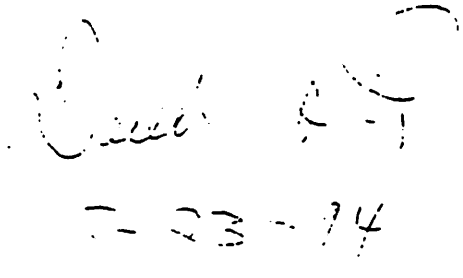
•The most disturbing aspect of the D4T application is the data on **anti-viral activity**. Antiviral activity indicates that a drug has an immediate inhibitory impact on the virus. This is substantially different from clinical efficacy, but is important nonetheless. Changes in the most widely-used measure of antiviral activity, p24 antigen, were non-significant in patients given D4T. No anti-HIV drug has ever before been recommended for approval without evidence of antiviral activity. After the hearing, one committee member, defending the committee's decision, commented to an activist that "CD4 cell increases combined with evidence of antiviral activity are reasonably predictive of clinical outcome." When reminded that D4T, at tolerable doses, failed to demonstrate antiviral activity, he shrugged, grimaced, and said, "Oh, yeah."

The Aftermath

Another trip to Rockville, another dinner in the mall, another nucleoside made it through. Pop the prozac, inhale deeply, and try not to think about the ghosts dancing before my eyes. There are now three anti-HIV drugs on the market, and D4T will probably be the fourth. Are we any better off? Are we getting closer to a cure? Who knows? We are in a desperate situation in AIDS drug development. We now have a mechanism to get drugs to market faster than ever before, but we have no way to determine if the drugs have any value. And no one -- not FDA, not industry, not NIH -- views this problem as their own. Their goal is to get drugs to market, not tell doctors and patients how, when or if these drugs ought to be used.

Going to the FDA always feels like an exercise in self-flagellation, because that agency only cleans up the mess that clinical researchers much further up-stream create. The FDA doesn't run, fund or control the studies. It only tries to interpret those studies that land on its doorstep. In order to change the type of data that are generated, we must change the way studies are designed and research networks are organized. And this is a daunting challenge for which there are no clear solutions and which will take years to fix. So what do we do with these drugs in the meantime? Who knows?

The FDA now must decide how and in whom to approve this drug. This is called the drug's indication. Drugs are approved at specified doses for use only in particular patient groups and for particular medical conditions. How the indication is written matters a great deal to drug reimbursement and, in this case, to the use of the accelerated approval regulations. We will be commenting to FDA very soon on the indication for D4T.



When to Begin Antiretroviral Treatment?

by Mark Harrington
Treatment Action Group (TAG)

10th International Conference on AIDS
Thursday, 11 August 1994
Yokohama, Japan
RT-25, 13:00

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Good afternoon. I would like to thank the conference and panel organizers for the opportunity to participate in this round-table session. The topic is obviously a timely one, not only for the AIDS field in general, but also for myself in particular. Some of you who were in Amsterdam two years ago may have seen me present slides of my left axillary lymph node, biopsied in April 1992, in situ hybridization of which demonstrated, in the words of one of my doctors, that my lymph node was "crammed with virus". At the time I had somewhat over 600 CD4 cells/mm^3; they are now, two years later, somewhat over 400, and I remain asymptomatic.

Over the last years I awaited with eagerness, and registered with disappointment, the results of a number of studies which I hoped might provide clear guidance in choosing an appropriate time to begin a useful antiretroviral regimen. While it is widely recognized that the drugs and regimens studied in these trials proved disappointing, it is less widely admitted that the trials too -- in their design, conduct, analysis and interpretation -- have been disappointing -- their design overoptimistic, their conduct flawed, their analysis and interpretation often relentlessly and falsely upbeat.

In preparation for this panel, I asked several AIDS physicians when (or if) they tended to initiate antiretroviral therapy in their patients. Answers ranged from, "As soon as I can talk them into it" to, "At 499 T cells" to, "Whenever they ask, [but never if they don't]" to, "Whenever we develop effective antiretroviral treatments" to, "Sometime between the second and third trimester of pregnancy." Obviously, the dcision usually is ours, not our physicians'. We are forced to make these decisions without clear evidence of when to start or what to take.

As the diversity of these answers indicates, the disappointing fact is that after eight years of study, we still don't know at what stage of HIV infection people with HIV begin to benefit from antiretroviral therapy. [We also don't know whether to begin with mono- or

combination therapy, or when to switch, add or stop treatment, but those topics aren't on today's menu.]

Last year's NIH state-of-the-art guidelines for antiretroviral therapy in adults outlined twelve clinical scenarios. Several are relevant to this discussion. For people with over 500 CD4/mm^3, no data warranted starting therapy. [Of note, the SOTA panel rejected EATG 020, which utilized a composite endpoint heavily weighted towards a CD4 drop to below 350/mm^3.] For those with between 200-500 with no symptoms, patients were given a choice of initiating AZT monotherapy or waiting; for those with between 200-500 and symptoms, AZT was recommended; as it was for previously untreated patients with below 200 CD4 cells. [The choice of 500 CD4 cells is essentially an arbitrary artifact, as Paul Volberding conceded at yesterday's press conference.]

In developing these guidelines, the NIH expert panel relied, appropriately, I believe, on randomized studies which measured benefit in terms of delayed clinical progression or death. The basis for the recommendation to initiate therapy somewhere between 200-500 CD4 cells, and around the development of symptoms, was based on the results of four placebo-controlled studies -- ACTG 016 and both strata of 019, on VA 298, and on the Concorde study.

The basis for recommending AZT monotherapy as initial treatment was based on ACTG 016, 019 and BW-02, and on two active controlled studies, ACTG 114 and ACTG 116A, in which, respectively, AZT showed a pronounced survival benefit, against ddC, and a modest delay in progression, against ddI. Nonetheless, the SOTA panel decried the lack of better data from well-controlled studies to define exactly when, and in whom, to begin antiretroviral treatment.

For, as the results of ACTG 076 in pregnant HIV+ women show, AZT can be a very powerful drug when used at the right time. Yet with adults, we still don't know how best to target its use.

The research community, since Berlin, wallowed in denial about the lessons of the Concorde study. It is important to point out that Concorde contained more clinical endpoints (and more deaths) than all other antiretroviral studies combined. Some complained that it was naive to study monotherapy, as resistance would surely eventually attenuate the efficacy of AZT. This post hoc complaint ignores four facts: 1) monotherapy was all there was when Concorde was designed and enrolled; 2) AZT is still the first-line monotherapy of choice; 3) combination therapy has yet to demonstrably slow the development of in vivo AZT resistance, or to prove clinical superiority to monotherapy; and 4) resistance alone does not account for the limited efficacy of these drugs.

Critics of Concorde (and of ACTG 155) also point out that the rationales for early treatment and for combination therapy remain intact. This flies in the face of current

clinical evidence. When a rationale is held against the data, reason becomes bias. Neither the data nor the rationale justify the routine provision of AZT to everyone with CD4 under 500.

Also often forgotten is the fact that, in 019, AZT reduced the rate of progression from 4% in the placebo arm to 2% in the treatment arm -- a relative reduction of 50% but an absolute reduction of only 2%! Yet, on the basis of 019, NIH began recommending the blanket use of AZT in all patients with CD4<500, an arbitrary number used in defining entry strata for 019; that is to say, they extrapolated that the delayed progression seen with AZT in the rapid progressors (4%) would also occur in the slower progressors (96%).

What both Concorde and VA 298, as well as the long-term follow-up of ACTG 019 itself, showed was that this did not, in fact, occur. All showed that there was, in fact, a short term benefit of AZT in rapid progressors, and that this benefit apparently disappeared after two years (Volberding, 1993, 1994). The problem was that it was difficult to identify the rapid progressors upfront. Otherwise, it would be possible to target the use of AZT in asymptomatics more precisely, to maximize the potential therapeutic benefit.

For the transient activity of AZT -- and of all classes of agents active against HIV currently available, including the nucleoside analogues, the non-nucleoside reverse transcriptase inhibitors and the protease inhibitors -- and the magnitude and duration of the reductions in viral load which they can accomplish suggest that using them too early may mean missing the opportunity to use them when they would really be of use. [Moreover, using combinations may be no better. First-line combination AZT/ddI and AZT/ddC in BW-34,225[1] did not delay the emergence of AZT resistance; second-line combination AZT/ddC in ACTG 155 provided no clinical benefit and 50% more toxicity; triple-drug combination at UAB did not delay the emergence of resistance either.]

Recent pathogenesis data suggest why antiretrovirals taken too early don't work. In the DATRI 003 study, reported on Monday by Oren Cohen, 32 HIV+ participants with CD4>250 were randomized to maintain or switch regimens for 8 weeks and underwent sequential lymph node biopsies at weeks 0 and 8. Half those patients not on AZT were randomized to AZT, and half to continue untreated; half of those on AZT were randomized to add ddI, and half to stay on AZT alone. Overall, there were no reductions in viral burden or expression (viral RNA or DNA) in the lymphoid tissue. There was a trend to

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[1] R Schooley, B Larder, M St Clair, M Moore, et al. "Combination Antiretroviral Therapy in Previously Untreated Individuals". Abstract, Wellcome Symposium on New Strategies for Treatment & Prevention of HIV Disease," 7 August 1994, Yokohama, Japan.

reduced load in those who added ddI; they had lower CD4 levels at baseline[2].

There are several points to be made about this: 1) lymphocyte levels, and viral infection levels, in peripheral blood account for only a tiny fraction of the whole-body lymphocyte and virus population -- just two percent of the CD4 population exists in peripheral blood; therefore, raising CD4 levels or reducing viral levels in peripheral blood give an exaggerated picture of the magnitude of impact current antiretroviral agents have on the ultimate end organs of HIV disease, the lymphoid tissues throughout the body, the destruction of which is one hallmark of frank AIDS.

Cohen, Pantaleo, Graziosi, Niu and Fauci concluded that "the effect of antiretroviral treatment on viral replicationa ppears to be more pronounced in late stage versus early stage disease."[3] If the trend they saw in the lower CD4 cell, ddI-receiving arm is confirmed, this suggests that nucleoside analogue antiretrovirals only affect viral load where it counts after destruction of the lymphoid tissue has reached the point where CD4 cells are around 300/mm^3. After all, the typical nucleoside reduces HIV levels by one log in the peripheral blood for 3-6 months. The "best" short term reduction in virus (with a protease inhibitor) reduces it by 3 logs for a few weeks or months.

The immune system reduces it by 3-4 logs for 8-12 years. But this is only in the peripheral blood. Viral burden in lymphoid tissue remains high. Moreover, antiretroviral therapy may not affect lymphoid destruction if that destruction is mediated by immunological factors, rather than direct viral cytopathicity.

In conclusion, using AZT when your immune system is still holding HIV in check, and your lymph nodes are still trapping virus, may be like using your last light-bulb at noon: it may be burnt out by dusk, and you'll be in the dark.

So the bitter paradox at the heart of our current understanding is that, while theoretically it will be better to start treatment early, when viral load is low, making it harder for resistance to develop, the truth appears to be that starting antiretrovirals too early wastes their limited usefulness while a much more effective immune response persists. Only when the immune system damage becomes so great that the person is somewhere on the verge of becoming symptomatic do we begin to have good evidence that current treatments improve clinical status.

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[2] OJ Cohen, G Pantaleo, C Graziosi, M Niu, AS Fauci. "Effect of Antiretroviral Therapy on HIV Burden and Replication in Lymphoid Tissue". Abstract #001B, Abstract Book Vol. I, 10th International Conference on AIDS, Yokohama, Japan, 1994, p. 7.

[3] Ibid.

So the short answer to the topic of the day is, sometime before my CD4 cells drop below 200, or before I become symptomatic, whichever comes first.

This is a pretty bleak, and vague, answer to give after scores of trials enrolling thousands of patients around the world and carried out over eight years. AZT sales were halved after Concorde. Even if researchers want to continue to believe in the discredited dogmas of yore, patients aren't buying them. Moreover, a growing number of clinicians, researchers and statisticians aren't buying them either. Indeed, the field of antiretroviral clinical research is getting a bad reputation, and justifiably so, in my view, for drawing unwarranted conclusions from inadequate data.

This perception jeopardizes the field, the funding, the clinical research networks, and most important of all, the lives and hopes of people with AIDS. All the advances in high-tech virology and immunology have yet to be applied or confirmed in well-designed studies which provide clinical evidence of benefit. Even if you've convinced yourselves, you haven't convinced us. So your work is in vain -- unless you learn the lessons of nucleoside analogue development and do a better job with newer agents.

The real question is: How can we do better in the future? A few groups have begun or proposed innovative studies which may offer a way out of the dark ages -- Donald Abrams' ComPACT-1 study of immediate versus deferred antiretroviral therapy; the Treatment Action Group's proposal for a large trial comparing the current standard-of-care to standard-of-care plus protease inhibitors; Paul Volberding's suggestion for "Large Sample Trials"; or Ellen Cooper's "large, not-so-simple trial" all contain elements which may lead to better answers. They all demand larger sample sizes, better follow-up, and an integration of primary care settings with academic research units to carry out the research and follow the participants. We also need more innovative studies of the impact of therapy – both antiviral and immune-based -- in lymphoid tissues as well as peripheral blood. But there won't be a renaissance in antiretroviral therapy until doctors and people living with HIV have better information about how to use the drugs we have, and those now in development. Even with imperfect drugs we can design more useful trials. Thank you.

*

ACTG 229: AZT/ddC/Saquinavir vs. AZT/Saquinavir vs. AZT/ddC

Results from ACTG 229, a randomized, 24-week, 302-patient study comparing AZT/ddC/Saquinavir (Ro 31-8959, the protease inhibitor) vs. AZT/Saquinavir vs. AZT/ddC, were released on May 31. The analysis was written up by Roland Bassett, David Schoenfeld and Ann Collier for the ACTG 229 study team. Doses used were AZT 200 mg 3x/day, ddC 0.75 mg 3x/day, and Saquinavir 600 mg 3x/day. All participants had between 50-300 CD4 cells/mm^3, and had received over 4 months of previous AZT. The principal endpoints were CD4 measurements and HIV load by PBMC co-culture. Analysis was by intent-to-treat. Only 10/302 patients (3%) took less than 80% of required study treatments.

Results: ACTG 229	AZT/ddC/ Saquinavir	AZT/ Saquinavir	AZT/ddC
N	95	98	100
Clinical Events + Toxicity			
Major clinical events	1	6	4
Deaths on study[2]	0	2	0
Severe/worse lab toxicity	27	31	30
Severe/worse clinical sign	5	11	12
Severe/worse lab tox. or clinical sign/symptom	31	40	37
Immunologic Activity			
CD4 cells returned to baseline @ 24 weeks	31%	37%	55%
CD4 NAUC[3]	12.5±2.1	6.3±1.9	-0.15±2.1
25 CD4 cell or 25% rise	63%	53%	33%
50 CD4 cell or 50% rise	39%	28%	21%
Virologic Activity			
PMBC reduced by 1 log	44%	9%	22%
p24 Ag reduced by 50%	61%	43%	28%
p24 Ag went negative	55%	30%	23%
Pl. viremia went negative	53%	40%	45%

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[2] Both attributed to "brain masses".

[3] "The mean normalized area (±SE) under the log change from baseline curve in log change/day."

" [ACTG 229] Efficacy [sic] Analyses: Primary Analyses: CD4: ...The analysis of the log-transformed CD4 slopes showed a significant treatment difference (p=0.005) with the triple combination having a significantly greater slope than ddC/ZDV (p=0.001) but not Saquinavir/ZDV (p=0.08)... Conclusions + Discussion: ... *Since ACTG protocol 229 was not designed with sufficient power to detect differences in clinical events, it is unknown if the favorable effect on surrogate markers seen with the triple combination in this 24 week study is associated with a delay in disease progression or enhanced survival...* The beneficial effect on CD4 cell counts was transient in some patients, as demonstrated by downward trends in mean CD4 cell count after week 12. The suppressive effect of the triple combination on viral load as measured by HIV quantitative PBMC microculture was better than the double drug regimens, and appeared to be sustained for the duration of the study... There is a need to be cautious about comparisons between the double-drug regimens, because the study had insufficient power to rigorously allow comparisons... The type, severity, and frequency of adverse experiences appeared similar in the three regimens used in this double-blind study... *The results of ACTG protocol 229 should be interpreted cautiously because it was a relatively small, short-term study, based upon laboratory endpoints.* However, the results support the conclusion that a triple combination regimen containing Saquinavir, an orally-administered HIV proteinase inhibitor, has antiviral activity... ***The clinical benefits of Saquinavir-containing regimens remain to be determined in future studies.***"[4]

Roche's Currently Planned "Pivotal Efficacy Trials"

NV14256A: Saquinavir alone vs. ddC alone vs. two doses of Saquinavir + ddC in AZT-experienced patients with CD4 50-300/mm^3.
Endpoints: Primary: safety, tolerance and first AIDS-defining event or death; Secondary: Survival, Karnofsky, lab markers, quality of life, resistance.
Design: Randomized, double-blind, 48-weeks minimum follow-up, stratified by baseline CD4 >/<100. Sample size: N=1200 patients, 300/arm; 240 evaluable/arm. Comments: The control arm, ddC monotherapy, remains unvalidated in this population, it is smaller than that in BMS-019, the "pivotal" d4T trial, which many doubt is large enough to validate d4T (N=800, 400/arm).

SV14604A: Saquinavir alone vs. AZT alone vs. two doses of Saquinavir + AZT in AZT-naive patients with CD4 50-300/mm^3.
Endpoints: Primary: safety, tolerance and first AIDS-defining event or death; Secondary: Survival, Karnofsky, lab markers, quality of life, resistance.
Design: Randomized, double-blind, 80-weeks minimum follow-up, stratified by baseline CD4 >/<100. Sample size: N=1800 patients, 450/arm; 300 evaluable/arm. Comments: The control arm, AZT monotherapy, is standard-of-care in this population. The sample size/arm is similar to that of BMS-019, the "pivotal" d4T trial, which many doubt is large enough to validate d4T.

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[4] Ibid., pp. 8-9.

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TAG

June 16, 1994

David Kessler, MD
Commissioner
United States Food & Drug Administration
5600 Fisher's Lane
Rockville, MD 20857

Dear Commissioner Kessler:

We are writing with reference to FDA's plans to regulate the development of a new class of anti-HIV therapies, known as "protease inhibitors," and with specific reference to possible regulatory decisions regarding Hoffmann-LaRoche, Inc.'s Ro 31-8959 ("Saquinavir").

As has been noted, both in meetings with you and your staff, and in FDA Advisory Committee hearings, many of us are very concerned about the level of data that will be required for marketing approval of new classes of antiretroviral treatments. As people with AIDS/HIV, advocates and physicians, we believe that people with AIDS are entitled to information about new therapies that is sufficient to make necessary risk/benefit analyses regarding their treatment. In regulating the first generation of antiretroviral drugs, many felt that a reduced evidential standard was appropriate, due to the absence of available treatments; now, however, we believe that the development of protease inhibitors offers a new opportunity to re-think this regulatory process in ways that will ensure reasonable access to new drugs, while producing clinically relevant information about their use. We would like to offer an approach to developing these therapies that combines access with the fundamental principles of clinical research. We believe that this approach can allow us to move as expeditiously as possible towards integrating the access and informational requirements of industry, FDA, and people with AIDS/HIV.

Specifically, we are concerned that Hoffmann-LaRoche, Inc. intends to apply for Accelerated Approval based on changes in CD4+ levels and virological markers observed in ACTG study #229 We feel that such an approval would penalize people with AIDS/HIV by setting an inappropriately low standard of evidential requirements that would govern the regulation of this entire class of therapies. We urge you not to invite Hoffmann-LaRoche to apply for Accelerated Approval of Saquinavir until we can complete further discussion between FDA, its Advisory Committee, the company and people with AIDS/HIV.

Saquinavir, unlike d4T or ddC, is not yet an appropriate candidate for an accelerated NDA because it has not been studied for safety in a broad enough patient population for a long enough time, because Hoffmann-LaRoche's proposed follow-up studies are flawed, and because the use of surrogate markers to evaluate potential efficacy in ACTG 229 is completely untested in this class of therapies. The current ddC-controlled NV14256A study does not use a validated control arm in this population, and, like the projected AZT-controlled SV14604A study, it lacks statistical power to determine probable magnitudes of treatment effect.

TREATMENT ACTION GROUP, 147 SECOND AVENUE, SUITE 601, NEW YORK, NY 10003; PHONE: (212) 260-0300, FAX: (212) 260-8561

People with AIDS/HIV require access to life-saving treatment information. We have learned through difficult experience that we cannot depend on the goodwill of pharmaceutical industry sponsors to produce the information that is necessary to make life-or-death treatment decisions. We believe that inadequate characterization of new therapies places PWA/HIVs in a deadly double bind: if a drug offers unmeasured benefit, then people who refuse treatment may be losing opportunities for added health and life. If a drug is only as good as, or even worse than placebo, then patients who take treatment may be wasting time and money, and risking premature morbidity and mortality.

We are concerned that, should Saquinavir be granted Accelerated Approval, future clinical investigators would then be ethically required to test new protease inhibitors against Saquinavir, despite the lack of demonstrated clinical benefit. As we have seen with the nucleoside analogues, this would compound the problems of characterizing future therapies, and compromise the ability of PWAs to obtain information about the utility of this entire class of therapies.

Instead of Accelerated Approval at the present time, we would suggest that sponsors of protease inhibitors combine strategies from past drug development processes in ways that are designed to produce maximal information at minimal cost. Instead of the traditional expanded access program, we would suggest a large, relatively simple trial comparing two doses of Saquinavir to placebo in all HIV-positive patients with $\leq$500 CD4+ cells/mm^3 (see attached concept sheet). Such a study would not need to limit or exclude concomitant medications, other than excluding other protease inhibitors, and, indeed, would allow people with HIV in the study to receive any nucleoside regimen they may wish to choose, in accordance with the 1993 PHS state-of-the-art guidelines. The study should be accompanied by a salvage protocol for patients who have failed on all standard therapies, or who have less than 50 CD4+ cells/mm^3. We believe that such a study, properly designed, could be faster and cheaper than the standard drug development process, could synthesize the twin goals of broad access and rapid, definitive answers, and could provide meaningful data on how best to use this new class of potential antiviral agents.

This issue is of particular concern in that Hoffmann-LaRoche has failed to honor previous agreements to conduct large-scale post-marketing studies to confirm the clinical efficacy of Zalcitabine. Before FDA provides input to Hoffmann-LaRoche regarding an application for Accelerated Approval for Saquinavir, we ask that all parties consider this proposal. We are currently scheduling meetings with manufacturers of the various protease products, including Hoffmann-LaRoche, and would like to meet with FDA as soon as possible. Please call Mark Harrington at (212) 353-8430, or contact him by FAX at (212) 777-8130, to set up a meeting in the coming weeks to further discuss these issues.

We now have a unique window of opportunity to plan prospectively a coherent, rapid and clinically useful development path for HIV protease inhibitors, and to learn from the lessons gained

by five years of disappointing and contradictory research on nucleoside analogues. We must not let this opportunity slip by.

We look forward to working with you to resolve these issues.

Sincerely,

David Barr
Gay Men's Health Crisis

Spencer Cox
Treatment Action Group

Lynda Dee
AIDS Action Baltimore

Gregg Gonsalves
Treatment Action Group

Derek Hodel
AIDS Action Council

Mark Harrington
Treatment Action Group

Derek Link
Gay Men's Health Crisis

Bruce Schackman
Treatment Action Group

CC: Dr. Janet Woodcock
Dr. Robert Temple
Dr. Randy Wykoff
Dr. David Feigal

Letter from Rockville

Another meeting with the (FDA) Commissioner. Rockville, MD. 11 July 1994. Bruce Schackman insisted that we all prepare overheads for our presentations, so we did. We took the train to Washington, D.C., and the Metro to Rockville. There we met Lynda Dee, resplendent in a peach-colored summer suit (with matching earrings, shoes and pocket book, no doubt), and Ellen Cooper at the new AmFAR CBCT office across the street from DAIDS, for a pre-meeting. The FDA met us in the Chesapeake Room in the Parklawn Building at 3:30.

David Barr pointed out that, as currently implemented, the Accelerated Approval regulations have failed to ensure that sponsors generate information about clinical utility post-marketing. People with HIV need access to information as well as to "un"-validated treatments. David Kessler took copious notes.

Gregg Gonsalves pointed out that the d4T hearing was badly programmed, and that the indication for which d4T was approved (salvage) is not the indication for which efficacy data may be forthcoming (second line). David Feigal pointed out that Bristol-Myers Squibb had promised to withdraw d4T from the market if BMS-019 does not prove clinical efficacy. "What if, as seems more likely, BMS-019 is inconclusive?" we queried. We don't want market withdrawal -- we simply want greater certainty that even modest treatment benefit will eventually be discovered.

David Feigal said the FDA Antiviral Drugs Advisory Committee would meet in the fall to review the current status or surrogate markers, expanded access and Accelerated Approval. Gregg Gonsalves pointed out that the 1962 Kefauver amendments were still the law of the land. He showed Tom Fleming's analysis of the 16 randomized nucleoside trials which provided the basis for the 1993 state-of-the-art (SOTA) guidelines. In only two of the studies did CD4 rises correlate with a survival benefit. The overall predictability of CD4+ T-cell changes was 50 percent, no better than tossing a coin.

"In only two of the studies did CD4 rises correlate with a survival benefit. The overall predictability of CD4+ T-cell changes was 50 percent, no better than the toss of a coin."

Spencer Cox showed overheads detailing problems with Accelerated Approval, and possible solutions. Surrogate markers (specifically, CD4) had proved disappointing. FDA should convene a periodic review of CD4 and other, newer potential markers, such as viral load measurements. FDA should require sponsors to hold a pre-phase II advisory committee hearing on their development plans is they were planning on applying for Accelerated Approval. The FDA could insure a "black box" on the labeling noting that accelerated-approval drugs had not yet been clinically validated (they had done this with d4T's label). Finally FDA might consider fining sponsors who failed to meet their post-marketing commitments. Commissioner Kessler questioned whether FDA had authority to do this.

Michael Ravitch presented some problems with the Inter-Company Collaboration (ICC) master protocol. David Feigal said that Ed Skolnick, at the National Task Force meeting in April, was receptive to randomizing this study. Michael riposted that David Barry had sent several condescending letters to the effect that randomization and controlling were unnecessary fetishes. David Kessler asked to see these letters, which we will forward to him. FDA was receptive to urging the ICC to design a better master protocol.

We discussed Roche's potential NDA for *Saquinavir*. FDA cannot disclose matters from on-going discussions with pharmaceuticals. Whatever FDA does with *Saquinavir* now will reveal whether it considers a six month study of 99 patients—without additional safety data and only the slenderest of surrogate marker results—to be sufficient for Accelerated Approval. "We made it clear with Accelerated Approval that we were not seeking any less data, but only a different kind of data," Feigal said.

Wrapping up, David Kessler returned to the importance of the point about how Accelerated Approval needed to ensure the eventual development of answers, not only access, and indicated he would reflect on our concerns in a forthcoming article on Accelerated Approval. Speaking the next day to a reporter, Kessler noted that the community wants access to information, not just to potential new treatments. †

PROPOSAL FOR A LARGE, RANDOMIZED, DOUBLE-BLIND STUDY COMPARING ONE OR MORE HIV PROTEASE INHIBITORS PLUS STANDARD-OF-CARE VERSUS STANDARD-OF-CARE ALONE IN HIV-INFECTED PERSONS WITH < 500 CD4 CELLS/mm^3

by Mark Harrington
Treatment Action Group

July 1994

WHY INITIATE STUDIES NOW TO PROVE CLINICAL EFFICACY FOR HIV PROTEASE INHIBITORS? Protease inhibitors are a new class of antiretroviral agents. They target a different viral protein from the reverse transcriptase inhibitors (RTIs). Preliminary data (from ACTG 229 and phase I Merck studies) indicate they induce a short-term rise in CD4 counts and a drop in viral levels. They have the immediate need to be studied, and if effective, used, in a broad population (e.g., CD4<500, rather than merely 'salvage' indication or nucleoside 'failures'). They display apparent low acute toxicity (although potential rarer toxicities and longer-term safety issues remain to be determined).

SURROGATE MARKERS STILL NEED TO BE VALIDATED CLINICALLY. Surrogate markers have proven disappointing in their ability to predict clinical benefit. Data on CD4 rises, p24 drops with nucleoside analogues is unimpressive, and often fails to predict clinical benefit (Fleming 1994). Newer markers (bDNA, QC-PCR, PMBC co-culture) have not yet been validated clinically, and will need to be validated prospectively (with new agents) even if they prove useful retrospectively (e.g., with ACTG 116B/117).

ACCELERATED APPROVAL DOES NOT REMOVE THE NEED FOR ULTIMATE CLINICAL CONFIRMATION OF EFFICACY. Accelerated Approval does not eliminate the need for clinical confirmation of benefit, it simply shifts it to the post-approval period. Confirmatory studies still need to be completed to validate apparent surrogate marker benefits. Confirmatory studies are most likely to succeed if they are well underway at the time of approval, and if they have sufficient power to detect a treatment difference. Confirmatory studies with drugs currently approved in an accelerated fashion (ddC, d4T) have either failed to confirm benefit (ACTG 155), were inconclusive (CPCRA 002), or are still uncompleted and may fail to demonstrate clinical benefit (Delta, ACTG 175, BMS-019).

EFFICACY TRIALS ARE LIKELIER TO SUCCEED IF THEY START SOON. We now have a historic window of opportunity to clearly define the clinical utility of protease inhibitors by combining expanded access with proper controls to yield large-scale efficacy trials. If protease inhibitors are approved without starting sufficiently powered efficacy studies, we may never know if they work clinically; past post-marketing experience has disappointed. If protease inhibitors are not approved now, demand for expanded access

will come from a much broader population than has traditionally enrolled in parallel track.

Current System	New Paradigm
Controlled trials inadequately powered	Controlled (phase II) trials nested within/conducted concurrently with placebo-controlled phase III trials in community-based settings
Expanded access programs inadequately controlled	
Treatment differences overestimated; trials are difficult to interpret	Sufficiently large studies can detect modest treatment differences easily
Rigid; restrictions placed on standard-of-care	Flexible; no restrictions on standard-of-care
Nucleoside analogues mandated as control and/or treatment arms in studies	Nucleosides allowed at patient discretion as per 1993 SOTA guidelines
Long-term follow-up inadequate; ACTG has difficulty following patients	Long-term follow-up built in at start; easier to conduct in primary care settings
Patients who progress, or take forbidden therapy, are forced off study, or to lie, and "cheat"	Patients who progress may switch among ddNs, stay on study, and are not tempted to lie or "cheat"
Homogeneous population; trials exclude >80% of applicants; trial results difficult to generalize	Heterogeneous population; entry criteria open to >95% of applicant population; trial results easily generalizable
Small, slow studies, unconvincing and/or contradictory results	Large, relatively quick studies, clear and unambiguous results
Vague indication/small market	Clear indication/large market
Surrogate markers seldom validated with sufficient clinical endpoints	Surrogate markers can be proved or disproved with statistical ease

CONCLUSIONS. We should take the opportunity we now have to incorporate lessons learned during development of the ddNs and to improve the way we study protease inhibitors and future antiretrovirals. These proposals are meant as a framework for discussion with FDA, industry and the community, and are not engraved in stone; they are a starting-point for a discussion of how best to study new antiretroviral agents.

A LARGE, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY COMPARING ONE OR MORE HIV PROTEASE INHIBITORS IN HIV-INFECTED PERSONS WITH <500 CD4 CELLS/mm^3: PROPOSAL FOR A CLINICAL EFFICACY TRIAL

GOALS

1. To detect reliably a clinically meaningful effect of the treatment;
2. To study possible correlations of effects on intermediate outcomes (e.g., immunologic and virologic markers) with clinical outcomes

FUNDAMENTAL DESIGN

* Randomized, double-blind, placebo-controlled
* Broad entry criteria and clinical endpoints
* Additional targeted studies nested within the phase III study
* Patient population: HIV-infected individuals with CD4<500/mm^3
* Products to be tested: Two protease inhibitors, or two doses, with a placebo control (2:1 treatment:placebo ratio)
* Limitations on concomitant medication: None (except for other protease inhibitors). No restriction on participation in other clinical trials.
* Primary endpoint: First new AIDS-defining event or death
* Time frame: One year of patient accrual; 2-4 years of follow-up. *Note:* the length of time until proof of efficacy appears depends on the N randomized and the magnitude of the treatment effect; *the larger the trial, and the better the drug, the shorter the trial*
* Stratification: Two strata, by entry CD4 level (<200, 200-500); stratified by nucleoside naive or experienced, symptomatic or asymptomatic; secondary analysis could be done by nucleoside regimen at baseline
* Sample size: Sufficient to detect a 25% reduction in risk
* Broad recruitment base, with patient entry open to all physicians and clinics interested in participating
* Central office for randomization, forms generation and distribution, data collection and analysis, and quality control
* Central repository for product distribution
* 1-800 number established for randomization
* Blood samples collected annually (possibly in a subset)
* Nested studies (virologic, immunologic, pharmacokinetic and drug interaction) conducted through existing multicenter clinical research networks, e.g., ACTG, CPCRA, AmFAR CBCTN
* Random sample of participating physicians selected for on-site data audit"[1]

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[1] Parts of this section adapted from NIAID/DAIDS "Issue Paper 2, Clinical Evaluation of Therapeutic Vaccines for HIV Seropositives: Approaches to the Design of Efficacy Trials", 11.23.92.

SAMPLE SIZE ISSUES

Size of potential treatment population/Number of potential endpoints

Number of Americans estimated HIV-infected:	1,000,000 +
Number of Americans developing AIDS each year:	50,000 +
Number of Americans dying of AIDS each year:	50,000 +

Size of Past Antiretroviral Studies (Approximate)

ddI Trials (ACTG 116-118)	2,250
ddI Expanded Access	25,000
ddC Trials (ACTG 114, 119, 155)	1,350
ddC "Expanded" Access	6,000
d4T Trial	800
d4T Expanded Access	10,000

Proposed Sample Size for Protease Inhibitor LST

CD4 Stratum	Per Arm	All 3 arms
200-500	3,000	9,000
<200	3,000	9,000
Total	6,000	18,000

Sample Size Assumptions

- Two to three-year follow-up
- Significant "noise" from participants adding, switching, changing ddNs
- Dropout rate lower than ACTG studies because of flexibility; losses to follow-up lower than ACTG because of primary care settings
- Relatively small treatment differences can be detected
- CD4 strata may be initiated *simultaneously* or *sequentially*

Nested Studies

- Correlations between clinical outcomes and laboratory markers
- Interactions with concomitant medications
- Other pharmacological, virological, and immunological studies
- Participants could choose to undergo a second randomization, e.g., to immediate vs. deferred nucleoside therapy, to monotherapy vs. combination therapy, etc., in studies carried out in multicenter networks

Treatment IND for People with Advanced HIV Disease

In addition to the placebo-controlled study, protease inhibitor developers may wish to consider a treatment IND program for patients failing standard therapy, or those with CD4<50/mm^3. This is a population in which it has been difficult to determine whether antiretroviral therapy per se is effective. Large, randomized dose-comparison programs with ddC and d4T in this population showed no difference between two doses, implying either equivalent efficacy or no efficacy. ACTG 155 suggested (in a post hoc subgroup trend analysis) that nucleoside combination therapy was more toxic, and possibly less effective, than monotherapy in this population. Finally, CPCRA 002 suggested a trend towards a survival benefit on ddC compared with ddI monotherapy. Nonetheless, for ethical reasons, and for practical ones, it might be useful for a randomized, dose comparison, non-placebo-controlled study to be done, enrolling people with CD4<50/mm^3, those intolerant to all nucleosides, and those reaching clinical endpoints in the placebo-controlled study.

Benefits of this Approach

* Faster accrual of clinical endpoints, quicker validation of efficacy
* Larger potential market than second-generation nucleosides
* Synthesizes currently antagonistic goals of access and answers within an acceptable time period
* Takes advantage of a historic window of opportunity
* Unites multicenter academic networks (conducting necessary nested studies) with primary care physicians and clinics around the country who have grown experienced in conducting parallel track studies
* This approach is the only one which can provide access for thousands of HIV-infected persons to a potentially useful class of compounds while at the same time clearly defining their clinical efficacy.

Issues for Further Discussion

FDA Issues: Sample size; Data requirements; data audit arrangements; N ested studies design and execution.

Industry/Sponsor Issues. Cost estimates: cost of drug plus logistics of trial; Cost of alternative development plans, e.g., small complicated trials plus uncontrolled expanded access programs; Manufacturing/supply issues; Data requirements; data audit arrangements

Community Issues. acceptability of placebo; Design and execution of alternative development plans; Follow-up and willingness to remain on study.

Questions and Answers about TAG's Proposal for Development of the Protease Inhibitors

Spencer Cox, TAG

We have tried to answer some of the frequent questions that have been raised about TAG's proposal for the development of the protease inhibitors. If you have any further questions, comments or suggestions, please don't hesitate to contact Gregg Gonsalves at TAG by phone at 212-260-0300 or by fax at 212-260-8561. You can also write to us at 147 Second Avenue, Suite 601, New York, NY 10003. We all share the same important goal: improving the health and lives of people with HIV/AIDS.

1) What do we know about available anti-HIV drugs, like AZT, ddI, ddC & d4T?

Despite lots and lots of studies, we still don't know very much about these drugs. We know that they all make T-cell counts go up, and we know that, in some cases, they make virus levels in the blood go down and may slow progression of disease. However, except for AZT in symptomatic disease, we don't know whether or not they can keep people alive for longer than taking nothing at all.

While many of studies of the available antiretroviral therapies, the "nucleoside analogues," have attempted to focus on the prevention of sickness and death, those studies undertaken have only been large enough to demonstrate a major effect (>40% improvement/deficit). So we know that any benefit (or, conversely, any harm) isn't very big. However, these drugs may have important but moderate beneficial or detrimental effects that these studies weren't designed to pick up. In order to detect small or moderate treatment effects reliably, it's necessary to study large numbers of patients. Its like looking through a microscope: in order to see smaller things, you need to increase the power of your instrument.

2) Won't the protease inhibitors have bigger effects than AZT, ddI, ddC & d4T?

The resistance and surrogate effect patterns of protease inhibitors are similar to those of the other anti-HIV drugs. At this point, it would be naive to assume that their clinical effects would be any greater because they appear to raise T cells and lower virus levels for no longer than AZT and its cousins. If the protease inhibitors have unexpectedly large effects, this would be rapidly noticed, and the studies could be stopped earlier.

3) What has TAG proposed for development of the protease inhibitors?

TAG has actually proposed two programs:

1. For people who have failed or proven intolerant to all available AIDS drugs, or who have under 50 T-cells, TAG proposes a standard expanded access program, in which all patients would receive protease inhibitor, but would be randomly assigned to either high-dose or low-dose. This program is identical in design to the recent expanded access program for d4T.

2. For other people with HIV, TAG has proposed a "large, simple trial." Essentially, all HIV-positive people would be eligible for participation, with those above and below 200 T-cells studied separately. Study participants would be randomly assigned to take either one of two protease inhibitors or placebo, or one of two different protease products and placebo. Other than their study treatments, participants would be able to take any other drug they wanted, approved or unapproved, and to pursue the best medical care they know how to get. If they later qualified for the expanded access program, they could switch over to be sure that they were receiving protease inhibitor.

Accelerated approval could be considered for the protease inhibitors in the large, simple trial, *before the study is completed.* Within a year, important information on the safety of the drugs under study and on the effects of the agents on T-cells and virus levels would be available. Soon after accelerated approval, the study would be able to provide clear answers on the clinical effects of these drugs.

4) What does TAG mean when it talks about a "large, simple trial?"

The development of two available treatments, ddC & d4T, have been accompanied by randomized expanded access programs, in which participants were randomly assigned to treatment with one of two doses of drug. These programs serve as proof that large, randomized studies can be carried out in primary care practices in AIDS. Physicians identified eligible patients, arranged for study entry and randomization, distributed treatment, collected and reported data, and, in a limited number of cases, proved to FDA and sponsor auditors that the data were sufficiently reliable to serve as part of an application for approval. These programs were similar to the "large, simple trial" that was used to detect the moderate effects of heart disease treatments!

A large, simple trial (LST) is a study which randomly assigns large numbers of patients to one of two or more treatment strategies, and then collects only the really important information on indicators of health in those patients. In AIDS, one would generally need to know if and when the patient gets sick, and how long the patient lives. Also, we've proposed smaller "nested" studies of T-cell levels, virus levels, and other important blood markers.

For patients, LSTs have two key advantages compared to other kinds of trials. First, because the study is simple, it's easy to take part in -- a wide range of patients can join, and the large numbers will average out differences that exist between one type of patient and another. There's no hassle, with few, or no, extra visits or tests or forms -- in other words, patients and physicians can usually make any decision they want about other kinds of treatments that the patient should use without influencing the outcome of the study. This is completely unlike

standard government-run studies, where you may be denied useful treatments, and certainly unproven treatments. Second, because the study is large, it produces dependable results about whether or not, on average, it's better to try a new treatment than not. As with results from other kinds of trials, individualizing therapy remains very important -- for example, a drug that may cause peripheral neuropathy, but offers some benefit, may not be appropriate for patients with a history of peripheral neuropathy. But, on average, one can be sure that, barring obvious reasons not to take the drug, a treatment that has shown efficacy in an LST is probably worth trying.

5) Shouldn't we just stop studying these "marginal" drugs and move on to look for something better?

In cancer and heart disease, significant improvements have been achieved by accumulating therapies of moderate effects. For example, scientists were able to reduce rates of death by about 50% during hospitalization after myocardial infarction (the most common form of heart attack), using the following formula:

Aspirin	approximately 20% reduction in death rates
Clot-busters	approximately 20% reduction in death rates
Beta Blockers	approximately 15% reduction in death rates

None of these treatment effects would be detectable by any AIDS drug trial that has ever been conducted. However, together they represented a major breakthrough in the treatment of heart disease. While we work towards finding better therapies or "home-run" drugs, we can make important contributions to the health of people with HIV today by realistically assessing the drugs we have now. Real advances may come incrementally: one moderate effect on top of another as four "singles" get you to "home base." TAG believes that we need to give people living with HIV today the best chance of living longer and healthier with this disease. People with HIV don't have time to wait for a cure. Should scientists have ignored the potential usefulness of aspirin, clot busters and beta blockers in saving lives, until there was a "cure" for heart disease?

6) Wouldn't this kind of study take a long time, and be very expensive? Wouldn't it "block up" the development pipeline, and prevent us from following better leads?

Conducting an LST of a new drug would be no more expensive that doing an average-sized expanded access program. Also, LSTs can be very fast. Because requirements for participation are much looser than in standard trials, people enroll much faster. For example, ISIS-4, an LST of heart disease treatments, enrolled 58,000 patients in 18 months, and reported early results within two years of starting. The d4T LST enrolled 16,000 patients in two and a half years. This is about the amount of time it takes to develop a drug now anyway. With studies of this size, endpoints of interest occur much more rapidly than in smaller, old-fashioned trials, quickly giving us clear answers about whether these drugs keep you healthier and living longer. An LST could also be used to reliably show that some of the new "surrogate markers" are useful predictors of the clinical benefit of antiviral therapy. This could provide a tool with which to quickly assess new drugs in development.

7) Why can't we just rely on "surrogate markers," like T-cell levels and viral burden measures, to tell us whether or not drugs work?

Someday we may be able to. Right now, we don't have enough information to reliably interpret the long-term effects of such changes. We thought that the kinds of small changes that we see in T-cell counts after using AZT, ddI, ddC & d4T could tell us whether people stay healthier and alive longer. We were wrong. Several recent studies have shown otherwise. In fact, one study suggested that it might be as effective to flip a coin.

Many people are confused by this. If someone's T-cells drop from 500 to 5, you know they are getting sicker. If a drug makes your T-cells go up, then why doesn't it mean a drug is working? Substantial declines in T-cell numbers are a good predictor of disease progression, but small, drug-induced, short-lived rises in T-cells are not always associated with the clinical benefit of a drug.

The new markers of the amount of virus in the blood have not yet been definitively shown to predict disease progression or to be a reliable tool in evaluating new therapies. Remember, even if increasing amounts of virus do mean someone is getting sicker, small, drug-induced, short-lived dips in the amount of virus in the blood may not be associated with the clinical benefit of a drug.

Nonetheless, we're not saying this information is useless. Measurement of these markers will still be important both inside and outside of LSTs. As part of TAG's current proposal, the LST will include "nested" smaller studies to see how good these new viral markers are at predicting the clinical effects of the protease inhibitors. We will also need to perform intensive marker-based studies to allow us to understand what treatments do in the body, as opposed to in the test tube. Major advances in our understanding of the disease and of the effects of treatment can come from these studies.

In the absence of a good surrogate marker with which to assess the usefulness of antiviral drugs, the only way you can show an anti-HIV drug prolongs health and life is to show it prolongs health and life. We could put our faith in one of the new viral markers, but even a marker that seems to be so closely related to the disease process has the potential of being misleading. There are many examples of this phenomenon from other diseases. For example, in Childhood ADL (the disease that Lorenzo's Oil was invented to treat), children experience a build-up of fatty acids, due to a faulty enzyme. This causes severe neurological disease. Lorenzo's Oil clears away all of those fatty acids, and should cure the disease. But it doesn't. As treatment for symptomatic ADL, the drug has been shown to be ineffective.

8) A lot of people have told me that TAG is really proposing this study to do away with expanded access programs. Isn't that really what you're doing?

No. Our proposal includes an expanded access program identical to that for d4T. So far,

TAG is the only activist group on record calling for expanded access now to protease inhibitors for people with less than 50 T-cells. In addition, by using a large, simple trial to assess these drugs, we hope to further expand access to protease inhibitors to people with HIV at all T-cell levels. The pharmaceutical sponsors of these drugs want to test these agents in smaller studies with more restrictive entry criteria as has been done in the past. Our proposal would offer broader access to the protease inhibitors than was available for the currently approved drugs for HIV infection before their approval.

9) Doesn't TAG really want to do away with accelerated approval?

Absolutely not. TAG wants to see that accelerated approval is fully and properly implemented. Accelerated approval allows an experimental therapy for AIDS to be marketed based on changes in surrogate markers that are "reasonably likely...to predict clinical benefit." However, accelerated approval also requires drug companies to conduct "adequate and well-controlled" studies to verify the clinical benefit of their drug. These "studies would usually be studies underway," at the time of approval although they could be completed afterwards.

Unfortunately, while drug companies have happily conducted the initial surrogate marker studies which allow their drugs to receive accelerated approval, they have not fulfilled the second part of the bargain and verified the clinical benefit of their drugs approved under this mechanism. Hoffman La-Roche has still not undertaken appropriate follow-up studies even though phase III studies of ddC failed to show clinical efficacy. Bristol-Myers Squibb has initiated one trial to confirm the clinical benefit of their drug, d4T. Although there have been questions raised about the ability of that study to answer the question it poses, Bristol-Myers Squibb has not planned any other studies to ensure that d4T prolongs the health and life of people with HIV.

TAG simply wants to see that drug companies honor the agreement they make when they apply for accelerated approval for their products in its entirety. Accelerated approval allows companies to market their drugs on the basis of preliminary suggestions of efficacy, but requires confirmation of the clinical benefit of these agents. Industry would be happy to sell drugs without having to prove that they work. TAG wants to fix accelerated approval by making sure that efficacy trials are well-designed and well-underway by the time approval is granted, so that we will know if a new drug is worth taking soon after it is on the market.

10) Why did the FDA turn Hoffman-La Roche down in July when Roche asked whether it would be appropriate to submit an application for accelerated approval for Saquinavir based on AIDS Clinical Trials Group study #229?

With d4T, there was five years of experience with the drug, including extensive long-term use, an expanded access program with 10,000 patients, and a medium-sized study in progress to assess the clinical benefit of the agent, when Bristol-Myers Squibb went to the FDA. With Saquinavir, there was less than one year of experience with the drug, three small phase I studies, a six-month study of 302 patients with only 99 patients on the proposed combination indication of Saquinavir + AZT + ddC and no real-world, long-term safety data whatsoever (which an expanded access program could supply). After the FDA meeting, Roche expanded one of its

phase III studies to 3,000 patients, or 750 per arm, which in light of the slim surrogate effects may still be too small to reliably assess the clinical efficacy of their triple combination.

11) Won't requiring companies to do these trials add too much cost to HIV drug development programs, particularly for smaller biotechnology companies? Shouldn't we be using accelerated approval to make HIV research and development more attractive to industry, since so many companies are considering getting out of AIDS research?

There are many complex reasons why pharmaceutical and biotech companies may be considering reducing their commitments to AIDS research. The pharmaceutical industry's profits are being adversely affected by lower prices and more use of generics by HMOs and other managed care buyers. As a result, companies are considering cutting back on research and development across the board, not just for HIV. Also, these companies are limiting the number of diseases they will research, leading to fewer companies active in not just AIDS research, but also in other diseases such as cancer. Biotechnology companies are also facing a shortage of investment capital due to some recently highly publicized product failures that were not in the HIV field and due to concerns about the impact of health care reform on the biotech industry.

We cannot expect accelerated approval to address these structural problems in the industry. What we can do is point out to industry that unless physicians have clear evidence of how their products should be used and the clinical benefits that can be derived from them, the companies are unlikely to be able to fully tap the sales potential of HIV drugs. It is not surprising, given the limited and confusing evidence available on the utility of HIV drugs already approved under accelerated approval, that their sales performance has been disappointing. Therefore, it is in the best commercial interest of the companies developing these drugs to fulfill their legal obligation to conduct adequate studies that validate surrogate marker data with clear evidence of clinical efficacy. Biotechnology companies facing capital constraints need to factor this additional cost and benefit into their financing plans and either look to large pharmaceutical companies to assist them in financing these studies (which appears to be the trend in the industry anyway) or to re-invest initial profits from sales after accelerated approval accordingly. If this requires special allowances for time delays in order to complete the required studies, there is certainly precedent that suggests that the FDA can adjust its requirements based on a company's size and financial resources. (for instance, the FDA has an adjusted fee schedule for smaller companies).

12) Aren't the protease inhibitors "the most complex, expensive molecule(s) ever made," as Merck and Co. claims?

Bristol-Myers Squibb insisted that ddI was hard to make, until they decided to initiate an expanded access program which made the drug available to more than 26,000 people with HIV. Hoffman-LaRoche claimed supply limitations on Saquinavir, but is now studying it in trials enrolling over 4,200 patients. Drug companies order drug long in advance, and Merck and Roche could just be playing hardball. They may just not want to make any drug for an expanded access program and would rather bottle up demand until they can sell their products.

13) Why do we need these studies anyway? Don't people with HIV with the advice of their doctors decide what is best for them? Aren't these studies irrelevant in the context of individualized therapy?

The approved antiviral therapies for HIV infection have well-documented toxicities, but little information on their clinical effects. Doctors may be wary of prescribing these drugs. The disappointing sales of these agents means they are not being used by many primary-care providers. Physicians in private practices with large HIV case loads may be more likely to experiment with these agents and people with HIV who feel more empowered about managing their own care may sometimes ask for drugs even if they are not suggested by their doctor.

We all know people who decided to take a given medication and had significant T-cell rises. We all know people who may have taken the very same drug and had side effects and little else to show for it. We all know people who have decided not to take anything and have been healthy for years. How did these people make their treatment decisions about when and if to start antiretroviral therapy? How did they know what to start with? How did they know when to change medications and what to switch to?

Without compelling information on the effects of these drugs on disease progression and/or survival, it would be hard to say that people with HIV and their doctors make treatment decisions based on a rational plan of action. Faced with a life-threatening disease, many people with HIV have decided to gamble with what is available to them. At best, their decisions are reactive. If a drug makes your T-cells rise, you stay on it; if they make your T-cells fall or you have serious side effects, you get off it or switch to something else.

However, what if one or more of the currently approved drugs or a combination of them truly offers a survival benefit when initiated early in disease and another only if started later? What if one or more of them actually shortens survival, although it slightly raises T-cells and pushes virus levels down for a little and a little while? What if one of these drugs may give you pancreatitis or peripheral neuropathy, but has no effect on survival at all? How do you and your doctor figure out what to do, if no one knows what each of these drugs does to you?

The reason we don't have some of the basic answers about the currently approved antiviral drugs to help guide clinical practice is because the studies on these drugs were over-optimistically designed to detect large effects. The ddC and d4T studies were designed thinking that these agents would be 50% better than the drugs against which they were compared (usually AZT in long-term AZT users). In addition, the studies often failed to follow the participants long enough to assess the long-term clinical effects of these drugs, or too many of the participants were lost to follow-up to make this possible. In the AIDS Clinical Trials Group study #019 of AZT, 75% of the participants entering with over 500 T-cells were lost by the end of the trial!

The lesson we should learn from the history of clinical research on antiviral drugs for AIDS is that we need larger studies with better follow-up of all participants if we are to reliably evaluate anything other than a "magic bullet" or "home-run" drug for the disease. We shouldn't

conclude that clinical research can't provide vital information with which to make treatment decisions, just because clinical research on AIDS has not served us well in the past. That's letting industry and the clinical research establishment off the hook and giving up on people with HIV.

14) Shouldn't we just assume that new treatments are better than nothing? I mean, the side effect of AIDS is death!

When people have no other treatment options, or are very ill, then of course we should let them make choices about risks. However, we can't assume that new treatments are better than nothing. During the ten years of the AIDS epidemic, we've seen several treatments that were worse than doing nothing. For example, suramin killed most of the patients in the study faster than AIDS would have. The vaccinia vector therapeutic vaccine was also deadlier than taking nothing at all. Last year, FIAU, an experimental drug for hepatitis which is a distant cousin of the currently approved antiviral drugs for AIDS, ended up killing many of the trial participants. Initial studies of that drug were actually done in people with HIV. We need to make sure that we're not hurting people.

If a treatment has large effects, such as a 50% to 80% improvement in survival time, you don't need to know whether the effect is really closer to 50% or 80%. Either way, this is a treatment that people should take. However, if you have a treatment that may increase survival time by 15% or may decrease survival time by 15%, then it's much more important that we know which number is more accurate. This may be a therapy that people should not take.

The drugs we have now are not benign; their use is, as too many of us know, often associated with seriously disabling and even life-threatening toxicity, as well as significant expense. If the products are offering essentially no benefit other than a brief elevation of CD4+ cells, then people with HIV/AIDS can save themselves the toxicity, the trouble and the expense. If the products are offering moderate benefits, then we can and should determine how to use them in combinations to achieve the most benefit possible.

15) Still, doesn't basing a large, simple trial on clinical endpoints mean that people have to die to prove a treatment works? Wouldn't your proposed study force people to stay on one treatment, regardless of whether they get worse or not?

Unfortunately, people with AIDS get sick and die every day. Most people with AIDS die without ever having participated in a clinical study. Recording the number of opportunistic infections or deaths in a study doesn't cause people to get sick or die. Basing studies on changes in the number of T-cells or levels of virus in the blood doesn't keep people healthy. In the absence of a validated surrogate marker, the only way you can prove a treatment prevents sickness and death is if it prevents sickness and death.

Smaller studies, where little variations in treatment can have big effects on study results, are fairly restrictive about the use of other medications, especially other antiviral drugs. An LST because of its large numbers of patients, allows participants to do whatever they and their

physicians think is best for them. That may include changing from AZT treatment to AZT + ddI + ddC. It may include an unapproved drug to prevent toxoplasmosis or an alternative and holistic therapy such as acupuncture or bitter melon. It may even mean dropping off of the treatment to which they were assigned. LSTs allow you to get the best medical care you can, without seriously affecting study results.

16) **Doesn't this proposal mean that we're giving up hope for better treatments.**

No, it doesn't. We all still hope for better treatments. Rather, it represents an effort to adjust our strategy to include the moderate effects of drugs available now; should much better treatments come along, and this kind of study become unnecessary, nothing would please us more. However, better that our proposed study should be proven useless than that five years from now, we should have ten drugs on the market, all with moderate or no effects, and no idea how or whether to use any of them.

17) **Doesn't this proposal roll us back to 1987, with placebo controls and clinical endpoints? I mean, what have AIDS activists been fighting for?**

Our assumption is that AIDS activists have been fighting for safe and effective treatments for HIV/AIDS and its associated opportunistic diseases. This proposal moves us towards that important goal.

This proposal puts medical treatment of participants in clinical trials back in the hands of the PWA and his/her doctor, where we think it belongs. That alone would be enough of a reason to use these methods. By selecting a placebo control, we wanted to avoid having to make all patients take AZT, for example -- there may be patients who don't want to take AZT, or who have already failed on AZT. Our study let's the participant choose what s/he will take in addition to study treatments. Let's be clear. No one on this study would be assigned to no antiviral treatment at all except by their own choice. While you would be randomized to receive a protease(s) or a protease placebo, you could also be on any approved antiviral or even an antiviral still in development such as 3TC if you so decided.

Also, these kinds of studies put power over our drug decisions back in our hands. Right now, if we want to start d4T therapy, we have to take Bristol Myer's/Squibb's word for it that the drug is safe and effective. That doesn't seem very empowering -- particularly when we're paying about $3,000/year for the privilege of taking it. Using the TAG proposal, we'd know whether the protease inhibitors work or not. Without ambiguity, and without having to take Hoffman LaRoche's word for it.

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A Rationale for Large Simple Trials in AIDS

Carlton Hogan, PWAlive and the University of Minnesota

New treatments for AIDS and HIV disease are imperative. Although there has been some progress, antiretroviral treatment is still of extremely limited utility and has made little impact on median survival from a diagnosis of AIDS. Progress has been made in the prophylaxis of opportunistic infections, yet these infections are not conquered, nor impressively diminished, and with the exception of pneumocystis carinii pneumonia, prevention of OIs has not produced longer life spans. Immune based strategies, while attractive in concept, remain wishful thinking at this point.

Perhaps more disturbing than all of the above is the fact that our methods have failed us so soundly. A recently convened state of the art (SOTA) conference at the National Institutes of Health reviewed all the available data on randomized trials using nucleoside analogue reverse transcriptase inhibitors (NARTIs). The panel used hypothetical clinical scenarios to guide their discussion. For the majority of the scenarios, the panel was able to come up with no specific indication as to when, how or even if NARTIs should be used. This despite hundreds of millions of dollars spent to date researching these drugs. Clearly our research has not been productive if it cannot answer these simple questions.

An unfortunate lack of critical thought has plagued AIDS research: much has seemed to have been designed by default, with little consideration given to the specific ramifications of choices of eligibility criteria, on-trial clinical management guidelines, endpoints analysis or interpretation. One would have hoped that the efforts of hundreds of researchers and thousands of patients would have yielded more useful results, and that we would be a little more sophisticated in our use of methodologies to meet specific goals at this late juncture.

The efficacy and indications for use of AZT, the only NARTI with reasonably certain clinical benefit at some point, are nebulous at best. For the other nucleoside drugs (ddI, ddC, d4T), the evidence is even poorer. The only trial to ever show true clinical benefit on survival was the original trial of AZT, conducted by BW and what would eventually become the ACTG. All trials in advanced patients since have been "anchored" to that trial using AZT as a standard of comparison. The majority of evidence collected in regard to these drugs have been laboratory measurements - the CD4+ lymphocyte count in particular. To this date, no one can say with any certainty what the impact of these drugs really is on your health and life span. All we can say with any confidence is that some of these agents may delay early manifestations of AIDS and all of them raise the level of a particular type of white blood cell. For a long time that was considered good enough by most people. We were so arrogant about our fundamental understanding of AIDS, we believed that a change in these counts "had" to imply clinical effect.

Unfortunately, two trials (Concorde and CPCRA 002) have soundly laid that notion to rest, and in the process should have humbled us. But the current rabid advocacy for unvalidated viral load measures show clearly that some individuals are unable to learn the lessons of history are doomed to repeat them. Investigators are arguing that viral load is different, that it's a direct measure of virus activity - sounds a lot like "CD4 is a direct marker of viral damage", doesn't it?

It's a very natural urge for us to want to believe that we have this virus figured out -- randomness and uncontrollability are very threatening. But until we have the courage to admit the deficiencies in our knowledge, and rely only upon empirically verifiable fact, we will continue to grope blindly in ever multiplying confusion.

In discussing CD4, Tom Fleming, in a recent paper, presents a meta-analysis of the randomized clinical trials that were considered by the state of the art (SOTA) panel convened in the summer of 1993 by the National Institutes of Health. He notes that the use of CD4 in retrospectively analyzing these trials produces findings in opposition to clinical reality. Further, he notes that the use of CD4, either alone or as a component of a combined endpoint would have resulted in the MRC-INSERM Concorde trial having a positive finding with respect to the efficacy of AZT in asymptomatic patients, an interpretation contrary to the clinical evidence.

Other surrogates that have been proposed to date remain poorly validated, or are of unacceptable accuracy, similar to CD4+ counts. There seems to have been substantial misunderstanding in the community in interpreting the limitations of CD4. It is popularly supposed that the results of Concorde and CPCRA 002 invalidate CD4 as a natural history marker. In fact, CD4 remains moderately predictive of future mortality and morbidity . It is as a response variable in trials of antiretroviral therapy that CD4 fails: in other words, while fairly gross changes in CD4 are OK for predicting your risk, small changes as a result of antiretroviral treatment seem to mean little or nothing about "real world" outcomes. The confusion around this issue underscores an important point. With much of the pathophysiology of HIV disease yet unknown, the only acceptable criteria for accepting a marker as valid is its calibration against clinical outcome in actual antiretroviral trials. Anything short of that is pure speculation. There are countless examples from other diseases of putative treatments that effect a surrogate associated with progression, yet are on the whole worthless.

It is worthwhile to note that there was initially so much faith in the use of p24 antigen titer as a surrogate in AIDS that a number of trials used it in either eligibility or as a primary endpoint . Now of course we know it to be a poor predictor, with many persons dying never having been p24 positive. p24 was a very reasonable candidate, based on the most impeccable science of the time, but was used without a lot of critical thought and validation.

All of these concerns are particularly timely given the recent enthusiastic and uncritical promotion of viral markers. Promoters of these tests are claiming that their use will eliminate the need for studying clinical outcomes. I more than anyone hope this to be true. But I know that wishing won't make it so. We have to actually test these markers to see how predictive they are, or we are in danger of repeating the mistakes of CD4 and p24 all over again. Even if these viral load markers are predictive in epidemiological cohorts, that doesn't mean they are appropriate for testing the effect of a new drug. As a matter of fact, if a drug worked entirely in the lymph nodes, where it would have the most effect in stemming disease, it might have little impact on viral load in circulating blood. This is just one possibility among many. We need to give up on wishful thinking and hare-brained optimism. The time has come to be nothing short of pragmatic. Our lives literally depend upon it.

I think it is fair to say that OIs and death are among the biggest concerns of people with AIDS. Any trial that ignores these unambiguously ascertainable, incontrovertibly relevant events in favor of the high tech test of the week (non-coincidentally massively promoted by drug companies) does so at our peril.

There has been a lot of resistance to "clinical markers" such as disease progression and death. Fine rhetoric like "body counts" obscures the discussion and inflames sentiment. I should know. I have to take responsibility for bandying these terms about in the past. What I ignored at the time, in favor of making a stirring argument, was that trials with clinical endpoints don't cause peoples' death - they merely write it down when it happens. I know that it's a certainty that I will die, and a probability that AIDS will be the cause. That seems unavoidable at this point, with the dubious treatments currently available. But my death will be a little bit less meaningless, a little less in vain, if at least some worthy nugget of information comes off it.

People with AIDS get sick and die. It's tragic and unavoidable. And that's what should be driving our research agenda, not the newest product that Roche (QC-PCR) or Chiron (b DNA) is trying to sell. The argument for clinical endpoints is really a tautology: we can't know if a treatment prevents disease or death unless it prevents disease and death.

Unfortunately, we have been pretty poor at conducting trials large enough, or long enough (generally the larger a trial, the shorter it can be, and the longer, the smaller) to be able to measure relevant events like OIs or death. The sheer data burden of doing a classic ACTG, VA, or EACG type trial restricts how large a trial can be. In addition, trials of this sort tend to constrain clinical care, limiting participant's treatment choices (more about that later), so it is unreasonable to expect people to remain on trial and compliant for any duration. One possible remedy is the "Large Simple Trial" (LST), an idea successfully being used in other diseases. An LST allows unprecedented discretion by patients and physicians : patients are randomized to a study treatment, but the rest of their care is their business. LSTs get around the data burden by collecting only major, unambiguously relevant events. No mucking about with blood work, fishing for something significant.

Critics from the AIDS community have recently called LSTs "dinosaur age trials". This reflects an abysmal lack of knowledge and historical perspective. LSTs are in fact a fairly new methodology, and have never been used in AIDS to date. It is only recently that investigators have realized that it is possible to loosen the tight grip exerted by standard clinical trials and allow patient and clinician discretion and initiative while retaining good science. Unfortunately, this new pragmatism has hard time trickling over into AIDS, as evidenced by the recent controversy. There are a lot of misconceptions about LSTs floating about, some understandable misapprehensions in grappling with this new methodology. Others are red herrings, manipulated by detractors of this methodology who know better. One criticism that is often heard is that participants have to remain on one treatment excluding all others for the duration of the trial. If that was the case, then a lot of the rhetoric about "body-counts" would have a lot more validity. But in truth, LSTs are some of the purest implementations of "intent-to-treat" methodology possible. Such restrictions are not only unnecessary, they are undesirable. LSTs don't ask "What is the effect of consistently taking this treatment (and ignoring all others) as compared to

no treatment?". We have tried to believe that other trials achieve this unattainable goal: LSTs don't even pretend. That rigid mechanistic "drug vs. placebo" model is far more suited to rats than humans.

HIV clinical care is a variable and complex saga of drug additions, substitutions, dose modifications and discontinuations. Polypharmacy is the rule rather than the exception. This has been ignored, or actively repressed by most trials to date. The prevailing trial model, with restrictions on eligibility, concomitant medications and clinical management can only hope to accrue and retain people very atypical of most people with AIDS. Complicating the picture further, drug intolerance and failure is common, and frequently associated with later disease. This has impeded the ability to follow participants in trials for any significant period of time, and current trials give answers that are useful to a narrowly defined group for only a limited duration. After participation in a trial, a participant may go on to other trials, open label treatment, or no treatment. The staggering heterogeneity of the "typical" HIV population is a compelling argument against the strict homogeneity of most trial populations. Patients appropriate for such trials are in great probability markedly abnormal, or merely poorly (or deceptively) documented.

Although misguided, draconian restrictions do have some rationale: by restricting care, and enrolling a narrowly selected population, variability is decreased in the experiment. You optimize your chances of finding any small benefit the drug may have. It's a model that's geared to approval, not to public health. It asks, "Is there a population where we can find an effect of this drug?" rather than "Is this drug a good choice for most people?"

All this restriction on eligibility and management can have other deleterious effects as well. If the trial climate is restrictive enough, participants may end up having to choose between their health and compliance. Even the most altruistic person will "forget" to mention an unapproved drug or short discontinuation of study treatment if to admit it is to risk access to study medication. The incentives for non-compliance are built into the current system. Research suffers, the participants suffer, and relationships between investigators and participants suffer. Nobody wins. We are now seeing perhaps the cruelest consequence of trial participation: PWAs trying to enter trials of new treatments are told they need to be "antiretroviral-naive." So all those who did their bit and came forward for trials of nucleoside drugs, who may have exhausted their benefit, are now thrown out in the cold. This is the fruit of sciences' futile quest to conduct rigid and irrelevant research.

LSTs, on the other hand, cultivate the diversity of clinical management strategies that exist in the community. LSTs seek to know whether it is a good idea to add a new treatment to standard of care. Standard of care, with all of the variations across geographic area, provider and patient beliefs, and community norms provides exactly the right experimental milieu.

Rather than naively presuming that people can be assigned to a treatment or placebo and will remain on it like good little lab rats, the LST asks, "What is the effect of starting this starting this treatment now, as opposed to another time (or never)?" You can drop off study drug the first day, and you will still be counted (and provide valuable information). This is called "the intent to treat" analysis and is very controversial in AIDS circles at the moment. It certainly has

counter-intuitive aspects to it. After all, if participants aren't taking treatment, how can the trial be considered a test of that treatment? Several alternatives to intent to treat have been proposed, such as counting only the time the participant is on drug, but these are all flawed for various reasons to be discussed below.

The "intent to treat" gives the truest, most unbiased comparison possible. To give an example of one reason why this is the case, a short example (kindly provided by Tim Peto of the Concorde team) provides more clarity than pages of theoretical discussion. Suppose that you are doing a trial of ampicillin vs. placebo in HIV infected persons. The incidence of toxic reactions to ampicillin is inversely proportional to CD4 count. The sicker you are, the more likely you are to have a toxicity. So sicker persons who are taking the ampicillin as opposed to placebo are far more likely to drop off the trial. If you then analyze the trial by those patients still taking study medication at the end of the trial, you will have sorted out all the sickest patients on the ampicillin arm, but not the placebo. The "average health" (or average CD4, or OI-free-time, or whatever) of the ampicillin group will increase. Voila! You have a result saying that ampicillin is an effective treatment for AIDS. Completely in opposition to the facts, but a result nonetheless.

This phenomenon is not restricted to this case in the least. The incidence of toxicities of most drugs is generally worse in sicker patients. Removing certain patients out of an analysis (or "censoring"them in statistical terms) for toxicity is always likely to distort the results of AIDS trials. Censoring for other reasons can also be problematic. Suppose you decided not to count those patients who were non-compliant, or who took forbidden concomitant medications. It is likely that patients doing well on a study arm would tend to stay on that treatment, whereas a patient who felt sicker, or saw their CD4 declining might seek out other treatments. If you exclude those patients from the analysis, you lose information on the inadequacy of the treatment that they were originally assigned to. Any time that you sort out specific patients who will not appear in the analysis, you are in effect "undoing" your randomization and destroying the validity of your trial. Intent to treat analyses protect you from undoing that vital randomization that assures the only difference between your groups is the treatment they are assigned to.

Many trials call themselves "intent to treat" when in fact they are no such thing: Trials that drop people for non-compliance, toxicity, or other reasons are not intent to treat. What we have done more often here in the United States is not to formally discontinue follow-up for these reasons, but often we do discontinue study drug. Often this has the effect of curtailing follow-up, as persons no longer getting drug are more likely not to come in for follow-up. But even for those altruists who continue to come in for follow-up after having their drug rudely yanked, the nature of the question asked has changed. No longer are we asking which is better, drug A or drug B (or drug A vs. placebo). Now we have changed the question: so instead of drug A, for example, we are asking about the strategy of starting with drug A and then discontinuing on non-compliance or whatever. We haven't been honest enough to admit these effects although they have been grossly prevalent in our trials. In antiretroviral trials in later disease, it is not uncommon for more than 30% of patients to be off of their assigned study drug by end of treatment. While the analyses and papers deriving from that study blithely pretend we still have a drug-drug (or drug-no drug)comparison.

LSTs, however, and other true intent to treat trials exploit this notion of "strategy." As previously stated, patients are counted by the arm that they are initially randomized into, regardless of how much drug they end up taking. In this way, an LST better mimics clinical practice. A physician may prescribe drug, but there is generally no one-to-one correspondence between the prescribed regimen and what the patient ends up doing. Some use those cunning little medication beepers, but for most people, drugs are rarely taken exactly at the intervals prescribed. People may temporarily stop drug because they are not feeling well, they forgot to pack it for a trip, or nine million other reasons. The diversity of adherence in the trial mirrors the climate in which the drug will be prescribed.

Depending on intent to treat analyses may dilute the drug effect seen if enough people skip their study drug, or if enough patients on both arms take a more effective drug than the one that is being studied. But no bias is introduced that can alter the substantive findings of the trial. A treatment may end up appearing a little bit less effective, but you minimize your chances of finding an ineffective treatment effective or vice versa. No other methodology known is able to protect from bias in this way. Anything that sorts out specific patients other than through the primary randomization risks inadvertently sorting them by a predictor of outcome. If we were omniscient, with god-like powers of observation and inference, we might be able to calculate all the combined effects of all the factors, currently known and unknown that might impact the finding, and adjust so as to be able to see the treatment effect in isolation. But we mere mortals will have to depend on randomization and intent to treat if we want answers we know we can trust.

Even given all the above, many critics oppose the notion of analyzing a trial by the treatment that a participant starts on. They argue that treatments taken later, after discontinuation of study drug will "muddy" the picture of what is going on in the initial comparison. This notion, while initially attractive is problematic in two regards. One is that it simply isn't realistic. Drug addition, substitution and discontinuation is the norm in HIV treatment. We simply don't have any drugs good enough to remain on for protracted periods of time. If our trials remain in stubborn defiance of reality, we will keep ending up with results useless to PWAs. The second answer to this criticism is that if the first drug has any efficacy at all, patient health will be different to some degree across the arms. It is not hard to see that the time of switching to a new drug, and possibly even the choice of drug, may be influenced by the effects of the first randomization. Subsequent treatments are consequences of the initial randomization, and therefore an integral part of the strategy of using that drug.

It is important to acknowledge that all these principles are most relevant when testing treatments of poor to moderate efficacy. In the above scenario, if the choice of drug that was switched to after the initial randomization was a true "winner", it would in fact wipe out the effects of the randomization. However, if in fact, we ever find such a wonder drug, I am sure that we might be willing to deal with any small inconveniences and ambiguities that might accompany it.

It is possible that using surrogate markers we might be able to sort various candidates, and get some kind of idea which treatments are likely to be useful. Why then do we need to go

through the effort and expense of establishing LSTs in AIDS? Wouldn't immediate access be better? Well, we are all hoping for a home-run, and there is a tendency to believe that a new drug is better than an old one, or no drug at all. Tragically, the clinical trials literature suggests the exact opposite. New compounds are far more likely to be harmful than helpful.

Brie Salzman, in an open letter to ACT-UP compares waiting for clinical information to "holding a gun to <his> head", "putting a mine under <his> doormat", or "a bomb under <his> pillow". But for those poor unfortunates who received Suramin, or the vaccinia vector therapeutic vaccine, a gun to the head might have been more humane. Thank god that the deadliness of these treatments was discovered before "accelerated approval". It would be great if early testing of toxicity, such as occurs in Phase I trials, could be counted on to uncover all deleterious effects. But some toxicities develop only in some persons, or only over longer periods of time. None of the phase I or II trials of AZT revealed the now widely recognized side effect of myopathy. It was only after large numbers of patients had taken AZT over long periods of time that myopathy became apparent. In more closely approximating the clinical milieu, LSTs offer the opportunity to observe those toxicities rarely seen in the hothouse atmosphere of restrictive clinical trials.

To capture both disease progression and toxicity effectively though, the endpoints in trials need to be clinically relevant. Just getting the"viral load" down in peripheral blood is not enough. AIDS is not the only horrible thing that can happen to your body. It's not a great stretch to imagine a potent antiviral that ends up doing more harm than good, while effectively shutting down viral replication. IV Bleach might be a good example, but obviously would not make it through phase I trials. A major rationale for LSTs in AIDS is the hypothetical, but extraordinarily plausible possibility of just such a toxic antiretroviral, whose effects don't show up immediately. FIAU was almost that drug for the community of persons with advanced liver disease. It is not specious to hypothesize that combination nucleosides may be so toxic so as to be worse than no treatment at all for some patients with AIDS (like those with CD4<50).

Despite all these concerns, many AIDS activists, and even some seronegatives who run large advocacy organizations, are actively campaigning for rapid approval of drugs based on surrogate marker information in limited groups. Unlike previous battles, they will be able to find ready allies on this issue. The pharmaceutical companies would love to have the skids greased for them, and to be relieved of the bothersome responsibility of proving that their compounds actually do something beneficial. The testing technologies companies would love to have a huge market for their products, without having to demonstrate scientific validity.

The irony of all this is readily apparent. As I said earlier, five years ago I was among the hordes flinging out inflammatory rhetoric about "body counts", and "unethical researchers, sacrificing PWAs for science". But during the intervening years I have grown more pragmatic. I have seen dozens of drugs fail that were winners in preclinical evaluation, theories of pathogenesis come and go, and four antiretrovirals be approved, and all my friends die nonetheless. Having more CD4s is great, as is having less viral load. I'm sure it helps one to sleep better at night. But these are abstract considerations. What I want for myself is to live long and healthy. I am now acutely aware of the limitations of medical science, and have no intention of holding my health

hostage to some ivory tower academic's idea of a surrogate of the month. I don't need drugs that can be finessed into impacting an arbitrary marker: I need drugs that will keep me alive. I see little impetus from the pharmaceutical companies to look for these, but I would like to be able to depend upon my community to support me. For those whom CD4 or viral load is more important, we can always get that information, either by nesting those studies into trials with clinical endpoints, or doing short ancillary studies. But please don't deny me the answers I need to live.

Xth International Conference on AIDS, Yokohama, Japan

Abstract

PB0835 The Effects of AZT on Survival: A Review of Published Randomized Evidence. R. Smith, D. Abrams, T. Mitchell, P. Meier, R. Peto, USA & UK.

Trial	Average Months Followed	Stage	Deaths/N on Controls	Deaths/N on AZT	Obs-Exp (O-E)	Standard Error of O-E Z value
BW 02	4	ARC/AIDS	19/137	1//145	-9.28	2.24 (4.14)
ACTG 036	10	Asym.	3/85	1/82	-0.96	0.99 (0.97)
ACTG 016	11	ARC	0/351	2/360	0.99	0.707 (1.40)
ACTG 019	13	Asym.	8/856*	4/910	-1.44	1.32 (1.09)
VA 298	27	Asym.	20/168	23/170	1.37	3.06 (0.44)
Concorde	36	Asym.	76/872	95/877	9.26	6.21 (1.49)
TOTALS			**126/2041**	**126/2544**	**0.06**	

The failure of all but the first placebo controlled AZT trial to detect a statistically significant survival benefit is often incorrectly viewed as evidence that there is no survival benefit associated with early intervention with AZT. A review of the totality of the currently available published evidence does not exclude the possibility of moderate benefit or, alternatively moderate harm from early AZT. In fact, even the Concorde trial result is compatible with a moderate survival difference between treatment and control. In order to reliably determine whether a moderate benefit on the order of 10-40% might be associated with earlier intervention with AZT, trials will have to be enlarged an order of magnitude.

Belief vs. Reason
Testimony Before the FDA Antiviral Drugs Advisory Committee
September 12, 1994
Dennis Davidson, Art Positive

Good morning, my name is Dennis Davidson. I am HIV positive and currently asymptomatic. I have no affiliation with the pharmaceutical industry. I want to thank the committee for this opportunity to participate in this public meeting.

I would like to speak to an underlying issue which, I believe, characterizes the debate before you. This debate has become polarized into two opposing camps: those who favor wider access to new drugs regardless of their efficacy or clinical benefit versus those who favor access to new drugs with proven efficacy and clinical benefit based, in some cases, on information gleaned from Large Simple Trials. I would like to frame it in a larger context of our society as a whole rather than just the subset of people in immediate need of new drugs.

The underlying issue is one of process based upon belief versus process based upon reason. It is a conflict which goes beyond drug development, and in many cases is intractable. In my professional work-day life I am a science educator and visualizer specializing in astronomy and space science. A similar polarity exists within my constituency. There are those who choose to understand the universe using a belief system called astrology versus those who choose to utilize reason and analysis to interpret their observations of the universe. I have found that the former is by far the largest and most vocal. For example, astrology columns are more common in newspapers than are astronomy columns.

It disappoints me to see the same trend away from reason and towards belief in the HIV treatment community. I am not here to name names or organizations. I am speaking from personal experience derived from conversations with people I encounter on a daily basis. It has become too common for people with AIDS to exclusively rely on anecdotal information and hearsay when making important treatment decisions. The clinical and research establishment has lost all credibility with a significant number of people with HIV largely because clinical trials have heretofore failed to provide clear-cut answers to our treatment questions.

In this light, the notion that every citizen with HIV has the right to access new and reasonably safe drugs which show some promise of efficacy, however meager or ambiguous, is certainly appealing. Given the cult of individuality which the American culture has so efficiently enshrined, it seems almost patriotic to demand universal access. However, should new and perhaps more informative clinical trials be held hostage to this demand? Should improvements to an inadequate clinical trial system be sacrificed for this individualistic need? I think not. Access and answers need not be mutually exclusive.

No one is saying that we should deny access to drugs, especially to those who need it the most, and are usually excluded by design, from many clinical trials. What I am saying, is that perhaps the time has come to defer immediate hypothetical "benefit", often couched in terms of rights of

access, to near-term and long-term benefits for all of us. This is known as altruism and by definition it means that individuals give up some immediate benefit for the longer term benefit of the group.

It may be harsh to frame this debate in terms of selfish individualism versus altruism, positive versus negative, or symptomatic versus asymptomatic, but demanding access for the individual without insuring a process to benefit the entire group becomes just that: the individual and perhaps a small circle of friends in the know might benefit while the majority is left with nothing.

Where is this trend leading? I believe that this is part of a national trend towards scientific illiteracy and is leading to a chaotic process of individualized testing of new drug products. There seems to be a conceptual blurring between individualized treatment programs versus individualized testing. (Many of us use individualized treatment programs and we all follow hunches or listen to our intuition when making treatment decisions.) How will we learn anything from a sample size of one? This is where belief clashes with any process which might obtain useful information for the group as a whole. It is a fundamentally different approach to obtaining knowledge than the scientific method.

The power of the scientific method is evident in its process. One does not have to even believe in it for it to work. Just be rigorous and objective in the process of testing and analysis, follow a specific set of rules, and take good notes for others to duplicate your process. Yet this rigor and objectivity is what is often rejected by those who base their decisions solely on belief. I would like to see many of the so-called alternative treatment therapies subjected to the same rigor in testing and analysis which we expect of traditional drugs. Perhaps we will learn something of clinical value which can benefit everyone.

A point I'd like to conclude with is this erroneous label of elitism which has been thrown around in this debate. It's time to stop and have a reality check. In terms of the world's population of HIV infected, everyone in this room and their constituents are the elite: positive or negative, symptomatic or asymptomatic. The majority of people infected with HIV world-wide will never have access (accelerated or otherwise) to any of the treatments we are discussing. So lets discard the inflammatory rhetoric and start working together in a reasoned and cooperative manner.

Yes, belief in a treatment and hope for our survival are an integral part of our healing process, but our hopes and beliefs must be tempered by the realism of analysis and reason. We have all given so much in this epidemic. Yet we must give more. I want to live as long as I can: to learn, to lead a productive life, to create art; but I want my death to be meaningful (and even useful) to the future generations of the infected.

In closing, we in the first world have a special responsibility for the many in the rest of the world who will not have the opportunities we have. It is a responsibility which places the good of the planet above the individual need. Of course, we need clear, unambiguous answers but we are not going to get these answers with studies which have a sample size of one. Saving lives and acquiring data are not mutually exclusive. Thank you.