

**Project Inform**  
San Francisco, California

## PLACEBOS: Time to Say No

People who volunteer for clinical studies often face two great risks in return for being first in line for a treatment which might work: they might receive a treatment which could do more harm than good, or they might receive a placebo (an inactive substitute) instead of a real drug. While this might have been necessary in 1985, it continues today, long after useful treatments and predictive lab tests have become available. This use of placebos occurs not out of scientific necessity, but in response to economic interests, knee-jerk thinking at the FDA, and misguided scientific dogma. We find placebo use in many studies today unethical and urge patients and activists to bring it to a halt.

Reports that FDA will now discourage placebo use are incorrect. The agency has merely described how its policy applies in current AIDS research. FDA, for example, still requires placebo testing of such thoroughly proven drugs as DHPG. We cannot consider this progress.

### Background:

The placebo serves as standard of reference against which the effectiveness of a drug is measured. Its use is intended to act as a control on a key research variable: the psychological and physiological effects patients experience by participating. Participation raises hopes, improves attitudes and belief in the potential of successful treatment. This improved outlook sometimes affects a patient's physical condition. Likewise, participation raises anxiety and awareness regarding side effects. The "placebo effect" principle says that patients who believe they are receiving treatment are more likely to experience improvements (and side effects)

than patients who don't have such beliefs. This effect has been demonstrated in many studies.

Placebos must look, taste, and be administered like the real thing. In classic *double-blind* studies, neither patients nor physicians know who receives drug or placebo. The charade is designed to distinguish the true impact of a drug from the placebo effect. Upon completion, a study is "unblinded": the researchers learn who received real drug. Statistical analysis then determines which effects, if any, can be validly attributed to the real drug.

The system sounds like a reasonable way to get

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valid scientific evidence. It goes astray however, when belief in the system is so strong, so dogmatic, that it forgets that this isn't the *only* way of getting valid information. When placebo-controlled studies are the only choice offered to people with life-threatening illnesses, patients are literally asked to act as sacrificial lambs, giving up critical months or years in their fight for life. Can this be justified at this point in the epidemic, now that reliable means for saving lives are at our command? We think not.

By their nature, placebo-controlled studies present a moral dilemma. Research should only be conducted on humans when there is reason to believe that patients might benefit from a drug.

When that belief is strong, it argues against use of placebos. When the belief is weak, it argues against conducting the study at all.

Nineteen patients on placebo died in 21 weeks in the first major AZT study, compared to only 1 on real drug. Researchers see this as a vindication of placebos, arguing that the value of AZT was clearly established in just 21 weeks. Patient advocates see the same study as needless slaughter. They argue that if the disease led to such rapid death, that if the "placebo effect" was in this case so ineffective, surely the impact of AZT would have been clear if all patients had received real drug in the first place. Some might be alive today had that been done. When 20 people received AZT in an earlier Phase I study, the response was startling and unambiguous. Researchers created the placebo study because they expected the drug to work. What the new study added was the ability to quantify results.

Consider a few examples of what the dogma of placebo control means in practice:

*continued*

- A study is recruiting 400 infants with AIDS or

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ARC between the ages of 18 and 36 months. These infants are treated intravenously, hooked up to an IV for up to 8 hours at a time, sometimes under restraint. Half will receive a placebo in their IV. The protocol requires the IV placebo to make sure that both the real treatment and placebo control groups share an equal risk of getting the infections which often accompany the insertion of an IV.

- A Canadian study is recruiting hundreds of AIDS patients for a placebo-controlled study testing whether aerosolized pentamidine prevents relapses of PCP. The study is set in Canada because the sponsor, Fison, knows U.S. patients would refuse to participate, that U.S. physicians and researchers consider aero-pent the standard of care for post-PCP patients, and that most would find the study unethical.
- The AZT seropositives study will put more than 1000 people on placebo. By design, the study is counting on large numbers of them progressing to AIDS over a three-year period, to prove that fewer who took AZT experienced the same problem.

### Who's to Blame?

It is unfair to characterize all researchers as the villains in this scenario. Most are acting according to their beliefs, however misconceived we find them. To some extent, they are often only following orders, orders which come from four interconnected sources :

- *The FDA*, which approves the design of studies and often dictates use of placebos.
- *The IRBs (Independent Review Boards)*, which rule on the ethics of studies. Critics believe that many IRBs primarily serve the interests of the systems for which they work (the universities, pharmaceutical companies, and the research establishment).
- *The traditions of the research establishment*, which must not be challenged if an individual researcher hopes to advance in his or her career. These traditions, which are not necessarily shared by researchers in other countries, are enforced by the medical journals, where use of a placebo control increases the likelihood that an article will be published.
- *The insurance industry*, which conveniently resists payment for treatments which haven't been "proven" beyond all doubt. Waiting for the time it takes to develop such proof saves them a lot of money.

Placebo proponents attempt to justify their views with several claims. They say:

1. The use of placebos allows the greatest control of variables, and thus produces the most inarguable results.
2. Placebo-controlled studies are the fastest way to establish the value of a drug.
3. Without placebo controls, we will never really know which drugs work and which don't.
4. Placebo use will save more lives in the long run, perhaps costing some in the short run. Those lives, they say, would be lost anyway.

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***Four years of placebo-controlled studies have largely left a track record of scientific ambiguities and contradictions. The theoretical advantages of placebos do not reliably occur in the real world.***

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What's missing is any deep concern for the volunteers as patients. Enrollees in AIDS-related studies are not mere research subjects but, first and foremost, patients exercising one of very few options - sometimes their only option - for treatment. Instead, they are consigned to the role of lab animals being sacrificed for the good of mankind. The justifications of the researchers can, and must be, soundly answered.

1. "...placebos control the variables..."  
This myth holds up only in an academic dream world. In the real world, many patients quickly learn whether they are on placebo or real drug. Ellen Cooper of FDA described the initial major AZT study as "unblinded" by doctor and patient awareness of lab values in a simple blood reading (*mean corpuscular volume*, which rises at least 10% during AZT use). Other patients send drugs out for analysis. If studies are to a large extent unblinded, then the "placebo effect" variable isn't controlled at all.

Control of variables is further diminished by unreported patient use of other drugs. Although we don't condone this, it is impossible to prevent it when people are fighting for their lives. Studies which are perceived by patients as contrary to their own interests are doomed to fail. With many diseases, the benefits of a drug, or its side effects,

are so evident as to render placebo use meaningless. Researchers are reluctant to acknowledge this because it makes study conclusions suspect.

2. *"Placebo studies are the fastest way to establish the value of a drug."*

This is true only if the objective is to seek approval of a drug for marketing under the current FDA system. If, instead, a study seeks only to identify compounds that have some value for patients in a worldwide, infectious epidemic, then smaller, less controlled studies may be able to reach reasonably sound answers more quickly, which later research can refine. The Phase I AZT study, for example, gave sufficient information to begin treating life-threatened patients immediately. Yet the system demanded another year of testing, during which time thousands died who might have been saved. It is the system under which drugs are licensed for marketing by FDA which makes placebo studies necessary, not scientific or human necessity.

3. *"Without placebo controls, we will never really know which drugs work and which don't."*

Not true. We just won't know which drugs meet FDA requirements, which is not the same thing as knowing whether or not a drug works. Other controls are available which can produce valid results. Under some circumstances, control groups may not be necessary at all. Dozens of drugs have been proven without placebos, as have virtually all surgical procedures.

4. *"The use of placebos will save more lives in the long run..."*

This is true only if points 1 through 3 are true. We have had 4 years of placebo-controlled studies which have largely left a track record of scientific ambiguities and contradictions. The theoretical advantages of placebos simply do not reliably occur in the real world. Placebo studies will always overlook drugs which work for some people but not for others. Because of HIVs variability and rapid rate of mutation, AIDS is a disease in which *no* drug will work for everyone.

Perhaps of greater concern is just whose lives "in the long run" will be saved at the expense of whose lives in the short run, or whether anyone will be left "in the long run" to save. Certainly, the unfortunates who first acquire a disease are going to be the losers. So far, the gay community has provided most of the guinea pigs of AIDS research. Are they doing so to provide eventual protection for late-comers to the epidemic? Only

time will tell.

### Alternatives

When a disease state is dramatic or relentless, simple research, without control groups, can often quickly tell whether a therapy works or not. It may not tell whether it works in comparison to another therapy, but it can show whether or not it works at all. The more serious the disease state, the less impact the placebo effect is likely to have, and thus, the less necessary a control group becomes. AIDS is such a dramatic disease state that the placebo

### Anything New at FDA?

- Mail importation policy (permits easier access of drugs from overseas; see page 10)
- Expanded use of trimetrexate (under threat of a lawsuit by Lambda Legal Defense)
- A proposal for eliminating the Phase III testing requirement for drugs meant for life-threatening illnesses (under pressure by George Bush's Deregulation Task Force)
- New delays in dextran sulfate imports (caused by increased volume at FDA/Customs ports)

effect is weak—no AIDS patient has been cured by placebo. Effective treatment, at least for full AIDS, can be spotted without controls.

When controls are necessary, several alternative types are possible. One is the use of *historical controls*, in which patients on a new drug are compared to previous patients (with a similar disease state) who did not use the drug. In AIDS, though, historical controls are not very useful because the course of full AIDS today is quite different than it was just a few years ago. The situation has not changed, however, for asymptomatic seropositives, so historical controls remain relevant with this group.

*Untreated controls* offer a more useful alternative.

In these, patients receiving a drug are compared to patients with a similar disease state who choose not to be treated. Since there are plenty of people who choose not to use experimental drugs, this is a feasible approach. Moreover, the untreated controls can be given, free of charge, the same testing, monitoring, and medical care as the treated patients. This makes them similar in all ways to placebo controls, except for ingestion of the bogus substance.

*Comparative controls*, another alternative, uses one drug to serve as the control for another. For example, patients on dextran sulfate might be compared to others on AZT; post-PCP patients might use aerosolized pentamidine and acyclovir as a control against AZT; an AZT seropositives study might use ribavirin or Imreg as controls, since both have shown some (if tentative) evidence of slowing progression to AIDS. Many combinations are possible. This approach, however, is stymied by FDA insistence that only drugs which are proven can be used as controls. This forbids use of various partially, but inconclusively, proven treatments. While insistence on proven drugs makes it easy to quantify results, it seems morally bizarre to prefer a true placebo, which is guaranteed not to work, to a drug which might offer at least some hope of effectiveness.

Another approach is to change the end points (measured outcomes) of studies. Endpoints such as *anticipated progression to AIDS*, *opportunistic infections*, or *death* make placebo-controlled studies difficult to justify when it is already established that some treatments can slow or prevent these outcomes. If, instead, lab values were used as the endpoints, patients might be protected from the most serious disease states even when placebos are used. Rather than counting how many ARC or seropositive patients progress to AIDS to measure a drug's value, studies might instead measure changes in T-cell, p24, white count, and beta<sub>2</sub> levels as the endpoints. If values improve, it should mean that a drug is working or at least moving things in the right direction.

Some (but not all) researchers argue against using lab values on the grounds that they don't know enough about these measures. Yet, at the same time, FDA and NIH use the lack of success against these markers as proof that some drugs don't work. They can't have it both ways. If the lab markers are good enough to disqualify drugs, then they are also good enough to serve as measures of a drug's success.

### Is There any Place for Placebos?

Placebo studies should be found morally acceptable only when there is no expected risk of patient

harm or regression during their use. This is little more than a restatement of the physician's Hippocratic Oath. Yet placebo studies are often based on an assumption of harm to patients, harm that may be prevented or lessened in the group receiving the real drug. However, if a study is brief enough that patients are unlikely to suffer harm due to lack of treatment, then a placebo may be acceptable. This, though, virtually demands that lab markers be used as endpoints.

Some argue that placebos are acceptable whenever no available treatment is proven to work. Although we would dispute this in the instance of a highly destructive and relentless disease such as AIDS, this is a moot point, since AIDS treatment research is well past its infancy.

### Conclusion

There are world renowned researchers who urge alternatives to the placebo. We believe it is possible to conduct valid, useful scientific research without the use of placebos. We even believe that there may be limited circumstances in which placebo controls may be appropriate. And we believe there are ways to fix ongoing placebo-controlled studies without shutting them down.

FDA's "new" policy merely says the agency will discourage placebo use on AIDS patients "when comparative studies" are possible. This has already been the policy of most IRBs for most life-threatening illnesses for the last 25 years. It leaves the door open to nearly all of the unethical use of placebos currently underway.

Placebo use must be banned in any new study which puts patients at known risk due to lack of treatment. Studies already underway must be revised to include "safety nets" which provide patients with preventive treatment for PCP and access to real drug whenever the lower limits of key lab markers are reached. Although such measures may make it more challenging to conduct research, any added difficulty it outweighed by concern for human life.

In the future, we must demand that researchers, regulators, and IRBs use alternatives to the placebo when it is in any way feasible. Today, the placebo is almost always the first and easiest choice for them to make. Patients and their advocates have also made this too easy a choice by putting up with it. Studies which violate our ethical standards aren't worthy of community support and are doomed to fail. IRBs which overlook community concerns should be challenged in court. And the regulators who, in their isolation from this terrible disease, continue to demand the use of placebos must be confronted at every opportunity and in every way.

The choice to do these things can begin today.

4. *Pre-arrange personal support for yourself.* Have a few friends or family on call, both when you pick up your test results and during the “worry-time” while waiting for them.
5. *Discuss it in advance with your lover, wife, husband, or regular partner.* Simply springing a positive (or negative) test result on one’s partner, without advance warning, is a plan for disaster. A partner needn’t be allowed to dictate your decision on testing, but neither should the partner’s needs and concerns be casually overlooked.

People in high-risk groups who test negative sometimes experience another sort of trauma called survivor’s guilt. In this reaction, a person feels guilty for being spared while so many others are not. It is another facet of the “Why me?” question. This reaction may last several weeks, and usually resolves itself. It is a time when many decide to work actively with groups fighting AIDS/HIV. Many find this to be an excellent form of therapy.

Whatever the location, there still seems to be ways to get the medical information needed to build a sound treatment strategy. How to do so will continue to vary from state to state until federal legislation is passed guaranteeing protection from discrimination on the basis of HIV status.

## Safe Testing

The issues of antibody testing vary from state to state, yet the goal for many people remains the same: how to get essential medical information without risking legal, economic, or psychological damage. Project Inform met recently with the PWA group of Colorado (PWAC), a state which has among the nation's most repressive laws on reportability and contact tracing. Even there, we learned, there are ways to get the information needed. The following recommendations, aimed at states which don’t offer anonymous testing, resulted from that discussion:

1. *Learn the local and state laws* regarding confidentiality before scheduling a test. Knowing what you’re up against is the first step in coping with it. Check with local and national legal organizations which support HIV-infected people. NGRA in San Francisco (415-863-3624) and Lambda Legal Defense in New York (212-995-8585) either know the local laws or can refer you to someone who does.
2. *Use a pseudonym when tested.* Colorado and some other states which don’t offer anonymous testing do not require formal identification. While using names like M. Mouse, E. Cooper, or J. Danforth Quayle makes for fun, it’s best not to deliberately provoke suspicion. The pseudonym should be written down and remembered in case follow-up or comparison is needed later.

When resistance is encountered at the test site, would-be testees are encouraged to discuss the situation with a PWA-experienced attorney before proceeding.

3. *Go to another state* (if possible) where there are less restrictive laws and, therefore, less anxiety. Check the situation in bordering states. You can avoid making two trips by having a friend there pick up your results.

**Whatever the location, there still seem to be ways to get the medical information needed to build a sound treatment strategy.**

6. *Schedule a counselling session for the day you get your test results.* Be sure the counsellor is aware of treatment strategies and local access to medical interventions. The antibody test information, while provoking an emotional crisis at the time, could also be life-saving.
7. *Know where to get information on treatment strategies.* Once a person gets the answer to the anti-body test, the need for additional information is often felt with urgency. Project Inform is a good place to start.
8. *Keep the results to yourself.* The only ones who need to know are those people you’ve asked to help support you. Some of the consequences of anti-body testing are set in motion by careless spread of information, even by well-intentioned acquaintances. Unless there’s a reason to tell someone, don’t.

About 3.5% of gay men tested in California have reported clinically significant emotional reactions, needing treatment. Many others suffer a fairly intense personal crisis of 3-4 weeks duration after a positive test result and then adapt to their situation well. For some others, testing confirms what they’ve known in their hearts. And for a substantial number, it provides a pleasant surprise. Having good information about available treatment strategies - knowing that there is something you can do about HIV infection - helps many people pull through the crisis.

*In memory...*

We dedicate this issue of PI Perspective to the memory of Ron Koslow.

At a time when the PI hotline was hanging by a thread, Ron stepped forward to fill the giant shoes of Tom Jefferson. He gave of himself until it hurt.

Ron found great purpose and joy in leading others on the path from anguish and despair to empowerment.

His memory will live on in the work that remains.

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## HIV as a Manageable, Chronic Infection

At the recent Stockholm AIDS Conference, a well-known American AIDS researcher declared early treatment intervention to be an “intuitively obvious” approach. Project Inform differs only in that we feel it was “intuitively obvious” as far back as 1985. There simply isn’t another disease model which calls for withholding treatment until illness advances to a life-threatening stage. By the time HIV results in significant symptoms, enormous and possibly irreparable damage has been done to the immune system. Yet, today, our hotlines remain deluged with calls from people throughout the nation who are being refused treatment until some arbitrary level of illness is attained. This is both absurd and increasingly unethical. Medical centers and insurance companies which still endorse such practices are living in 1986 and doing their patients an injustice.

What has finally brought many researchers and leading physicians to this accept view is the accumulating body of evidence that early intervention, even with today’s imperfect treatment options, can result in improved immune response and delayed (if not totally prevented) progression to serious disease states. That this should be the case is little more than common sense. If AZT and similar drugs can reduce the level of viral activity, then certainly the time required for breakdown of the immune system will be extended. And if the side effects of such drugs are less severe in basically healthy people, as all the research demonstrates, any argument for delaying treatment simply vanishes.

Perhaps the most compelling and inarguable example of the benefits of early diagnosis and intervention is found in the use of preventive treatment against PCP. PCP prevention, using aerosolized pentamidine when possible or such oral drugs as Septra, has proven astonishingly successful in the *secondary prevention* of PCP (preventing the recurrence of PCP after a first bout). Studies already presented and others nearing publication have established this beyond question. The most important application, however, is not for those who have already had their first bout, but for *primary* (first time) prevention by people whose suppressed immune systems make PCP likely. As it stands today, not one more person needs to come down with a sudden, unexpected bout of pneumocystis. Practically speaking, PCP has

become a preventable disease. And since PCP is the AIDS-defining event in the vast majority of cases (65% or more), the occurrence of AIDS itself is profoundly affected by its control.

Despite the clear case for prevention of PCP, numerous insurers deny payment for aerosolized pentamidine on the grounds that FDA has not yet approved this use of the drug. Reluctant physicians resist on the grounds that the studies validating this approach have not reached the medical journals. Yet, they willingly promote the use of

of science.

Fortunately, a rapidly growing number of physicians can see their way past this economically motivated smokescreen. Physician groups have formed across the country demanding access to this and other reasonably proven therapies. When this is the case, the next move - and it’s a big one - is up to the patient community.

All that’s necessary to take the next step forward is for people to know when they are at risk of PCP.

Studies have repeatedly shown that T4-cell counts near or below 200 are predictive of PCP and other opportunistic infections. FDA itself feels so strongly about this dividing line that it uses it as a standard for ruling on potential biases in the design of clinical studies: patients with fewer than 200 T4 cells are must be carefully and equally distributed among treatment and control groups if a study expects to pass FDA approval. When seropositives know when they are at or near this line, they have all the information needed to prevent the occurrence of PCP.

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the oral drugs whose use as preventive medicine is sometimes less well-supported by data and which always presents a higher risk of side effects. The motive: it is cheaper for the insurance companies and it asks less of the doctors. Amazingly, the same people willingly pay for and prescribe the toxic use of intravenous pentamidine in hospital care of PCP.

On the most important application - using “aero-pent” as a primary preventative - similar irrationality surfaces: “*the data isn’t in yet,*” “*we haven’t done those studies,*” “*show me the citations.*” It is difficult to understand how intelligent professionals can’t see the relationship between *secondary* and *primary* prevention. It is as if they believe proof of one tells them nothing about the other. This is an example of taking science so literally and dogmatically as to contradict all common sense and rational thinking. Turgid-thinking researchers call for placebo studies to test aero-pent in primary prevention. If we must await placebo-controlled studies to prove what is patently obvious, approval will never come. No one in his right mind at risk of PCP would (or should) consent to a placebo-controlled study of aero-pent. Truly informed consent will prevent any patient from participating in such a study, and the Hippocratic Oath should prevent any physician from being a party to such an abuse

### A Model for HIV Management

The requirements for managing early stage HIV can be drawn from the model used in the management of other chronic illnesses: an intelligent system of monitoring followed by responsive and flexible use of available treatments. This is in sharp contrast to current approved HIV methodology, which is often based on ignoring the patient’s condition until critical illness occurs, followed by relentless use of AZT and/or chemotherapy until the patient no longer can tolerate it or dies.

**STEP ONE:** Intelligent monitoring begins with learning one’s antibody status (“taking the test”). Where patients have access to adequate health systems, continued arguments against testing *per se* are simply irrational. The challenge isn’t whether or not to take the test, but to determine how to learn one’s antibody status and monitor immune health without risking employment, insurance, or legal status. Tens of thousands have successfully learned how, although the methods vary from state to state. Since our lives are at stake, it behooves us to find the way rather than to avoid the question.

**STEPTWO:** Immune health must be continually monitored. Today, this includes, as a minimum, quarterly testing for T-4 counts, p24 antigen, beta<sub>2</sub> microglobulin, sedimentation rate, and basic

# HIV as a Managable Chronic Illness (continued)

blood and liver panels. Where cost effective facilities are available, these may be supplemented with viral culturing. Collectively, these tests provide an accurate and essential picture of immune health. Since there is legitimate debate about the clinical significance of some of these markers, it is not sensible to judge one's condition on the basis of any one them. T4 counts, for example, are not a complete measure of immune health, nor is the p24 antigen an absolute measure of viral activity. However, when all the available measures are used together and evaluated by an experienced physician, we get the best possible information.

**STEP THREE:** The only sensible purpose of a monitoring program is to use its output to guide and adjust an active, flexible treatment protocol. Using monitoring, as some still do, to disqualify patients for treatment is simply bad medicine. Used properly, lab markers tell a physician when certain drugs might be appropriate or inappropriate. Many physicians, for example, feel that when a high T4 count is accompanied by low or negative p24 and beta<sub>2</sub> levels, a potent reverse transcriptase inhibitor such as AZT may not be needed or even ill-suited. Some are experimenting with a responsive approach which uses AZT to bring p24 and beta<sub>2</sub> levels down, after which the drug is either withdrawn or continued at a lower dosage. Simultaneously, a drug such as dextran sulfate, which appears to block cell-to-cell infection, and acyclovir, which fights possible co-factor DNA viruses, is continued. And, of course, the monitoring continues so that if p24 or beta<sub>2</sub> rises, AZT can be restarted.

One physician we know who is using this responsive approach has found that p24 levels which rise again after withdrawal from AZT can be sometimes be brought back under control in as little as three days. This concept of prescribing medication flexibly, rather than in a knee-jerk fashion, has obvious benefits. It appears to avoid or postpone the build-up of side effects from the strongest drugs, while retaining the opportunity to use them when truly needed.

Other concepts under development include the use of different anti-virals at different times, depending on the status of the patient's infection. Some anti-virals block the virus in the early steps of viral reproduction, some block cell-cell infection, while still others seem to block final assembly of new virus. As knowledge and flexibility grow, physicians come to realize that they need not simply put all patients on one drug, at one dosage, for all conditions at all times. As radical as this may sound to some AIDS clinicians, it is little more than a standard approach to therapy for a number

of other chronic illnesses. All a physician needs today to use such common sense approaches is the courage to make use of the full range of available interventions and not feel restricted by the tiny number of FDA-approved remedies or what their conservative peers will think.

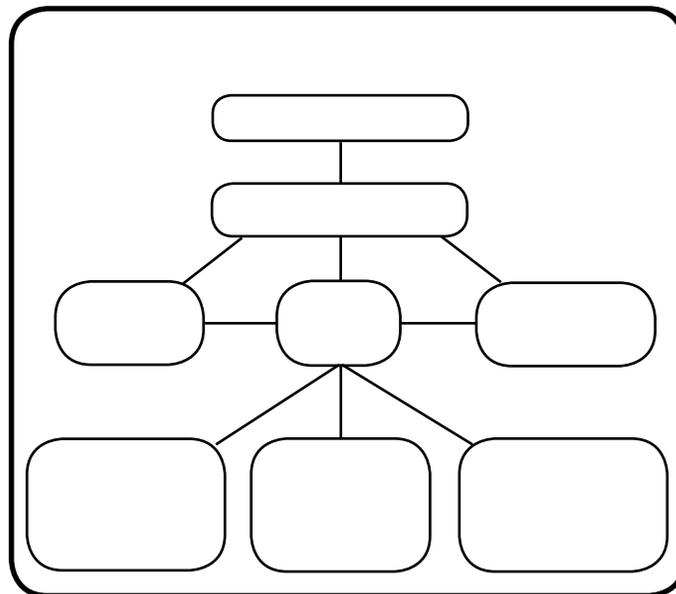
Eventually, almost every physician comes to practice AIDS medicine in this fashion, adjusting or withdrawing treatments based on the patient's condition. There are few left who urge AZT on a patient who develops anemia or bone marrow damage. Only a small minority continue the combination of AZT and transfusions for any length of time, even though this was initially standard practice when the drug first became available. Experience has already taught most physicians to routinely adjust treatment in response to lab markers, rather than waiting for a patient's body to demand the change.

As clinicians gain skill and confidence, we believe that HIV will come to be considered a managable chronic illness when early-stage intervention is employed. It is the belief in this notion that motivates the incredible investment being made in the giant AZT seropositives study. For those fortunate patients today whose physicians have the necessary conviction and are willing to work with available tools, this vision is already a reality. For healthy seropositives, it is already possible to reverse or control all laboratory blood markers which are predictive of HIV progression - without serious toxicity. Critics argue that this is only short-term evidence, that we must be concerned about what happens when patients use AZT for 10 to 15 years. This is twisted logic. Without such treatment, no one will last 10 - 15 years. For the moment, we need only be concerned with getting through the next few years, buying time until better treatments emerge.

Whatever a physician's views, however, effectiveness of response is greatly enhanced when the patient is diagnosed and begins treatment at the earliest possible stage of infection. To the stubborn "wait and see" medical conservatives who feel the practice of AIDS medicine has not yet reached this stage, to those who continue to refuse treatment until clinical illness is evident, we ask whether they can demonstrate that their current approach has

proven to offer greater hope and effectiveness. On this point, the record is abundantly clear.

(An earlier version of this article first appeared the D.A.I.R. Update)



Standard Fact Sheets Currently Available from PI	
<u>Anti-virals</u>	<i>Most recent version</i>
Acyclovir .....	8/88
AL721 .....	8/88
AZT .....	6/88
Dextan Sulfate .....	8/88
Ribavirin .....	7/88
<u>Immune Modulators</u>	
DNCB* .....	6/88
DTC/Imuthiol .....	6/88
Isoprinosine .....	7/88
Naltrexone .....	6/88
<u>Other</u>	
PCP Prophylaxis .....	10/88
The Syphylis Connection .....	4/88
*not a PI publication	

## Clinic Update

**AL721- Trials:** The only U.S. trial of an AL721-like product visibly underway is the New York CRI study of EL-10, a lipid substance commercially sold (and donated for this study) by Jarrow Formulas. Ethigen, the patent holder, bowed out of U.S. clinical research when it began selling their product over-the-counter as a food supplement. Most of the small NIH studies which began late last year seem to have quietly closed and few public reports have been made of their results.

Studies in Israeli are apparently continuing. Israeli research reported in Stockholm found no changes in T4 counts and mixed results on p24 antigen levels. Patients, however, anecdotally reported symptomatic improvement. Some improvements were also noted in immune response as measured on the skin. Some researchers are unconcerned about the lack of response against p24, since this is not necessarily to be expected from this type of product.

The study at St. Luke's Roosevelt in New York reported less than enthusiastic long-term findings in the August issue of *Antiviral Research*. The researchers reported that 4 of 8 patients progressed to AIDS and that 2 of the remaining 4 became symptomatic, while 2 others remained symptom free. AL721 appeared to have no change in p24 levels or T4 counts. Many supporters of AL721 feel this study was so flawed as to be irrelevant. They note that patients were taken off treatment for 3 months and that the supply of AL721 used was quite old. Nevertheless, the researchers contend that it didn't produce the hoped for results, and reportedly feel the study gave the product a fair chance.

A consistent pattern in AL721 research seems to be that T4 cell and p24 levels are unchanged. While the lack of p24 changes can be explained, the continued lack of a T4 cell response is troubling. Other effective anti-virals (and some immune modulators) seem to have some affect on T4 counts, even if only a temporary one. However, PI continues to receive anecdotal reports of symptomatic improvement. While this could be due to the placebo effect, it may also be that any AL721 antiviral activity is secondary to its action in restoring the function of immune and other cells, as the Weizman Institutes own research originally showed.

**User Notes:** In the U.S., the "lipid wars" between competing manufacturers continued. Greater attention is now being given to the way in which lipid products are tested. We feel this is a constructive change, since previous testing relied too heavily on reports from a single laboratory

and a single type of test. Because of input from additional labs and test methods, however, it has become almost impossible to compare one brand to the next or to compare previous test results to present ones. Thus, for the time being, the best

reported test results. For buyers who must know what the tests show, it has become very important to look beyond the numbers put out by the single laboratory previously considered the standard setter. There is apparently a great deal more to a good lipid product than simple PE numbers.

Some users now report that AL721-like products seem to reduce the side effects of AZT. Researchers, worry that this effect might be the result of the product interfering with AZT absorption. Both viewpoints are largely speculative, as no one has actually studied the matter.

**Ampligen - Trials:** This has been a confusing and disappointing period for Ampligen watchers. In August, the giant DuPont company withdrew its support of HEM Research, the small company which owns Ampligen. Although DuPont denied it, most believed that this was done as a response to discouraging interim findings in the on-going Ampligen studies.

Because Ampligen is an expensive drug, and because it is used intravenously, researchers have long believed that it needed to score a very big success in clinical studies to make it worthwhile. The implications of DuPont's action suggest that this hasn't happened. Project Inform has discussed the current studies with two investigators in the ACTG system, both of whom confirmed that they had so far seen little evidence of benefit. Even though the studies have not yet been unblinded, the researchers said they saw little improvement in any patients, let alone a clear pattern of half the group doing better. On the other hand, the PI hotline was contacted by a patient from a 3rd study center who told us that researchers reported positive results at a patient meeting following completion of the local study. When we called the investigator, however, he was unwilling to confirm or deny the patient's report. We were a bit confused by the patient's claims, since it is unlikely that the study data had yet been unblinded (this usually isn't done until all study centers have finished), but if the study hadn't been unblinded, it would be unusual for the researchers to make a positive report to patients. Our own informal contacts with patients in these studies suggests an inconclusive result, as we haven't heard any stunning success stories.

New *in vitro* results reported in Stockholm seemed to contradict previous lab studies. In this report, Ampligen was compared *in vitro* to AZT and dextran sulfate in lab cultures which were meant to more closely duplicate conditions in the human body. Under these circumstances, Ampligen showed no anti-viral effect (and dextran sulfate's was shown to be much more powerful than

### PI Perspective...

- Distributes information on a limited number of well-qualified treatment options;
- Advises on access to treatment;
- Encourages personal empowerment through active treatment strategies;
- Increases awareness of the obstacles which heed progress in research.

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- A national toll-free treatment hotline, the newsletter, outreach on early diagnosis and treatment strategies, and our efforts to enable sane research and treatment access policies.

policy might be for buyers to stick with a product they feel they have had good results with and not be overly concerned with statistics or the latest

AZT's). The previously claimed synergistic effect of combining the drug with AZT or dextran was also contradicted, with the new study suggesting that Ampligen would diminish the effectiveness of either drug.

Because of these findings, we fear that stock market game players will soon begin making a spectacle of Ampligen and HEM Research, spinning wild stories for and against the drug. Thus, it will probably become difficult to get a straight story on Ampligen in the near future. At the very least, however, it is becoming increasingly clear that the drug will not be the breakthrough so many had come to expect. The challenge, as with previous drugs in these circumstances, will be to keep eyes and minds open to smaller but still useful benefits should the research find them.

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**AZT - Trials:** New and ongoing studies of AZT are too numerous to list. Perhaps the most important of these is the enormous protocol 019, the AZT seropositives study. This study will follow up to 3200 people (1/3 on placebo, 2/3 on two different doses of AZT), for 3 years. The intent is to provide a definitive answer to questions about AZT's usefulness in early intervention. If it works as expected, the drug should slow progression to clinical AIDS. Unfortunately, the study is designed to make its case by comparing those on drug to some 1000 others on the placebo. The study is thus counting on a large percentage of the placebo patients to come down with AIDS. We have ethical concerns about this which are discussed elsewhere in this issue.

Studies presented in Stockholm indicated real benefit for KS patients treated with AZT. Since this is contrary to some popularly held notions, KS patients should take note. Other Stockholm data confirmed most previously described AZT findings and limitations. Most importantly, study after study confirmed that AZT side effects were less severe when the drug was used with healthier people. Such studies lay the groundwork for effective early intervention. While absolute proof is still some time off, every study to date that tested AZT in early intervention concluded positively, while none have reached negative conclusions.

Other interesting AZT studies underway seek to determine the importance of taking the infamous nighttime pill, full dose versus half dose, and the value of combining AZT with acyclovir.

**User notes:** AZT is increasingly used by healthy seropositives in hopes of slowing or stopping the progression to AIDS. While some may want to wait the years it will take to develop hard proof, many physicians and patients feel there is already sufficient data to warrant this use of the drug. Clearly, studies have proven that the drug slows progression to AIDS among ARC patients, so it seems highly unlikely that it would produce less of an effect, or a contrary effect, among healthy seropositives. The major dilemma would-be users face is the risk of AZT side effects. Even these, however, are already well established to be less severe among healthier patients. Most healthy seropositives who use AZT do so at something less than the standard 1200 mg. per day dose. Half dose, 600 mg., is common, and some are even using it at 300 mg. and reporting positive results.

Contrary to what some insurance companies and doctors tell patients, there are no restrictions to the prescription of AZT. A doctor may prescribe it for anyone he or she feels to be in need. Insurance, however, often balks at paying for patients who

don't meet the original guidelines under which FDA approved the drug (under 200 T-cells, or post PCP). Patients and physicians who fight back against reluctant insurers, however, sometimes succeed in getting reimbursement outside those guidelines.

**Dextran sulfate - Trials:** NIH sponsored Phase II studies of dextran sulfate should be currently underway. These studies will seek to determine the effectiveness of the drug at doses of either 2700 mg. or 5400 mg. daily. If the higher dose is well-tolerated, researchers plan to further increase it. Much of the concern over dosage stems from the continuing concerns over whether dextran sulfate is absorbed into the blood. The Japanese sponsor (Ueno) of the initial dextran study has failed to produce a test for determining blood levels. It is disturbing to us that Phase II studies are beginning before this key question is answered. With all the resources of the NIH and the FDA available, we can't help but ask what the problem is. If dextran is not well-absorbed in oral use, researchers ought to know as quickly as possible so that other approaches, such as IV infusion, can be prepared. The *in vitro* data on dextran sulfate is so impressive that every effort must be quickly explored to find a way to get it into the body as efficiently as possible. Fortunately, we are aware of a private, non-NIH effort which is testing an assay to measure dextran sulfate blood levels. Those involved are confident that the question of absorption will be answered definitively and very soon.

Rumors continue to spread across the country regarding the outlook for dextran. We keep hearing from researchers, doctors, and patients who supposedly heard that the Abrams/San Francisco General study now showed little promise. Such stories are bizarre, as the data from that study hasn't changed, and no new studies have anything to report. From the start, reports from SFG have been a strange mix of positive and negative signals. Some believe this represents an effort to discourage widespread use of the drug until clinical studies are completed. For the record, this is what Dr. Abrams at San Francisco General has said about his dextran study:

- The drug was generally well tolerated at all dosage levels.
- The most common side effect was an "urge to purge" which many experienced as diarrhea; other side effects included some central nervous system disturbances (insomnia, twitches, etc.), minor liver problems, and a few patients had white count problems; most problems occurred in patients with full AIDS.

- Evidence that the drug is properly absorbed into the blood has not been established; however, it is equally true that there is no clear evidence that it isn't absorbed.
- Dr. Abrams acknowledged that there was a trend toward increasing T-4 cell counts at doses of 2700 mg. and beyond; the trend appeared dose-dependent.
- The study found no evidence of p24 antigen reduction; Abrams acknowledged, however, that very few patients were p24 positive when entering the study; thus, the study really says nothing about dextran and p24. Abrams acknowledges that p24 testing may be the wrong way to evaluate dextran sulfate.
- At the health conference in Boston, Abrams acknowledged that some blood samples from the study were sent to NIH in Washington to measure cell-to-cell infection rates; preliminary results suggested that the drug reduced cell-to-cell infection (this has not been stated publicly before).

There is no other data on dextran sulfate from any formal clinical studies, and Dr. Abrams has not submitted any new data beyond that presented already. Thus, any recent stories suggesting new news or discouraging results are fiction. Nothing new will be known until the present studies are completed.

*User Notes:* Clinics monitoring patients on dextran sulfate continue to report promising results. The Positive Action Health Care Clinic in San Francisco, however, recently reported bloody diarrhea in 6 patients who have been using dextran for long periods at doses of 3000 mg. or more daily. Symptoms cleared upon withdrawal from the drug, and reuse at the lower doses did not cause the problem to recur. Whether this is due to dextran sulfate or to the total combination of drugs these patients were on is unclear. The Abrams study did not report bloody diarrhea, even at 5400 mg. per day.

Availability of dextran sulfate has been expanded as a result of the new formal FDA policy permitting its importation (see related article on New FDA Import Policy). We are increasingly concerned, however, by the appearance of uncertified or unknown sources of dextran being aggressively promoted individually and to buyer's clubs. We currently recommend only dextran sulfate from name brand Japanese sources and are testing an independent product provided by a reliable source

in Tulsa. We discourage purchase of any other products and are dismayed that some sources of dextran have claimed our endorsement for products we clearly do not support. Many such products are coming from a single, highly commercial source and are sold under ever-changing names.

**Imreg - Trials:** Imreg has unfortunately entered a regulatory and media twilight zone, possibly pushed there either by unfair press coverage or by overly aggressively stock market interests. While every direct source we have contacted continues to suggest that the product showed useful results in the recent round of clinical studies, stock market speculation has caused everyone from congressional committees to the investigators themselves to take a cautious look at the data. The infamous "Dingell Commission" (a congressional committee noted for its witch hunts against pharmaceutical manufacturers) is



said to be investigating reports of irregularities in Imreg data reporting. About the only known fact that anyone can refer to is that one of the study researchers removed his name from the presentation of the study in Stockholm, leading some to suspect a problem. Some stockbrokers and media people quickly blew this story all out of proportion. Our own conversations with the particular researcher suggested that this is mostly a tempest in a teapot that could easily have been avoided. Yet, if the Dingell Commission follows its previous pattern, only those sources which suspect something wrong at Imreg will be invited to testify. Imreg spokespeople, or even the researchers themselves, will not be welcome.

Media reports that FDA is investigating Imreg are distorted. The investigation was a routine, pre-marketing site inspection and had nothing to do with the charges flying about in the press. In

fact, there is as yet no new information available on the Imreg studies. The data has not yet been handed over to FDA, which has angered activists and fueled speculation of problems. The truth is that small companies like Imreg simply don't have the manpower to process data as quickly as a Burroughs-Wellcome. No one should be surprised that it could take them many months to report on a study.

The Imreg story presents a sorry example of how stock market interests can hurt the development of AIDS drugs. Speculation on Imreg has been furious. "Short-sellers," who make their money betting that a stock will go down (and doing all they can to make that happen), are undoubtedly involved in the stories appearing in the press. One nameless source called PI to claim he was an "insider" with data proving irregularities in Imreg data. He promised to call again with proof. After smearing the company and the study, he never called again. We wonder if he also called the Dingell Commission.

On the other side, one broker who was pitching the stock urged Project Inform to convene a meeting of AIDS activists in Madison Square Garden to pressure FDA for early approval of the drug. He also told of impersonating journalists in his efforts to get researchers to reveal study information. When PI refused to become an enthusiastic, no-questions-asked booster of Imreg, he planted false information in the gay press, accusing a PI director of being in cahoots with the "short-sellers." Such nonsense, from either side of the market interests, actually slows the approval of a drug by raising suspicions where they might not otherwise have existed.

Imreg, the company and the drug, are both ill-served by such behavior, to say nothing of patients who still do not have access to what may be a very important drug. At worst, the company can only be faulted for a strategic mistake in the early release of its primary findings without release of the supporting data. And even this might be argued to be a legitimate response to the needs of patients in the study.

Before we can take a final position for or against the value of Imreg, we need more data. Accepting the impressive-sounding claims regarding delayed progression to AIDS requires knowing the balance of the groups in terms of starting T-cell counts and other lab measures. However, we'd be inclined to support the company's findings unless there is evidence of many dramatically sicker people in the placebo group (this issue of imbalanced groups was also greatly exaggerated in FDA and media coverage of last year's ribavirin

studies). We'd also like to know about the long-term follow-up of the patients, since so much time has now passed since the study was completed. Such data might help clear up any doubts raised by relatively small size of the study groups.

Meanwhile, the Imreg situation spotlights a few other things which need to be fixed. For one, it's time someone investigated the Dingell Commission itself to learn why only one side of a story is sought in its hearings, or who the Commission gets its information from in the first place. Another point to consider is what can be done to help small companies like Imreg more quickly assess the outcome of their studies. Although the delay may not be the company's fault, it nonetheless is detrimental to patient interests. There seems to be plenty of money to investigate the slightest suspicions about such companies, but not a nickel to help them bring a life-saving drug through the regulatory morass.

A bottom line? If the Imreg data is at least arguably sound, then the product should be released under a Treatment IND ASAP. When it is, someone should be held responsible for any delays caused by regulatory, congressional, media, or stock market personnel.

*(Correction: in Issue 4, PI Perspective incorrectly described Imreg as a synthetic product. Imreg is natural product derived from human blood. We stand by our contention, however, that Imreg bears at least some similarity to Transfer Factor, as both products are derived from similar roots and, up to a point, by similar methods)*

## FDA Import Policy: What it Means

At a Gay and Lesbian Health Conference in Boston last July, Commissioner Young of the FDA announced a new policy permitting improved access to drugs which are available from overseas sources. Young tossed the policy out to a sometimes hostile audience. To a casual observer, it might have appeared as sincere attempt by the master to calm his restless minions. Although Young tried to make it look like the policy was an expression of his personal compassion, it was in fact the result of some six months of dialogue between FDA's Office of Regulatory Affairs and a small team of AIDS activists, including Jay Lippner and David Barr (Lambda Legal Defense) of New York, and Curtis Ponzi (BALIF and THAF) and Martin Delaney (Project Inform) of San Francisco.

The policy arose out of efforts to solve problems people were having with dextran sulfate importation. Although most packages from Tokyo successfully passed through the mails, several were detained by FDA. Each time a detention occurred, the activist team interceded to get the package released to the buyer. Since this was a nuisance for both sides, Young eventually ordered an internal task force to draft a consistent policy covering all foreign-sourced drugs which would make case-by-case negotiations unnecessary. Both the task force and the activists suggested various parts of the policy. The final procedures were worked out during negotiation over release of a package sent to a Florida man. The buyer graciously offered to take his cues from the activists, who used his situation as a test case. The policy was first stated in a letter sent to Project Inform in June.

The activists were somewhat surprised when, after the letter was received, FDA gave notice that no formal statement of the policy would be made until Young's appearance at the health conference at the end of July. Young wanted to be seen as the source of the policy.

### What the Policy Provides

The policy is only for drugs used with life-threatening illnesses (as defined in the Treatment IND regulations). It says that individuals may purchase products which are readily available overseas and have them mailed to them at home in the U.S. It requires that the products are :

- known to be safe and for personal use under the care of a physician
- not intended for commercial distribution

- to be shipped in an amount not to exceed a three-month supply
- to be chosen at the patient's initiation, not in response to any commercial sales effort

When these conditions are met and the product is sent through the international mail, most packages will reach the buyer unheeded. However, FDA has pointed out that it will periodically "detain" and inspect some packages to monitor compliance. When a package is detained, it will almost always be released after the patient certifies compliance (discussed in detail later in this article).

All of this sounds simple enough, yet it has created a wave of confusion, misinformation, and mixed signals.

One common item of misinformation is that the policy is nothing new at all, since FDA has always allowed importation of personal use quantities of a drug. The policy, however, includes several important new elements. First, the old policy specifically forbade mail importation of many types of drugs, including dextran sulfate. Secondly, requirements for getting a product released after a detention occurs have been changed in direct response to activist concerns. Finally, the old system merely ignored such mail importations and the actual practices employed were pretty much up to the local office. The new policy spells out uniform, formal procedures for permitting the mail imports.

Another area of misinformation is that the policy has opened the borders to unsafe and unproven drugs. That it is absolutely not the case. FDA has stated that it will block the importation of a product under any of the following conditions:

- when there is any question about its safety
- when there is evidence of commercialization (efforts to solicit the business of U.S. patients)
- when evidence accumulates that the product is ineffective

FDA has come under heavy attack over the policy from many quarters. A conservative physician, a member of our own community, ranted that the policy would result in "genocide". Consumer protectionists in Congress saw it as opening the borders to unscrupulous pharmaceutical companies and snake oil salesmen. Right-wing homophobes and other latent homosexuals decried it as a cave-in to AIDS patients. The Wall Street Journal gleefully

characterized it as a “core meltdown” of the drug approval process. Even Congressional committees have gotten involved, demanding documentation of how FDA reached this decision and demanding proof that it has not abandoned its role as lord protector of our health. One FDA spokesman told us that, since people on all sides were complaining, the policy must have landed fairly and squarely in the middle.

To demonstrate that it means business, FDA blocked the importation of Canadian dextran sulfate from the Polydex Corporation only one week after announcement of the new policy. Polydex, whose product and business practices had already raised concerns among U.S. buyers, went into high gear after the policy was announced, pitching both their product and the company’s newly enlivened stock shares. FDA issued an Import Alert, blocking the Polydex product at the border. Polydex even bragged that they would soon begin manufacturing and selling the product directly in the U.S., going so far as to say that FDA was encouraging them to do. Not so, FDA said, repeating its threat to immediately shut down any U.S. production of dextran sulfate on the grounds that it is clearly an unapproved drug - not a food substance.

### **Making the Policy Work**

To be sure that dextran sulfate ordered is brought into the country, the following procedures should always be followed:

- Don’t order or send more than a single person’s 3-month supply in one package; this means a maximum of 2000 pills. Larger shipments will be viewed as commercial and will be seized.
- Make sure each package is shipped directly to the individual for whom it is intended; FDA will allow no one, even buyers clubs, to act as distributors in the U.S. They may, however, act to collect and process orders.
- Each package should include a signed letter from the purchaser, stating the shipment is for personal use. To be safe, the letter should also include the name of the person’s physician who is supervising the use of the drug (the physician will not be contacted).

^ When possible, the package should include an English translation of the Japanese instructions for use. Although these instructions have nothing to do with our intended use, it makes the bureaucrats feel better.

While FDA has acknowledged the right of buyer’s clubs to facilitate ordering, it is strongly opposed to the creation of third party companies - either

here or in Japan - whose sole purpose is the sale of dextran sulfate. This is a sticky point, as there must be some mechanism by which people can make purchases. FDA needs to believe that the purchasing takes place solely between the U.S. buyer and existing Japanese suppliers. Well-intentioned groups who have asked about creating new mechanisms for importing dextran have been repeatedly turned down when they asked for FDA permission. Just how this differs from what the buyer’s clubs do is unclear.

FDA will look unfavorably upon anyone, including buyer’s clubs, who see this as an opportunity to make big profits, no matter what those profits are used for. In recent days, FDA officials have been increasingly concerned about the buyer’s clubs becoming big businesses. A congressional committee has already demanded that FDA explain why it is not regulating the buyer’s clubs as retail health food stores.

### **What to Do in Case of Detention**

FDA will occasionally detain packages to monitor compliance with the policy. When this occurs, the buyer will receive a formal “detention notice.” This is not a reason to panic; it doesn’t mean the buyer is accused of breaking the law, nor does it mean the buyer won’t get the package. To arrange for release, the buyer may be asked to certify in writing that the package is for personal use and supply the name of his or her physician. If the package already contains such a letter, detention is thus very unlikely. Buyers may also be asked to identify their intended use of the substance, which in this case is treatment of AIDS or HIV infection. We encourage buyers to politely refuse to comply with this request. We see no reason anyone should be asked to self-identify themselves as HIV carriers to a branch of the federal government. The packages will be released without doing so.

### **In Sum**

The new mail import policy is not a major breakthrough, but it does represent a substantial change. It requires awkward positioning by FDA, balancing the needs and objections of many groups. The agency should be commended for its willingness to meet our needs, in spite of the harsh criticism it has received for doing so. We should not, however, believe that this policy will solve problems of access to experimental therapies. The best potential treatments, now and in the future, are very likely to come from the U.S. Patients still have no access to these outside of clinical trials. We must continue the pressure to change the restrictive and often irrational regulatory policies which allow people to die while partially proven therapies set idle on the shelf.

## **Project Inform: The Basic Message**

- Learn your options and line up your support.
- Get tested, *anonymously*.
- If positive, consider anti-viral treatment.
- Monitor T4 cells quarterly, charting the trend.
- If the trend of T4 cells is downward or falls consistently below 500, consider both anti-viral and immune boosting therapy.
- If the trend of T4 cells falls below 200, consider prophylactic (preventive) treatment against pneumocystis (aerosol, is possible).

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## FDA Proposes to Give Itself a Placebo

Acting on direct orders from the Bush presidential campaign, FDA Commissioner Young has drawn up a proposal to overhaul regulations for the licensing of drugs. Although the proposed changes look reasonable and may help in the long run, the lessons learned from last year's Treatment IND shell game suggest that the proposal may have more to do with politics than saving lives. Although the new policy does make more sense than the current system, no one should be fooled into thinking it will solve the problems of access to drugs for HIV patients.

In short, the new proposal:

- concerns only drugs which are intended to treat life-threatening illnesses, such as AIDS (its application for ARC and seropositive people is unclear)
- calls for approving drugs for marketing at the end of Phase II studies when sufficient proof exists of their effectiveness
- requires drug companies to conduct Phase III studies when evidence from Phase II isn't strong or clear enough
- calls for creation of an optional Phase IV post marketing surveillance period, in which drug companies may (but are not required to) conduct long-term studies of safety and effectiveness
- describes a series of costly and useful initiatives FDA might take, if it is funded to do so, to better guide the development of this type of drug

The model for the new program is once again FDA's handling of the development and approval of AZT, which the agency sees as the high-water mark of drug regulation. Yet, in fact, FDA already has the authority to do all of the things proposed in the new initiative, and has already done them in the case of AZT. Thus, one might ask: "What's the big deal? Why are new regulations being proposed?"

The answer is both obvious and not obvious. On the simplest level, the timing of the proposal tells

a great deal. George Bush wants to be seen as taking decisive action, slicing through the red tape. Conservatives will like this because it sounds like deregulation (but it is not). He hopes republicans and so-called "Reagan democrats" who are concerned with AIDS (?) will like it enough to vote for him. At the very least, the campaign hopes this will help blur the distinction on AIDS issues between the two candidates.

On less obvious levels, several agendas are in play. For Young, it is another step taken to try to save his job. If he can keep angry AIDS activists out of Bush's hair and off the campaign trail, he has a chance to win his private campaign to retain his job in a Bush administration. Young also likes the proposal because it retains, even solidifies, FDA's dictatorial control over approvals. The hurdle for approval of an AIDS drug now becomes "sufficient" evidence in a "well designed" Phase II trial. Internal FDA document suggests that they will look for dramatic evidence of benefit in Phase II studies before approving a drug for marketing. How these terms are defined is up to him. For the record, however, dramatic evidence of effectiveness is extremely rare. Finally, Young likes it because it provides the appearance of change without requiring him to make any changes in the efficacy standards, whatever they are. As in the Treatment IND fiasco, he gets to look progressive while being required to deliver nothing. Of course, no one will know that for sure until long after the election. Like a true placebo, it is disguised to look like and taste like the real thing, when in fact it may be just another worthless sugar pill.

Others who will like it include the major pharmaceutical houses. This one change might offer them the chance to save some money, but not necessarily make that option available to smaller competitors. Each company will get one big shot at an early approval with each drug. If they miss the brass ring in Phase II, Phase III requirements must be met as before. Just which size company is likely to show the skill, influence, and savvy needed to pull off a major win in a Phase II study? Pharmaceutical houses of all sizes will like it because Young's expensive Phase IV surveillance period is only optional. In a memo to the Secretary of Health and Human Services, Young says that he expects the companies will voluntarily comply, good citizens that they are. After all, it will only cost them millions of dollars.

Another group who will like the proposal are the physicians and researchers who defend FDA and the government handling of the AIDS crisis (yes, there are such people). They will stand and say "See - look at the compassionate, intelligent responses being made. Aren't you ashamed of all

those nasty things you've said about Ellen Cooper and Frank Young?" Since such people haven't the faintest idea of what really goes on in the bureaucracy, they will readily believe that the proposals represent substantial change. They even believe that the Treatment IND rules are speeding access to AIDS drugs.

While several groups might find something to cheer about in the new proposal, AIDS/HIV patients should realize it will not result in a sudden flood of new treatment options. There are three problems which presently limit access to experimental treatments, none of which are addressed in the proposal.

The first problem is economic - many people simply don't have access to approved drugs, let alone experimental remedies. The access provided by the \$30 million AZT funding is already drying up, with little hope of renewal. Methods must be found to pay for treatment, for all people. Instead, an ever widening gap is developing between the treatment options available to those with money and those without.

The second problem limiting access to treatment is the requirement for proof of effectiveness before a drug is released to anyone. Project Inform has discussed this issue repeatedly in previous issues of PI Perspective. Until the level of proof required is changed (or even eliminated, as the Wall Street Journal and others recommend), FDA will continue to stand between patients and their treatment of choice. Nothing in the new proposal addresses this. Likewise, nothing creates a court of appeal in which researchers or manufacturers can contest FDA's imperial and often unfathomable decision-making process.

The third problem of access is caused by product liability laws. Presently, even when FDA is willing to release a drug under the Treatment IND program, manufacturers, at the advice of their lawyers, refuse to play ball. Companies fear that supplying drugs prior to full proof of safety and effectiveness will lead to product liability lawsuits from disgruntled patients. Presently, there is no legally reliable way for patients to release physicians or pharmaceutical companies from the risk of such lawsuits, even if the patient wants to. We believe that a majority of AIDS/HIV patients are willing to assume a higher degree of personal risk in return for having access to experimental therapy. In fact, they are already doing so with a wide range of unapproved substances. There must be a way for them to sign away the right to sue, to accept the risk personally. This could allow them

*continued on page 13*

to choose experimental treatments under a doctrine of informed consent. Unless legislation is created to ease these liability concerns, physicians and drug companies will continue to resist facilitating access to experimental treatment, no matter what FDA says. The Presidential AIDS Commission, among others, has recommended such legislation.

Yet, with all the false hopes inherent in these proposals, we still conclude that they represent a more rational approach than the status quo. We support their approval, since they establish a sound basis for decision-making for future commissioners. Right now, a hurried approval such as that given to AZT, is accomplished solely at the whim and initiative of the commissioner. By defining this process in regulatory language, it sets a standard for the future. We must be wary of the possibility of future commissioners who might be even less sympathetic to our concerns.

Although the new proposal is flawed and incomplete in many respects, it makes little sense to withhold our support in anticipation of a more perfect solution later. Further regulatory reform could build upon what's good in this proposal while addressing its many weaknesses.

In sum, there are three critical mistakes we must avoid in responding to this initiative. (1) No one should expect that it will solve the problem of access to treatment for HIV patients. We must continue, even redouble our efforts to solve this problem.

(2) No one need applaud either George Bush or

Frank Young for their election year "gift." If their intentions truly are not political, as they insist, then we owe them no political acclaim and must not insult them by offering any.

(3) Finally, we shouldn't reject these proposals simply because of who made them or when they were put forth. They should be judged solely on their merits as regulatory practice. On that score, we feel they are better than the previous policies - though falling far short of a solution to our problems. But they are not irrelevant and we must take each step forward whenever we have the opportunity.

a new San Francisco organization, KAPAU, formed to negotiate improved treatment for AIDS/ARC/HIV patients at the local branch of one of the nation's largest HMO's, Kaiser Hospital. Kaiser has the second largest AIDS case load in San Francisco. Kaiser patients raised concerns at PI meetings about the varying quality of health care provided. KAPAU is calling for the creation an outpatient HIV clinic as well as clearly defined standards of care for patients. San Francisco city officials have offered to take a role in the negotiations. We expect this action to serve as a model for establishing fair standards of care for all health care providers and insurers, standards which support the option of early intervention and comprehensive diagnostic monitoring. Because of a growing level of discontent, we expect that patients of the VA system may soon follow in the footsteps of the KAPAU pioneers.

Project Inform Town Meetings, held for the last 3 years in San Francisco, are now being set up in other major cities. The meetings focus on helping communities and individuals embark on strategies of early diagnosis and treatment intervention in HIV. Initial meetings in cities are conducted by PI co-Founders Joe Brewer or Martin Delaney. A follow-up program will supply materials and training to responsible groups who wish to implement the educational meetings on a regular basis. Call PI early to get in the schedule, as we can only handle two cities, maximum, per month.

Organizational Update

PACIFIC TELESIS CORPORATION has made a special grant to Project Inform to fund the translation of our treatment materials into Spanish. PI is deeply grateful for this opportunity to extend our service to the Hispanic community. Local Hispanic AIDS organizations will work closely with us to get the job done. Project Inform has assisted in the start-up of

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