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PI Perspective

Project Inform
San Francisco, California

AIDS Research & Politics in 1994 - Are You Better Off Today... ?

Sixteen months into the new Administration in Washington, it is clear that the change of political stewardship has not made a major difference for people living with AIDS. High hopes that the sympathetic tone of the new Administration would translate into better policy, faster research, or an improved prevention effort have come crashing back to reality. Whether this is due to any fault of the Administration, or just a consequence of unrealistic expectations, is open for debate. At the very least, there is little evidence that this Administration has made AIDS any more of a national priority than the previous one. And, depending on how it addresses five key issues facing AIDS research today, it could eventually earn the reputation of doing more harm than good.

The nightly news, and the President's attention, is dominated by crime, the economy, foreign and military affairs and general health care concerns. While the Administration is struggling to convince the public that a few more million dollars for CARE and research programs is a big step forward, we learn that $750 million in new money has been allocated to support US companies manufacturing lightweight color computer screens, that billion-dollar military spy satellites are lining up on the launch pad, and that the 1995 budget for nuclear weapons development exceeds $24 billion. There has been no Bill Clinton "Town Meeting on AIDS." The President has appeared twice on MTV, but has yet to take questions at an AIDS service organization. Leaders of the automotive industry have been escorted into the Oval Office to collaborate with the government on making more fuel efficient cars, and Hollywood stars have been given phone lines and office space in the White House, but AIDS researchers have had no such access and no such invitation. At best, AIDS has provided an occasional photo-opportunity for a few people to pose with the President.

After collecting big money in the campaign on the promise of important things to come in AIDS research, the Administration has since spent an inordinate amount of time explaining why Clinton really didn't mean it when he called for a "Manhattan Project" on AIDS.

We do have a new "White House" AIDS policy coordinator, but her first several months in office suggest that she has been given little if any authority to take action on anything, let alone carry the authority of the White House in her job. Similarly, we have a newly appointed Assistant Secretary of Health and Human Services (who controls both the NIH and the FDA), a new head of the National Institutes of Health, and a new director of the Office of AIDS Research - all fine men (yes, once again they are all men, white ones at that). New committees, task forces and advisory bodies are being formed, taking over where the last bunch of committees, task forces and advisory bodies left off. One bright spot is a new enthusiasm for strategic planning - largely a response to activist pressure and apparently a new idea in medical research - but few people engaged in the process have ever seen, let alone studied or written a strategic plan before. Some reports from the first budget and planning meeting on AIDS research suggest that, because there is still no real process for setting priorities, the effort was little more than a review of last year's expenditures.

AIDS research is reeling and in serious need of detoxification. Because of change in personnel, combined with growing public pressures and uncertainties, five key issues are up for grabs. Each represents both an opportunity for positive change as well as a risk of making major missteps. It is a situation ripe for a five-step program.

In this issue

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Problem 1: *The overall AIDS research effort is now being led by people who have neither AIDS experience nor expertise in management skills required or called for in the Office of AIDS Research reorganization.*
Solution Step 1: The Office of AIDS Research should seek the advice of proven experts in strategic planning, project management, efficiency and quality assurance. As new people have been given responsibilities for managing the AIDS research effort, they have been selected on the basis of scientific resumes, not their knowledge of AIDS or skills in major enterprise management. If they get the proper professional support and guidance, they might be effective and bring fresh thinking to the effort - hopefully with a minimum of time lost while "getting up to speed." If they assume they know how to write and pursue a strategic plan, establish balanced, long-range priorities, assure process efficiency and quality and effectively oversee the management of research, we are headed for trouble. These skills simply are not part of a scientist's background and are all too often looked down upon as "process skills" by "real" scientists. On the contrary, the ability to plan and manage effectively in the thicket of AIDS research is fundamental to success.

Problem 2: *Key players at the NIH seem convinced that a return to the laboratory to pursue "basic research" rather than clinical questions is needed. If they are wrong, research and spending priorities could be misdirected for years to come. Currently, both clinical research programs and drug discovery programs are being targeted for possible funding reductions.*
Solution Step 2: Make no changes in the balance of priorities until scientists, policymakers and advocates agree upon a clear set of terms and definitions and an in-depth, independent and honest assessment of the real needs of AIDS research takes place. No field is more rife with buzzwords and fashion-frenzy than AIDS research. One of the current fashions rushing through the NIH is a call for a return to "basic research." Wise scientists, bureaucrats and activists nod gravely in agreement. But each person in seeming agreement actually has conflicting definitions of "basic research" - definitions remarkably consistent with each one's own field of interest:

- To the new NIH director and other cell biologists, "basic research" means more on fundamental laboratory exploration not tied to any specific disease and not geared to development of any particular therapy. They argue that this is the font of real innovation. Perhaps so, though critics argue this perspective may be motivated more by self interest regarding funding streams than by science.
- When virologists applaud "basic research" they envision investigation into the molecular biology of HIV (the study of the virus itself). This, they feel, is where we will learn to cripple the disease. Possibly, but aren't these the same people who have told us for years that we have learned more about the biology of HIV than any other organism in history? How much more do we need to know and where will it get us?
- Other scientists argue that "basic research" is the study of the immune-pathogenesis of HIV, how the virus interacts with and breaks down the immune system. Indeed, this is very important, but it's possible that the answers will be found most quickly through clinical studies involving people, rather than through basic laboratory explorations. The opportunity for such clinical studies will be lost if the pendulum swings unduly in favor of more laboratory, and less clinical, work. Another view is that giving excessive attention to the study of pathogenesis might itself be unproductive, since history records that most diseases which have been conquered were beaten long before scientists fully understood their workings.
- When some of the community voices call for "basic science," their description sounds suspiciously like a demand for more rapid preclinical drug development. Important indeed, but definitely not what the others are talking about when they use the term.

So far, the call for "basic research" sounds more like confusion than consensus. The outcome of the debate will determine the priorities, spending, and thus the programs, of the next several years of research. No substantive change of direction should be taken, especially in an environment of limited resources, without first conducting a critical, independent and impartial assessment of the state of knowledge and the true needs of AIDS research. If the balance shifts too far in favor of "cell biology" benchwork or HIV molecular virology, we will see less emphasis on developing and testing new therapies for the next 5 to 10 years, and consequently fewer new emerging options for people struggling against AIDS. This could spell disaster for the generation of people who will face the greatest need for therapy in the next five years. People with AIDS will be best served by a program which seeks to maintain a reasonable balance between bench science, pathogenesis and clinical research.

Problem 3: *Some voices in and outside of government believe that no therapeutic approach currently in development is likely to be a cure for AIDS. Thus, they argue for a de-emphasis of drug development in favor of developing completely new solutions.*
Solution Step 3: Before de-emphasizing therapy development, let's try a concentrated effort to speed the development of the most promising drugs already in the labs. Recent data from protease inhibitor studies are so intriguing that some scientists believe what's needed is an all-out engineering effort to maximize the benefits of this new class of drugs, along with an accelerated effort to test them in combinations. The striking, if time-limited, response seen to one of the protease inhibitors may provide the first hint that antiviral research is indeed on the right track, a notion many had begun to lose faith in. If so, then the greatest benefits in the near term are likely to come from developing this model, rather than looking for completely new approaches.

Similarly, many avenues of therapy development are floundering not for lack of promise, but for lack of sponsorship by government or industry. These include products which target cellular, rather than viral mechanisms critical to viral replica-

tion, integrase inhibitors, LTR inhibitors and other approaches targeting the virus in novel ways. Moreover, there is a backlog of interesting products in the field of immune-based therapies which receive little or no attention or funding. There is an unmet need for new forms of collaboration between government, industry and academia in developing new avenues of therapy - and little evidence that the Administration is moving to meet it.

Problem 4: *AIDS research is increasingly characterized by rapid swings in belief about clinical trial design, diagnostic markers and drug development strategies. The first time a belief or concept fails to produce significant results, it falls from fashion, leaving patients, physicians and drug developers in a state of confusion. Currently, that state of confusion is threatening the hard-won right of people to early access to promising new therapies.*

Solution Step 4: Understand that uncertainty may remain a hallmark of AIDS for many years to come. Adhere to logical, common-sense approaches to research, at least until they are proven conclusively wrong - stop changing direction with each shift in the scientific breeze. When small changes in CD4+ counts in a single study failed to predict the benefit of therapy, a lemming-like herd rushed for the cliffs declaring that CD4+ counts were meaningless, and that drugs shouldn't be approved merely on the basis that they improve CD4+ counts and quality of life. In another startling turnaround, mechanisms like parallel track and accelerated approval are under attack by voices urging restricted access to new therapies and demanding long, survival-based studies before further therapies are licensed for sale. While anyone is welcome to choose such beliefs to guide his or her own therapy, many people with AIDS want the opportunity to access promising experimental therapies while they're still around to try them. If scientists or regulators continue to place emphasis on quantifying small differences between today's at-best modestly useful drugs, no one will benefit and the costs will drive industry away from AIDS drug development. Instead, such drugs should simply be available for those who choose to use them, while the profits gathered from their sale must be invested in developing a better generation of therapies and new diagnostic markers.

Long-term studies which seek to prove survival benefits of mediocre drugs have proven all but impossible in the rapidly-changing field of AIDS research. People refuse to stay in such studies for more than a year or two. Care providers are unwilling to encourage patients to remain on a therapy which is failing just to provide data for these studies. Ethics demands that people be permitted to switch therapies when the existing regimen fails. Long-term studies measuring survival will only become practiced when we have a generation of drugs capable of producing long-term beneficial activity without major side effects. We need no further studies to prove that we are not yet at this point. Over time, the restructuring of the Office of AIDS research will almost certainly lead to greater focus and less duplication of effort - but that change will not be noticed quickly. While the train moves ever so slowly forward, we must make sure that people with AIDS continue to have the earliest reasonable access to therapies which might help them. The fundamental right of freedom of choice, won in hard battles fought in the late 1980's, must not be lost in a debate over the conflicting results of studies conducted on today's mediocre generation of drugs. No bureaucrat, whether inside or outside the community of people with AIDS, should be permitted to threaten this right.

Problem 5: *AIDS activism is dead, dying or increasingly entwined within the bureaucracy. The healthy spirit of criticism which produced so much progress in the past has grown quiet as individual activists have passed away, become care-givers or burned out. There is a sense of complacency driven at least in part by the mistaken assumption that our interests are being taken care by the new Administration.*

Solution Step 5: Renew the aggressive spirit of AIDS activism which was so productive in the past. AIDS research is at a crossroads. A year ago, people with AIDS hoped that the start of a new Administration would lead to newly invigorated, better-managed and more aggressive programs of AIDS research. That moment of opportunity has come and gone with only modest changes to show for it. There will be no new major programs or initiatives for at least another year. Regardless of its more supportive rhetoric, the Clinton Administration should feel no less pressure and demand from the streets than the Bush and Reagan Administrations. More, not fewer people are dying of AIDS today than at any time in history. Will Clinton be content to be remembered as the President on whose watch we saw the greatest number of deaths from AIDS? Kind words are not enough, nor are modest improvements in funding. To paraphrase a line from candidate Clinton, we will never see a cure for AIDS until people find the will and the courage to implement change. Change, in this case, begins with recognizing that the current effort is still not good enough.

Hope for Preventing Mother-to-Child Transmission

by Virg Parks

The AIDS Clinical Trials Group (ACTG) recently announced preliminary data from ACTG 076, a Phase III randomized, placebo-controlled trial to evaluate the effectiveness, safety and tolerance of AZT in pregnant women and their infants. Data reveal an impressive reduction in the rate of transmission of virus from mother to child. The results of ACTG 076 may have significant impact on reducing the incidence of pediatric AIDS. While there are a number of questions still to be answered, preliminary data from this study represent a major victory in the battle against AIDS. Additional questions will be answered by further analysis of this and other studies in progress. Appropriate responses to public health questions concerning testing or treatment of pregnant women will become clearer as more detailed and thoughtful analysis takes place with regard to these studies.

ACTG 076 began in April 1991 at 59 sites, including 9 in France. The study included women with CD4+ cell counts ranging from 200-1800 who had not taken antiretrovirals during their current pregnancy, had no symptoms of disease and had been pregnant for only 14 to 34 weeks. The study population was reflective of the AIDS epidemic in women, with the majority of study participants being women of color. Women were given 500mg AZT or placebo daily from time of enrollment until they went into labor, then IV AZT or placebo at a loading dose of 2mg/kg body weight and a continuous infusion of 1 ml/kg/hour during labor and delivery. Within 24 hours of birth, the infants began oral AZT 2mg/kg 4x daily or placebo, which was continued for 6 weeks.

Preliminary Results

As of December 1993, 421 of the targeted 748 infants were born. Of those, 364 infants (180 on AZT) had at least one HIV test available and could be included in the preliminary analysis. Results of ACTG 076 are impressive. Transmission was reduced from 25.5% in the placebo arm to 8.3% in the AZT arm. In other studies of women in good health with excellent prenatal care, transmission rates without therapy have been shown to be as low as 11%. In America, however, transmission rates run from 20-80%, depending on a variety of factors including the status of a woman's health during pregnancy, access to prenatal care and various immunologic and virologic parameters. Reducing transmission rates to 8.3% is quite significant. Because of these results, the ACTG decided to unblind the study, allowing women to know if they were receiving AZT or placebo. It was further decided to close the study to enrollment, and offer AZT to all women in the study.

The long-term effects of fetal AZT experience are as yet unknown. With the exception of anemia, researchers reported no immediate toxicities or side effects in the infants. In all cases, the anemia resolved when AZT was discontinued. Some researchers and advocates are concerned over potential toxicities of AZT, especially long-term effects, such as cancer. In the mean time, we must live with some uncertainties. These concerns will be addressed in long-term follow-up and we won't fully comprehend the effects of fetal exposure to AZT until the children from ACTG 076 become adults.

Seven of the children on AZT and eight children on placebo had birth defects which were consistent with those seen in the general population. In addition, seven children in each arm died. Most deaths were attributed to serious birth defects or rapid progression of HIV. No birth defects or deaths in ACTG 076 were attributed to AZT use.

Women reported typical side effects associated with AZT (see *Project Inform AZT Fact Sheet*) and six women, including three on placebo, discontinued therapy due to perceived side effects. None of the women died during the course of the study.

Follow-Up and Further Analysis

Children will continue to be followed for 18 months, at which time confirmatory HIV-testing will be done. Long-term follow-up of children will be conducted through ACTG 219, which will continue to evaluate children until the age of 21. Women who are considered adolescents (ages 13-21) will also be followed in ACTG 220. ACTG 220 provides some basic gynecological care, including pap smears, and will be revised to incorporate concerns regarding initiation of AZT during pregnancy. ACTG 220 will not follow 'adult' women who enrolled in ACTG 076.

Unanswered Scientific Questions

Studies have suggested that viral load has an impact on perinatal transmission (see *PI Briefing Paper # 13*). It is not clear if AZT reduced the rate of transmission because it lowered levels of the virus. Without this information, it's difficult to know if other

antiviral therapies would have similar effects on perinatal transmission. An analysis of the women who transmitted the virus to their children has not yet been conducted, which leaves many unanswered questions about possible cofactors in transmission, such as CD4+ counts and amount and type of virus. With more information, it may be possible to develop guidelines regarding AZT in pregnancy, which might better characterize women who may best benefit from this intervention. Further analysis of the study will be presented later this year, and should help clarify some of these issues.

Other Studies

Because ACTG 076 targeted a select group of women, who were healthy with high CD4+ cell counts, it's unclear if the results of ACTG 076 will apply to women with symptoms of HIV-disease, or women who have previously been on AZT for an extended period of time. Other studies will shed light on this question. ACTG 185 is a study of pregnant women with less than 300 CD4+, already taking AZT (or ddI if AZT intolerant), who will receive either IVIG or HIVIG during pregnancy and delivery. Infants will be infused at birth. IVIG and HIVIG are blood products rich in antibodies. HIVIG uses HIV+ donors so that the product will have high concentrations of HIV specific antibodies, while IVIG uses HIV- donors. High transmission rates have been observed in women with low CD4+ counts, and it is hoped that the addition of HIVIG will provide antiviral support and prevent transmission. HIVIG is only available through small studies, while IVIG is an FDA approved blood product. Women will be followed for 26 weeks after they deliver to see if temporary administration of HIVIG impacts the course of HIV-disease. At this time, continuation of HIVIG postpartum is not planned. Preliminary data from this study are not expected before 1996. Phase I studies evaluating therapeutic vaccine approaches during pregnancy are also in progress.

Regulatory, Access and Policy Concerns

Reduction of perinatal transmission is good news, yet extremely complicated issues arise with the results of ACTG 076. AZT is not currently approved for use during pregnancy and insurance companies and Medicare/Medicaid may not be willing to pay for the drug for this indication. To address the needs of pregnant women who are intolerant to or have failed AZT, small studies of promising compounds should be conducted. Furthermore, observational studies which evaluate the differences in women and the outcome of their pregnancy may help determine how and when a woman is more likely to transmit the virus to her child. Data from these types of observational studies will be useful in revising prenatal guidelines. Because the long-term effects of fetal exposure to AZT and many other compounds are unknown, a database to follow children into adulthood would prove invaluable.

While preliminary results of ACTG 076 do not warrant the need for mandatory testing, they do indicate a need for establishing guidelines regarding testing of pregnant women and prenatal care of HIV+ women. Statements supporting routine testing of pregnant women have been released by influential organizations, mandatory testing legislation is pending in at least one state, and a policy change by the New Jersey Health Department encouraging routine testing is underway. Project Inform and other advocacy organizations have received hundreds of calls from women and their partners who fear mandatory testing.

Although the words "routine" and "mandatory" have two distinct definitions, for many the words are synonymous. Supporters of routine testing are concerned that results from ACTG 076 may be ignored by the medical community, and that children will continue to be born HIV-infected despite a promising intervention. Most pregnant women, when offered testing for HIV and other disorders, agree to voluntary testing. Guidelines which promote routine testing of pregnant women may discourage some women from seeking prenatal care out of fear that results may be used in a way harmful to herself or her family. Routine, unbiased and non judgemental HIV

Resource Notes:

National Trials Hotline. The AIDS Clinical Trials Information Service provides information on federally sponsored studies (and many others) open to enrollment nationally. Call 1-800-TRIALS-A (1-800-874-2572). 800-AIDS-012 TTY/TTD serves the deaf and hearing impaired. The service also provides free copies of the ***AMFAR Treatment Directory***, which also lists studies conducted by private industry.

National AIDS Hotline. The National AIDS Hotline operates 24 hours a day and provides referrals to local services throughout the United States, and information about a wide variety of non-treatment related topics. Call 1-800-342-AIDS (2437). Spanish -speaking operators are available 8 AM to 2 AM EST at 1-800-344-SIDA (7432). For the deaf and hearing impaired, call 10 AM to 10 PM EST at 1-800-AIDS-TTY (243-7889).

WORLD is a newsletter and an organization for, by and about women facing HIV disease. *WORLD* strives to break the isolation of HIV+ women by providing a forum for communication and treatment information of interest to women. For more information on *WORLD* call 1-510-658-6930.

Treatment Newsletters:

AIDS Treatment News	800-873-2812
Treatment Issues (Gay Men's Health Crisis, New York)	212-337-1950
Test Positive Aware (Chicago)	312-472-6397
BETA (San Francisco AIDS Foundation)	415-863-2437

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AIDSWATCH '94

The annual battle to ensure that adequate dollars will be available from the federal government to fund necessary the National Institutes of Health's (NIH) AIDS research effort is underway. This year the President has requested a $78 million dollar increase for AIDS research, but once again the request falls far below the professional judgment budget, the budget which reflects scientific needs, submitted by NIH scientists. This year also brings new funding threats as individuals and some of the media promote the myths that the epidemic has peaked and that research is incapable of producing effective therapies. As the U.S. domestic fiscal realities become increasingly difficult, some lobbyists will suggest funding their interest at the expense of others. AIDS funding is far from invulnerable to this attack.

In this highly charged and complex political reality, given an administration that has still not made AIDS a real priority, **your voice and your advocacy are more important that ever.** For the third year in a row Project Inform constituents, along with constituents from AIDS organizations across the country gathered in Washington, D.C. to bring their concerns to elected officials during AIDSWATCH '94.

The importance of this event cannot be underestimated. Washington needs to see and hear the depth of the suffering and the bravery of the response to this life-threatening pandemic as funding decisions are being made. Each year, people living with AIDS, their friends, families, and advocates must counter attempts to minimize HIV/AIDS in the light of other problems this country faces. AIDSWATCH participants have been effective in bringing a clear, strong message to elected officials that HIV and AIDS is a problem confronting all of us. In FY 1994, Ryan White moneys in California were increased due to efforts during AIDSWATCH and a substantial increase in NIH research dollars was protected by AIDSWATCH citizen advocates.

In addition to the critical mission, the experience of AIDSWATCH is empowering and exciting. The event opens with a briefing, which includes interactive skills building or 'lobby training' sessions, to help prepare people for meetings with Congressional representatives or their aides. These Congressional visits establish a firm base for an ongoing relationship between AIDSWATCH participants and their elected officials. Social activities provide a place to meet fellow lobbyists, debrief, share experiences and techniques. Through this event, AIDSWATCH participants invest themselves in the political process and can make a significant difference in the lives of people with HIV.

AIDSWATCH '94 took place on May 22-24. For information on how you can join the continuing grass routes campaigns and receive advance notice of next year's AIDSWATCH event, call Project Inform at (415)558-8669 and ask for Dan Perdios or David Lewis.

Together We Can Have A Voice In Our Future

Health Care Reform

Health Care Reform is one of the most critical issues facing Americans today, particularly people living with HIV and other life-threatening illnesses. If a cure were discovered tomorrow, nearly 50% of people with AIDS in this country might not be able to access it due to inadequate health care coverage. Monitoring of the various health care reform bills and pressuring Congress with citizen letters, phone calls and meetings must be maintained as the debate over reform intensifies. Delivery of health care has become a highly profitable industry with many powerful and influential players. A health care system that meets the needs of people is long overdue and possibly within our grasp, but achieving a workable system is unlikely if decisions are left to Congress, the Clinton Administration and industry lobbyists. Now is the time for concerned individuals to register their needs, comments, questions and support for substantive health care reform.

Guidelines For Evaluating Reform Proposals

Figure 1

The following are some guidelines for evaluating reform proposals. Any adequate reform proposal should *minimally* offer:

- ☑ Universal coverage for everyone, with reasonable implementation dates (including the poor, those with pre-existing conditions, and others who are "redlined" or systematically excluded from current health plans)
- ☑ Employer mandates to pay for employee coverage
- ☑ Government guarantees of coverage for low income people
- ☑ Portability of coverage (ie. you will not lose coverage by changing jobs)
- ☑ Proposed individual benefits fully outlined and written into the bill itself
- ☑ Coverage for long-term care
- ☑ Guarantee of affordability
- ☑ Choice of physician and specialist care
- ☑ Coverage for care expenses related to experimental treatment and coverage of "off label" treatments
- ☑ Availability of multiple therapy options to treat or prophylax against a specific disease
- ☑ Option for states to select a single-payer (Canadian-style) system

We do not have the space here to discuss all of the reform plans before Congress. More information is available from Project Inform's policy department

President Clinton has declared health care reform to be his "#1 policy priority." Reform of the health care system is also a high priority for many people living with HIV and their advocates. The issue is being hotly debated across the country, and with an estimated $1 trillion to be spent on health care in 1994, many individuals, businesses and some well funded powerful special interest groups have a stake in its outcome. The health care industry has poured over $150 million into Congressional campaign coffers to influence the outcome of this debate, but in the end it is voters - *people like you* - who will have the final word.

While the numbers of insured versus uninsured people living with HIV are unknown, the statistics for those living with an AIDS diagnosis are not reassuring. Only 29% of people with AIDS have private insurance. Around 50% of people with AIDS who lack private insurance are covered by Medicaid, which is not accepted by many health care providers, or Medicare, which does not provide prescription coverage. Many people with AIDS have no insurance coverage either because they cannot afford it, have been denied coverage because of preexisting conditions or have been dumped by a previous insurer as a "bad risk." Even those with insurance often find that their coverage is inadequate. Caps (upper limits on how much a company will spend on a given illness or condition) are becoming increasingly popular in the insurance business, as are exclusions of "off-label" drug use (using a drug developed for another condition to treat an HIV-related condition) and expensive procedures. Insurance companies, and not doctors or nurses, are increasingly calling the shots on what treatments are available and making decisions regarding hospital admissions and home care.

"Tony" had a standard private insurance policy. He was allowed to keep the policy when he went on disability, but maintaining the paperwork, paying deductibles, and communicating with insurance company personnel and health care providers became a full time job for his mother, herself an insurance agent. During Tony's last hospitalization, his doctor noted that Tony was in the terminal stage of AIDS. This determination allowed Tony's insurance company, a major national provider, to discontinue payment for a number of treatments. Tony was evicted from the hospital on insurance company orders, against the wishes of his family, doctors, and other providers. Treatments were withheld, and his care during his last days was transferred to family and friends as his insurance would not pay for 24 hour nursing. While physicians, friends and family are often effective advocates for a person unable to advocate for themselves, they are not always successful when an insurer refuses to make payment.

While some of the proposed health care reform plans seek to address the problems faced with insurance reimbursement, there is another issue illustrated by Tony's story. The delivery of quality health care is in part dependent on hospital and physician standards and ethics. Many hospitals as well as private physicians groups will not take patients who don't have insurance. Some Health Management Organizations have made specialist care difficult to access. Hospital administrations sometimes do not allow physicians to give palliative treatments to people in terminal stages of disease on insurance company orders. We must continue to monitor, question and advocate against this lack of ethics, not only on the part of the insurers but also on the part of hospital and HMO administrations.

Tony's case is not unique, but it is notable because he had a *good* private insurance policy. His case demonstrates a sad truth about our health care system: for many, it breaks down completely exactly when it is most needed. Health care reform is, for many people, literally a life and death issue. While a number of health care reform proposals are on the table, the Wellstone/

McDermott (Single Payer) and Clinton (Managed Competition) plans are the only proposals which come close to addressing the important concerns outlined in *Figure 1*. Other plans insufficiently address these bottom line needs. The challenge of health care reform will be to keep acceptable plans from being watered down by the Congressional committee process and to ensure that critical issues not covered in the plans are addressed. It will be essential to maintain public interest in what will be a complex and politically charged debate.

It is not too late to get involved in the health care reform debate. Your participation is vital *now* to counterbalance the very significant influence of powerful business interest groups which are primarily interested in protecting profits. We can't allow profit lines to have more influence than people's needs. If a health care bill is not passed this year, or if a weak one passes, it will be a long time before we have another chance at meaningful reform.

Many issues in health care reform dramatically affect people living with HIV/AIDS and their loved ones. More about these issues, such as the pitfalls of a managed care (or HMO) program, coverage of undocumented persons, and what is to become of the current health care "safety net" before and during reform, is available from Project Inform's Policy Department at 415-558-8669.

WHAT YOU CAN DO?

Call your Congressional representatives!

- ☎ Let them know how important health care reform is to you.
- ☎ Ask for their position on health care reform and whether they are co-sponsoring or supporting a particular plan.
- ☎ Make sure the plan they support encompasses *bottom line* needs outlined in *figure 1*.

Look over the existing plans and choose the one that best meets your needs. Doing this kind of research might seem daunting, but many organizations,such as Project Inform, offer simplified charts for purposes of comparison.

Consider the source of information on health care reform. If you are watching paid advertising or reading an editorial, look for the fine print - who is putting this out and where might they stand to profit? Seek out new sources of information.

- ✉ Write your representatives, then write *again* (make this a monthly exercise) - remind them that you are watching. 1994 is an election year and elected officials are paying attention to what their constituents want.
- ✉ Mobilize friends and family to write letters and make phone calls. Remember: in our system of government, only vast numbers of grass-roots actions can counterbalance vast sums of money spent to affect legislation. Start a conversation about the importance of health care reform whenever the opportunity arises.
- ☎ Contact local non-profit organizations and ask them to be proactive in supporting health care reform.
- ☎ Contact local media outlets and give them *your* story. When talking about health care reform, personal stories make the most impact. You do not have to become an expert on the issues, you just need to have experienced the drawbacks of the current system and be willing to talk about your experiences.

Let us know if we can be of assistance.
Write or call Project Inform and ask for David Lewis or Anne Donnelly.

Don't underestimate your own power as an advocate for change!

d4T - Recommended for Accelerated Approval

d4T, also called stavudine or Zerit, is an antiretroviral drug similar to AZT, ddI, and ddC. All these drugs are *nucleoside analogues* which work by inhibiting an enzyme called reverse transcriptase. This enzyme is necessary for HIV reproduction. d4T, made by Bristol-Myers Squibb, has been studied in humans for five years. To date it has been given to almost 11,000 people. Early studies of d4T looked very promising, showing CD4+ cell increases sustained for 18 months. These results were from studies involving a small number of people. Final data from a larger Phase II/III study and the Parallel Track program have yet to be released. Preliminary data from the Phase II/III study were presented at the Food and Drug Administration (FDA) to the Antiviral Drug Advisory Committee on May 20, 1994. As we go to press, the Committee has recommended that FDA grant d4T Accelerated Approval.

Preliminary Phase II/III Study Results

While the study was designed to look at clinical endpoints, the effect of d4T on disease progression and survival, only preliminary data on *surrogate markers* are currently available. Therefore, the Antiviral Drug Advisory Committee is assessing the drugs' toxicity relative to AZT, as well as its ability to improve CD4+ counts and decrease levels of virus in the blood in people with 50-500 CD4+ cells, with a long history of prior AZT therapy. Changes in CD4+ count, p24 antigen, HIV viral titer, and weight gain were consistently superior in the d4T-treated group than in the group receiving continued AZT treatment. Data on clinical endpoints will not be available until early next year, after the completion of the study.

The Phase II/III study enrolled a total of 822 participants. Volunteers were randomized to receive either 40 mg. d4T twice a day, or 200 mg. AZT three times a day. Preliminary data were presented on 359 people who had been on study for at least 4 months. Study participants had a long history of prior AZT use. The average volunteer had been

on AZT for over a year and a half prior to entering the study. The median duration of prior AZT use among study participants was 81 weeks in the d4T arm and 89 weeks in the AZT arm.

The median CD4+ cell count of volunteers entering study was relatively equal in both arms of the study, with the group receiving continued AZT having a slightly higher counts. Viral activity, measured by p24 antigen-positive status, was relatively equal between the two groups at study entry, with 42% of people on d4T and 40% of people on AZT having positive tests. While the AZT-treated arm showed a mean drop in CD4+ counts after 2 weeks, the d4T-treated arm showed a mean CD4+ cell increase through 20 weeks, after which CD4+ counts began to drop below baseline. CD4+ data were available for some volunteers who had been on study for 76 weeks. These showed a mean CD4+ decrease of 18 in the d4T arm, versus a decrease of 70 in the AZT arm, suggesting that the benefit of d4T may diminish over time, but for folks with a prior history of AZT therapy, d4T appears to slow the progression of CD4+ decline. Changes in p24 antigen showed that the AZT-treated arm had p24 increases throughout the study and the d4T-treated arm showed p24 antigen decreases through week 20, after which p24 began to rise above baseline levels. At 12 weeks, HIV viral titers, as measured by viral culture, had decreased by 53% in the d4T arm and rose 11% in the AZT arm. An analysis of changes in body weight demonstrated that people on d4T showed some weight gain compared to the AZT group who showed weight loss. Other analyses measuring quality of life and mental performance status showed d4T to be superior to continued AZT therapy.

Side Effects and Adverse Events

The most common side effect of d4T is neuropathy (6% in the Phase II/III study, 14% in the low-dose arm and 24% in the high-dose arm of the Parallel Track program.) The increased risk of side effects in the Parallel Track program may be due to the fact that people on Parallel Track were generally less healthy than those in the Phase II/III study. Pancreatitis, a potential life-threatening condition, was seen in just under 1% of study participants, and may not have always been related to d4T use. Other side effects reported from the parallel track program are: headache (<2%), nausea and vomiting (1.2%), cough and labored breathing (0.5%), depression (0.3%), confusion (0.3%), abdominal pain (1.2%), and diarrhea (1.5%). Of note, the incidence of side effects reported on d4T are much lower than what has been seen with other antivirals. The most frequent laboratory abnormalities reported thus far are elevated liver enzymes and creatinine phosphokinase (CPK) in 5% of patients. (CPK is a muscle enzyme — Myopathy, strenuous exercise and heart attack can increase CPK levels.) The phase II/III study reported modest elevations of liver enzymes associated with d4T compared to AZT; however, severe liver enzyme elevations (>5 times normal) were comparable to those seen in people treated with AZT. In the Phase I studies, the most common side effects were peripheral neuropathy and liver toxicity.

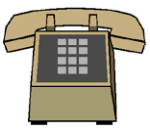
Evidence of insomnia, anxiety, and skin rashes reported by some activists and patient advocates have not been confirmed by the study. In the Phase II/III study, there were more cases of insomnia reported in the AZT-treated arm (23%) than in the d4T-treated arm (15%). Anecdotal information from some physicians indicates that adverse events like neuro-psychiatric disorders (panic attacks) and neuropathy are causing almost 20% of their patients to drop off the Parallel Track program. These same symptoms were reported in early studies of AZT, ddI, and ddC. Although the company has asked all investigators to be attentive to patients' complaints and report them in monthly case report forms, a study designed to evaluate potential neuro-psychiatric effects of d4T may still be warranted.

Resistance and drug interactions

Studies looking at resistance have been going on for almost 24 months. So far, the company says there is no evidence to suggesting the development of d4T resistance. However, *in vitro* (test tube) studies have shown cross-resistance between d4T and ddC. This means that d4T may have decreased antiviral benefit for people who have failed ddC. Thus far, no drug interaction studies have yet been done with d4T in humans. This is problematic as clearly, if d4T is approved, people will be using d4T with other drugs including common OI prophylaxis and treatments and possibly other antivirals. There are reports that there may be increased risk for pancreatitis for people taking d4T with oral ganciclovir or IV pentamidine. Test-tube studies combining AZT and d4T resulted in less anti-HIV activity, possibly because both drugs compete for the same enzyme, thymidine, in order to inhibit reverse transcriptase. Further analysis of the phase II/III studies may result in *some* drug interaction data as there are many people with low CD4+ counts in this study who are taking several other medications concurrently (especially OI prophylaxis).

What's Next

What will be d4T's indication (guidelines for how a drug is to be used) if it is approved? That decision will be based mainly on the Phase II/III study which compared d4T to AZT in people with between 50-500 CD4+ cells and at least 6 months prior AZT use. The FDA determines the indication of a drug based on clinical studies. That being the case, the drug may be indicated for people who have failed or are intolerant to AZT. When the FDA makes final decisions on the indication for d4T, it will probably be three to four months before the drug is available in pharmacies. Upon approval, the company will offer parallel track volunteers free drug for 1 month. The company has also noted that when d4T is approved it will provide drug to those who cannot afford it through a patient assistance program. What will it cost? Drug pricing takes into account factors such as development costs and the



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The "AIDS Cure Act" - Science or Politics?

In May, H.R. 3310, "The AIDS Cure Act," was introduced in Congress by Congressman Jerrold Nadler of New York. Also known as "The Barbara McClintock Project," this bill calls for the creation of an expansive new program of AIDS research, something of a "Manhattan Project" on AIDS. Since many groups, including Project Inform, have been calling for a "Second Front" on AIDS - effective reforms and new AIDS research initiatives - it's important to read the fine print. Not all proposals are alike and though well intended, not all are likely to speed the search for a cure. Many people have asked whether Project Inform supports this particular bill, and some wonder whether it is the same thing as the "Second Front" that we have called for and written about in previous publications. Project Inform supports the general concept of taking bold new initiatives in AIDS Research, and applaud Congressman Nadler for sticking his neck out on behalf of people with AIDS. Overall, however, Project Inform cannot support this bill in its present form, for the reasons described in this article.

First, there are several insightful suggestions in the "AIDS Cure Act" which are consistent with views expressed by several groups, including Project Inform. These areas of common interest include:

☺ **Initiation of an intensified program of AIDS research.** It is both scientifically and politically important in the current climate to make a "fresh start" on AIDS, to announce and implement a reinvigorated and more aggressive program.

☺ **A focus on clarifying the pathogenesis of AIDS.** While a great deal has been learned about HIV, less is known about how it causes damage. There are many competing theories of how the virus causes disease, but there does not appear to be a clear federal program for prioritizing and testing these theories. Until HIV pathogenesis is better understood, the element of chance will continue to play an unduly large role in the development of new therapies.

☺ **A call for greater collaboration among scientists.** AIDS research presently operates on an essentially competitive, rather than collaborative model. This model is mostly a reflection of 19th century traditions of science. It is not a model designed to produce the fastest or best results. The synergistic effects of teamwork, goal orientation, strategic planning, efficiency and quality assurance are the hallmarks of modern management practices in almost every other field of endeavor, but not in federally-funded biomedical research.

☺ **A call for scientists to work in a more scientifically focused environment.** Today, it is all too common for AIDS researchers to serve many masters competing for their time and attention. Teaching duties, writing grants, university faculty responsibilities, consulting contracts and professional and political roles all impinge upon the time of many researchers, often to the detriment of their focus on AIDS.

☺ **A call for a greater emphasis on project management.** Much time and effort is lost in AIDS research because of the entangling web of bureaucratic and regulatory requirements. Giving a management team the authority to cut or streamline nonproductive government requirements would indeed be helpful.

While these areas of interest make sense to most people, several other aspects of the "AIDS Cure Act" are troubling and, we believe, run the risk of hindering rather than speeding progress. These areas of concern include:

☹ **The call for a sweeping, new, all encompassing program which will run alongside, but not replace, existing programs.** By definition, this implies a massive duplication of effort. The vast majority of work likely to occur under the proposed program is work that is already being done, perhaps in a different fashion, under existing programs. Since the majority of scientists interested in AIDS are already working in the existing system, it is difficult to understand where the personnel for the new project would come from. It is unclear how or why Congress could be motivated to fund a second massive program while maintaining support for duplicative parallel research. Similarly, it is unclear how such duplication of effort would demonstrate efficiency in facilitating research into new areas.

☹ **An undue concentration on ideological issues.** The "AIDS Cure Act" is excessively concerned with the exploration of "alternate" theories of the cause of AIDS. While better structures to support the development of complementary and alternative approaches to *therapy* are needed, alternative *theories* of AIDS are quite another matter. At this stage of the epidemic, all theories are not equally worthy of support or funding, nor should their study be politically mandated. There is sufficient opportunity within the existing scientific peer-review process for the testing of compelling new pathogenesis theories. Where such approaches have failed to achieve respected status, it has almost invariably been because they have failed to prove themselves in both human and laboratory experience.

☹ **An insistence upon centralization of decision-making and a primary work location.** When centralization was demanded in the original Manhattan Project, its primary purpose was driven by security needs of the top-secret project. There may be benefits of working in close physical proximity, but they must be weighed against the enormous costs of uprooting hundreds of scientists, their families and their labs, as well as the time lost to relocation. While centralized information exchange, communications and management make sense, the principal effect of centralized labor would be a powerful *disincentive* for the best qualified scientists to participate.

☹ **An insistence that participating scientists sever all other ties.** Securing an increased amount of a scientists' attention is a good thing, as is gaining assurance that conflict of interest will not bias their

work. But forcing researchers to literally "marry" a project for its duration would be counterproductive. Scientists should not be forced to pay a large personal and professional price to participate and contribute to AIDS research. As conceived, the proposed project would expect scientists to abandon professional objectives, such as career-long university posts. Few are likely to be interested. Similarly, they would be asked to sever all industry consulting relationships. In the current system, such relationships are key to the flow of technology and thinking between government, academia and private industry. There are better and less destructive ways of handling concerns about conflict of interest.

☹ **An insistence on majority control of the program by people with AIDS and their advocates.** It is well-established that scientific programs benefit when the voices of people with AIDS and their advocates are heard. This is a long way from saying that majority control of programs should be left to the lay public, however well-informed the public may be. Scientific programs should be primarily directed by properly trained scientists, with appropriate input from people living with HIV/AIDS and their advocates. Most importantly, the control issue should be discussed openly and not determined by language buried in the middle of complex legislation.

☹ **An emphasis on force rather than incentives.** The project talks of the use of eminent domain as means of seizing patents and products. An approach which favors incentives, rather than force, would be more likely to enhance cooperation, while avoiding the inevitable and crippling litigation that seizures would invite.

☹ **A general misunderstanding of how drugs are developed.** As proposed, the project model seems to place responsibility for drug development in the hands of government. Neither government nor academia has the capability or resources for doing major drug development work. The vast bulk of this work is done in private industry. The implied creation of new publicly owned resources and facilities for drug development purposes would be an enormous waste of taxpayer money, and any effort to seize existing resources would surely result in litigation. However, reforms which enable government to quickly fill gaps in drug development could well prove beneficial. Instead of creating an atmosphere which is hostile to industry, AIDS research would be best served if government learned to work more effectively with industry, letting each party do what they are best equipped to do. Rather than trying to subsume industry's role, government should avoid creating obstacles to industry and encourage concentration on AIDS drug development.

Whatever Project Inform's views, the "AIDS Cure Act" seems unlikely, in its present form, to receive the needed support of Congress or the scientific community. It seems likely that many individuals and organizations signed on to the bill as a statement, in general, in support of a reinvigorated new effort or "Second Front" in AIDS research. Project Inform also believes in the wisdom of a new approach, a "Second Front," but not in all the specific aspects of the "AIDS Cure Act." Any new initiative should be considered a pilot program, an effort to test new organizational and management approaches before any major step is taken to overturn current models. Even though such improved management models have worked well in other fields of scientific endeavor, they have not previously been employed in a federally-funded biomedical research program. Any such new program should focus initially on a single aspect of AIDS research, ideally one where there is a crying need and opportunity for advances. The *"Accelerated AIDS Research Initiative,"* an outgrowth of last year's Future Directions in AIDS Research meetings, is a draft model for such a project, one which provides most of the meaningful benefits, and none of the more controversial aspects, of the AIDS Cure Project. Copies of the proposal, a summary of which appeared in the most recent Project Inform *Briefing Paper*, are available from Project Inform upon request by calling the Project Inform treatment hotline at 800-822-7422, or in

Project Inform

The Basic Message

- **Learn your options** and line up your support.
- **Get tested**, *anonymously*.
- If positive, **maximize your health**, get a complete physical and full immune health workup and get educated! Learn about your options and consider **antiviral treatment**. For women, also get "gyn" and Pap tests every six months.
- **Monitor CD4+ cells quarterly**, *(no matter how high your count),* charting the trend.
- *If the CD4+ trend is downward or consistently below 500,* **optimize nutrition and consider antivirals** (ideally a combination).
- *If the CD4+ trend stays below 300,* **consider preventive treatment against PCP** (oral drugs if possible). If the count continues to fall below 200, reconsider antiviral therapy if not already on and consider preventive treatments against other opportunistic infections. Learn about drug interactions.
- *If the count stays below 75,* **intensify monitoring,** consider preventive action against MAC/MAI and fungal infections. Learn about other preventive therapies.

It's NEVER too EARLY to take CHARGE of YOUR health!!

Drug Interactions

As more drugs are available to treat HIV and prevent or treat opportunistic infections, the potential for drug interactions become an increasing concern. Developing a health management plan and deciding which therapies to incorporate into a comprehensive plan can seem daunting. Not only does each particular therapy have potential side effects, but how each therapy might augment or diminish the benefit of another must be considered when weighing options. Many people are taking a wide variety of therapies simultaneously, ranging from experimental and approved antivirals and prophylaxis for opportunistic infections to complimentary approaches and over-the-counter medications. How therapies interact is not always considered, and may play a major role in the success of any plan for managing HIV-disease. The following are some guidelines to help decrease the likelihood of drug interactions, as well as keep health care provider's and pharmacist's attention focused on monitoring for potential drug interactions:

- ❑ Brown Bag Medicine Check-up - each time you see your health care professional, put all your medications, including over-the-counter and complimentary products, in a bag and have your health care provider conduct a personalized review of your medicine for safety, appropriateness, compatibility and instructions for use.
- ❑ Each time you are given a prescription for a new medication ***ask*** your health care provider and pharmacist if it will work safely with the other therapies you are on.
- ❑ Talk to your health care provider about making a 'medicine check-up' part of your regular visits, and discuss how best to monitor for the potential effects of drug interactions. Bring the *Project Inform Drug Interaction Fact Sheet* with you to your appointment.

How To Use the Drug Interaction Chart

To use the drug interaction chart, identify the name of a therapy in a gray bar. The drugs listed below the gray bar are therapies which may potentially interact with the drug in the gray bar. For example, identify the gray bar for ddI. Scan the list of compounds and substances listed below ddI. You will note that if you take ddI with food or right after you've eaten, the food will decrease the absorption of ddIand this will result in decreased blood levels of ddI. Therefore, it's not wise to take ddI with food as you may be 'under-dosing'.

ddI (Videx)

Food in stomach	May decrease ddI levels

Antivirals

Acyclovir (Zovirax) ***plus***

AZT	Increase antiviral activity in test tubes
Interferon-alfa	Increase antiviral activity in test tubes
Probenecid	May increase acyclovir levels and decrease acyclovir clearance

AZT (Retrovir) ***plus***

Acyclovir	Increase antiviral activity in test tubes
Amphotericin B	May increase risk of bone marrow toxicity
Antineoplastics	May increase risk of bone marrow toxicity
Clarithromycin	May decrease AZT levels
Dapsone	May increase risk of bone marrow toxicity
ddC	Increase antiviral activity in test tubes
ddI	Increase antiviral activity in test tubes
Delavirdine	Increase antiviral activity in test tubes
d4T	May decrease antiviral activity
Flucytosine	May increase risk of bone marrow toxicity
Food in stomach	May decrease AZT levels
Foscarnet	Increase antiviral activity in test tubes. May increase risk of anemia
Interferon-alfa	Increase antiviral activity in test tubes and risk of bone marrow toxicity
Ganciclovir	May increase risk of neutropenia
Methadone	May decrease AZT metabolism and increase AZT levels
Pentamidine	May increase risk of bone marrow toxicity
Pentoxifylline	May increase risk of bone marrow toxicity
Probenecid	May increase AZT levels and decrease AZT clearance
Protease inhibitors	Increase antiviral activity in test tubes
Pyrimethamine + sulfadiazine	May increase AZT levels and increase bone marrow toxicity
Ribavirin	Decrease antiviral activity in test tubes
Rifabutin	May decrease AZT levels
Rifampin	May decrease AZT levels
3TC	Increase antiviral activity in test tubes
TMP/SMX	May increase risk of anemia, neutropenia. May increase AZT levels and decrease AZT clearance (high dose TMP/SMX)

ddC (Hivid) ***plus***

Aminoglycosides	May increase ddC levels and increase risk of neuropathy
Amphotericin B	May increase ddC levels and increase risk of neuropathy
Antineoplastics	May increase risk of neuropathy
AZT	Increase antiviral activity in test tubes. May increase risk of pancreatitis
Chloramphenicol	May increase risk of neuropathy
Cisplatin	May increase risk of neuropathy
Dapsone	May increase risk of neuropathy
ddI	Should not be used in combination
Disulfiram (Antabuse)	May increase risk of neuropathy
Food in stomach	May decrease ddC levels
Foscarnet	May increase ddC levels and increase risk of neuropathy
Ethionamide	May increase risk of peripheral neuropathy
Hydralazine	May increase risk of neuropathy
Iodoquinol	May increase risk of neuropathy

- Potential Drug Interactions

ddC (Hivid) *plus* ...*continued*

Isoniazid	May increase risk of neuropathy
Metronidazole	May increase risk of neuropathy
Pentamidine (IV)	May increase risk of neuropathy and pancreatitis
Phenytoin	May increase risk of neuropathy
Ribavirin	May increase risk of neuropathy

ddI (Videx) *plus*

Antineoplastics	May increase risk of neuropathy
AZT	Increase antiviral activity in test tubes
Cimetidine	Needs to be taken two hours apart
Dapsone	Needs to be taken two hours apart otherwise dapsone has no activity
ddC	Should not be used in combination
Delavirdine	Needs to be taken an hour apart otherwise decrease in delavirdine levels. Increase antiviral activity in test tubes
d4T	Increase antiviral activity in test tubes
Food in stomach	May decrease ddI levels
Ganciclovir	Oral ganciclovir increases ddI levels by up to 70% and ddI decreases oral ganciclovir levels by up to 20%. May increase risk of pancreatitis
Ketoconazole	Do not take within two hours of ddI otherwise ketoconazole has no activity
Pentamidine (IV)	May increase risk of pancreatitis
Quinolones	Do not take within two hours of ddI otherwise quinolone has no activity
Ranitidine	Needs to be taken two hours apart
Ribavirin	Increase antiviral activity in test tubes

Delavirdine (U-90152) *plus*

Antacids	Needs to be taken an hour apart or decrease in delavirdine levels
Astemizole (Hismanal)	May increase astemizole levels
AZT	Increase antiviral activity in test tubes
Barbiturates	May decrease delavirdine levels
Carbamazepine	May decrease delavirdine levels
Cimetidine	May decrease delavirdine levels
Clarithromycin	May increase delavirdine levels
Cyclosporine	May increase cyclosporine levels
Dapsone	May increase dapsone levels
ddI	Needs to be taken an hour apart or decrease in delavirdine levels. Increase antiviral activity in test tubes
Digitalis	May increase digitalis levels
Diltiazem (Cardizem)	May increase diltiazem levels
Erythromycin	May increase delavirdine levels
Estradiol	May increase estradiol levels
Hydrocortisone	May increase hydrocortisone levels
Itraconazole	May increase itraconazole and delavirdine levels
Ketoconazole	May increase ketoconazole and delavirdine levels
Lidocaine	May increase lidocaine levels
Loratidine	May increase loratidine levels
Lovastatin	May increase lovastatin levels
Midazolam	May increase midazolam levels
Nifedipine	May increase nifedipine levels
Phenytoin	May decrease delavirdine levels

Delavirdine *plus* ...*continued*

Prednisone	May increase prednisone and delavirdine levels
Prednisolone	May increase delavirdine levels
Progesterone	May increase progesterone levels
Quinidine	May increase quinidine levels
Ranitidine	May decrease delavirdine levels
Rifampin	Should be taken together otherwise delavirdine levels significantly decreased in blood
Rifabutin	Decreases delavirdine levels
Terfenadine (Seldane)	May increase terfenidine levels
Testosterone	May increase testosterone levels
Triazolam	May increase triazolam levels
Warfarin	May increase warfarin levels

d4T (Zerit) *plus*

AZT	Decrease antiviral activity in test tubes
ddI	Increase antiviral activity in test tubes
Ganciclovir	May increase risk of pancreatitis
Pentamidine (IV)	May increase risk of pancreatitis

Nevirapine *plus*

Amoxicillin	May increase risk of Stevens-Johnson syndrome
Astemizole (Hismanal)	May increase astemizole levels
AZT	Increase antiviral activity in test tubes
Cimetidine	May decrease nevirapine levels
Clarithromycin	May increase nevirapine levels. May increase risk of liver toxicity
Dapsone	May increase dapsone levels
ddI	Increase antiviral activity in test tubes
Erythromycin	May increase nevirapine levels. May increase risk of liver toxicity
Itraconazole	May increase itraconazole levels
Ketoconazole	May increase ketoconazole levels
Phenytoin	May decrease nevirapine levels
Prednisone	May increase nevirapine levels
Ranitidine	May decrease nevirapine levels
Rifampin	May decrease nevirapine levels
Rifabutin	May decrease nevirapine levels
Terfenadine (Seldane)	May increase terfenadine levels
Ticarcillin	May increase risk of Stevens-Johnson syndrome
Warfarin	May increase warfarin levels

Protease inhibitors *plus*

Cimetidine	May increase protease inhibitor levels
Fluconazole	May increase protease inhibitor levels
Ketoconazole	May increase protease inhibitor levels
Itraconazole	May increase protease inhibitor levels
Rifabutin	May decrease protease inhibitor levels
Rifampin	May decrease protease inhibitor levels

It's Never Too EARLY...
To Take Charge of Your Health!

continued on page 14...

...continued from page 12

Drug interactions can take different forms and may occur immediately or may take weeks to develop. Potential interactions may prohibit the use of two therapies together, while in other instances careful monitoring is sufficient to detect emergency problems, which can guide treatment decisions to avoid complications. Interactions can occur when one therapy affects how another is absorbed, broken down (metabolized), distributed or excreted in the system. Interactions can also occur when one therapy alters the effect of another. A common form of drug interaction can occur when two drugs have similar types of potential toxicity. For example, both ddI and ddC can cause peripheral neuropathy, a tingling or pain in the legs, hands or feet. Because of the similar toxicities of the two drugs, it is not recommended that they are used together as this may increase the potential for neuropathy. Similarly, AZT and ganciclovir, a treatment for CMV, may both cause bone-marrow suppression, which results in neutropenia. With the addition of a third drug, G-CSF (also called Neupogen), this drug interaction may be managed, however.

The issue of drug interaction is becoming of increasing concern as prevention of multiple opportunistic infections (OI), by taking a number of different drugs, is being proposed or is already considered standard practice by many physicians. Multiple OI prevention brings the issue of drug interactions to a critical head. It is possible that drug interactions may cause more harm than good in some multiple OI prevention regimens. For example, one drug could reduce blood levels of another drug, which may lead to the development of drug resistant organisms or result in the drug having no prophylactic value. In other words, drug interactions could result in the development of a disease which is not responsive to standard treatment. It is also possible that the added toxicity of taking numerous therapies outweigh their potential benefit for preventing disease. For these reasons, health care providers and people living with HIV/AIDS should carefully choose OI prevention regimens, monitor for drug interactions and other side effects and make informed decisions about combination therapies and OI prevention approaches.

Unfortunately, most drug interaction studies are done with only two drugs and most people with HIV take many more than that. As a result, very little is known about how all the commonly used drugs may interact with each other. For this reason, ACTG (AIDS Clinical Trials Group) and CPCRA (Community Programs for Clinical Research on AIDS) are proposing to conduct multiple opportunistic pathogens prophylaxis studies (MOPPS), to determine the benefits of preventing all the major opportunistic infections versus the potential toxicities and drug interactions of these commonly used therapies (fluconazole, rifabutin, clarithromycin, azithromycin, TMP/SMX, dapsone, oral ganciclovir, and valacyclovir).

In the meantime, it is important to discuss potential drug interactions with a health care provider and a pharmacist. Before starting a new therapy, be it approved, experimental or complimentary, factor in the potential for drug interactions and possible side effects. Not everyone experiences side effects of drugs and many problems of drug interactions may be managed by careful monitoring and adjusting dose or discontinuing therapy as needed.

A more comprehensive *Drug Interaction Fact Sheet* is available by calling the Project Inform Treatment Hotline.

Common OI

Acetominophen	May decrease atovaquone levels
Acyclovir	May decrease atovaquone levels
AZT	May increase atovaquone levels
Benzodiazepines	May decrease atovaquone levels
Cephalosporins	May decrease atovaquone levels
Fluconazole	May increase atovaquone levels
Fatty foods	Increase atovaquone levels
Laxatives	May decrease atovaquone levels
Prednisone	May increase atovaquone levels
Rifampin	May decrease rifampin levels

Azithromycin (Zithromax) *plus*

Antacids	Needs to be taken two hours apart or reduced azithromycin levels
Cyclosporine	May increase cyclosporine levels
Food in stomach	May decrease azithromycin levels (only azithromycin capsules)
Phenytoin	May increase phenytoin levels
Rifabutin	May increase rifabutin levels

Ciprofloxacin (Cipro) *plus*

Antacids	Needs to be taken two hours apart otherwise decrease in ciprofloxacin levels
Caffeine	May increase caffeine levels
Cyclosporine	May increase risk of elevated serum creatinine
ddI	Needs to be taken two hours apart otherwise may decrease ciprofloxacin levels
Food in stomach	Decreases ciprofloxacin levels
Iron supplements	Needs to be taken two hours apart otherwise may decrease ciprofloxacin levels
Probenecid	Increases ciprofloxacin levels
Sucralfate	Needs to be taken two hours apart otherwise may decrease ciprofloxacin levels
Theophylline	May increase theophylline levels
Warfarin	May increase warfarin levels
Zinc containing multivitamins	Taken two hours apart otherwise may decrease ciprofloxacin levels

Clarithromycin (Biaxin) *plus*

Anticoagulants	May increase anticoagulants effect
Astemizole (Hismanal)	Should not be taken together, may increase risk of cardiovascular toxicity
AZT	May decrease AZT levels
Carbamazepine	Increases carbamazepine levels
Cyclosporine	May increase cyclosporine levels
Digoxin	May increase digoxin levels
Phenytoin	May increase phenytoin levels
Rifabutin	May increase rifabutin levels by up to 80% and decrease clarithromycin levels by up to 50%. May increase risk of painful eye inflammation, arthritis, joint pain, tenderness or pain in muscles.
Terfenadine (Seldane)	Should not be taken together, may increase risk of cardiovascualr toxicity
Theophylline	Increases theophylline levels
Triazolam	May increase triazolam levels

- Potential Drug Interactions

Dapsone *plus*

AZT	May increase risk of bone marrow toxicity
Clofazimine	May decrease effectiveness of clofazimine
ddC	May increase risk of neuropathy
ddI	Needs to be taken two hours apart otherwise dapsone has no activity
Probenecid	May increase dapsone levels and decrease dapsone clearance
Pyrimethamine	May increase risk of hematological reactions
Rifampin	May need to take higher doses of dapsone because it is more rapidly excreted
Trimethoprim	May increase both trimethoprim and dapsone levels

Fluconazole (Diflucan) *plus*

Astemizole (Hismanal)	Should not be taken together, may increase risk of cardiovascular toxicity
Cimetidine	May decrease fluconazole levels
Cyclosporine	May increase cyclosporine levels
Hydrochlorothiazide	May increase fluconazole levels
Oral contraceptives	May decrease effectiveness of oral contraceptives
Phenytoin	Increases phenytoin levels
Ranitidine	May decrease fluconazole levels
Rifabutin	May increase rifabutin levels by up to 80% in blood
Rifampin	Decreases fluconazole levels
Sulfonylurea oral glycemic drugs	Increase risk of low blood sugar levels *hypo-*
Terfenidine (Seldane)	Should not be taken together, may increase risk of cardiovascular toxicity
Warfarin	Increases prothrombin time

Ketoconazole (Nizoral) *plus*

Alcohol	May increase risk of nausea, vomiting, hypotension
Antacids	Take two hours apart otherwise may decrease ketoconazole levels
Astemizole (Hismanal)	Should not be taken together, increases risk of cardiovascular toxicity
Cimetidine	Take two hours apart otherwise may decrease ketoconazole levels
Cyclosporine	May increase cyclosporine levels
ddI	Take two hours apart otherwise may decrease ketoconazole levels
Isoniazid	Should not be taken together, may significantly decrease ketoconazole levels
Phenytoin	May alter both drug levels
Prednisolone	May increase prednisolone levels
Ranitidine	Take two hours apart otherwise may decrease ketoconazole levels
Rifampin	Decreases ketoconazole levels
Sulfonylurea oral glycemic drugs	Increase risk of low blood sugar levels *hypo-*
Terfenadine (Seldane)	Should not be taken together, increases risk of cardiovascualr toxicity
Testosterone	May decrease testosterone levels
Warfarin	May increase prothrombin time

Pentamidine (Pentam) *plus*

Antineoplastics	May increase risk of bone marrow toxicity
AZT	May increase risk of bone marrow toxicity
ddI	May increase risk of pancreatitis
Foscarnet	May increase risk of severe low levels of calcium and kidney toxicity
Interferon-alfa	May increase risk of bone marrow toxicity

Rifabutin (Mycobutin) *plus*

Analgesics	May decrease effectiveness of analgesics
Anticoagulants	May decrease effectiveness of anticoagulants
AZT	Decreases AZT levels
Barbiturates	May decrease effectiveness of barbiturates
Clarithromycin	May increase rifabutin levels by up to 80% and decrease clarithromycin levels by up to 50%. Increase risk of painful eye inflammation, arthritis, joint pain, tenderness or pain in muscles
Corticosteroids	May decrease corticosteroid levels
Cyclosporine	May decrease cyclosporine levels
Dapsone	May decrease dapsone levels
Diazepam	May decrease effectiveness of diazepam
Disopyramide	May decrease effectiveness of disopyramide
Estrogen	May decrease effectiveness of estrogen
Fluconazole	May increase rifabutin levels by up to 80%. Increase risk of painful eye inflammation, arthritis, joint pain, tenderness or pain in muscles
Ketoconazole	May decrease ketoconazole levels
Itraconazole	May decrease itraconazole levels
Methadone	May reduce activity of methadone
Mexilitine	May decrease effectiveness of mexilitine
Oral contraceptives	May decrease effectiveness of oral contraceptives
Progesterone	May decrease effectiveness of progesterone
Quinidine	May decrease quinidine levels
Sulfonylureas	(oral low blood sugar levels drugs)May decreas sulfonylurea levels
Theophylline	May decrease theophylline levels
Verapamil	May decrease effectiveness of verapamil

TMP/SMX (Bactrim, Septra) *plus*

Antineoplastics	May increase risk of anemia, neutropenia
AZT	May increase risk of anemia, neutropenia. May increase AZT levels and decrease AZT clearance
Diuretics	May increase risk of thrombocytopenia
Phenytoin	May increase phenytoin levels
Pyrimethamine	May increase risk of anemia
Theophylline	May increase theophylline levels
Warfarin	May increase prothrombin time

New News on Q

by Mark Frey and Rick Flynn

The names *Compound Q, trichosanthin,* and *GLQ223* are often used interchangeably to describe the natural and synthetic form of a plant protein extract from the root of the Chinese cucumber called *Trichosanthes kirilowii*. In China, it has been used for many years to induce abortion and to treat some forms of cancer. It is currently being studied as a potential treatment for HIV. Laboratory studies have shown Compound Q to selectively kill HIV-infected macrophages and CD4+ cells. GLQ223 is manufactured by Genelabs and is available through clinical trials. Trichosanthin, imported into the US by Buyer's Clubs, is used in some doctor's offices and in "guerrilla clinics."

Preliminary data from a Phase II/III study of GLQ223 were presented in October 1993. The study was designed to gather preliminary information on the use of GLQ223 in people with AIDS and ARC who had been on long-term prior AZT therapy, and to evaluate clinical, immunologic and virologic parameters. The study compared GLQ223 to GLQ223 + AZT to AZT alone in 148 volunteers. GLQ223 was given every 3 weeks at doses of 36, 50, and 100 micrograms/kilogram (mcg/kg) of body weight, escalating every other dose, followed by 10 doses of 150 mcg/kg, for a total of 16 doses. The drug was administered intravenously over a three hour period. AZT dosage was the standard 500 mg/day.

Study endpoints were:

1. Time to treatment failure, defined as:
   - 25% decrease in CD4+ cells sustained over 6 weeks
   - new opportunistic illness
   - death
2. Five-fold reduction in blood levels of HIV RNA (viral load) as measured by QC-PCR *(QC-PCR is a highly sensitive blood test designed to accurately measure and quantify levels of virus in the blood.)*

Based on these criteria, there were no significant differences among the three study arms. Five people in the AZT arm had clinical progression, five confirmed and one suspected clinical progression in the combination arm and one confirmed and two suspected in the GLQ223 arm. Time to treatment failure was about equal among the three groups. Subsequent analysis has shown that disease progression in the AZT arm occured during the course of study, while all cases of progression in both GLQ223 arms occured during follow-up, after volunteers had gone off study drug. Interestingly, QC-PCR (viral load) proved to be a good predictor of disease progression. Virtually all cases of treatment failure in the GLQ223 arm of the study, as measured by CD4+ decline, were related to the use of steroids as a pretreatment to GLQ223 therapy. According to the company, *early* analyses of the data suggest that people in the GLQ223 arms of the study developed fewer opportunistic illnesses after cessation of treatment. Confirmation of this awaits further data analysis.

The most common side effects of GLQ223 were acute allergic reactions, a flu-like syndrome and elevated muscle and liver enzymes. The severity of allergic reactions was reduced with changes in dose regimen. At the beginning of the study, participants receiving GLQ223 were given the drug every 3 weeks. Due to a large number of study drop-outs because of side-effects (especially in the form of allergic reactions), the protocol was amended to administer drug once a week for the first four weeks, then continue subsequent infusions every three weeks. Apparently this change helped volunteers tolerate GLQ223 much better.

The company is committed to continue research on GLQ223, feeling initial data warrants further investigation.

Compound Q: Most of the information about Chinese Trichosanthin remains in the anecdotal experiences of people who have used the drug on the *underground*. Anecdotal reports cover the entire spectrum from desired to undesired results. Some people report improvement in CD4+ counts, while others who tried the drug are no longer alive. In as much as reports are quite varied, it's only safe to say that the drug certainly warrants continued study.

In the meantime, Compound Q is legally available, with a few essential restrictions. The *underground* practice of administering Compound Q is a 2 to 3 hour infusion every 3 to 6 weeks. People normally start out with an infusion of 35/mcg/kg and gradually increase the dose in subsequent infusions until they reach a 100-150 mcg/kg dose. Longer infusions and higher doses have been tried by a few people, however it is yet unclear what the optimum dose and schedule are. Infusion costs can vary from $40 to $80 on the *underground*, where the drug is given by skilled nurses equipped with the proper medications to control adverse reactions, to $100-$250 in more formal settings with doctor's supervision. Compound Q is sold in vials costing 8 to 10 dollars each. Low starting doses are 2 to 3 vials per infusion and higher doses require 10 to 20 vials. Compound Q is not inexpensive, and people considering therapy with Compound Q, as with any approved or experimental therapy, should talk to people who have tried Q, discuss the issue with their health care provider, learn about the drug and its potential side effects and make an informed decision.

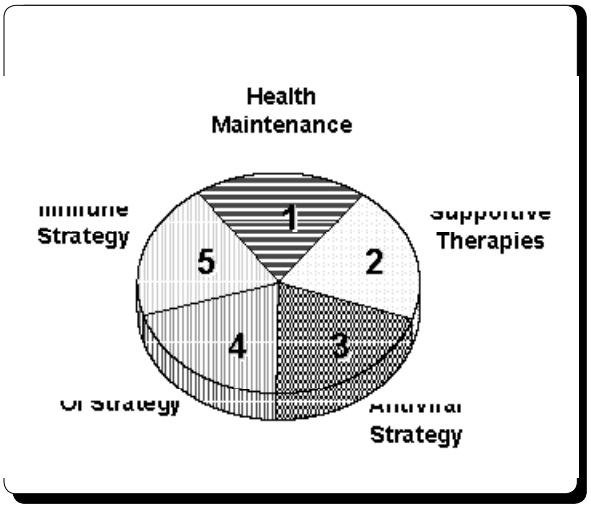
The most dangerous complication seen with the drug is anaphylactic shock - a sudden, severe life-threatening allergic reaction. Between 10 and 20 percent of people may experience this reaction during one of their first 6 infusions. *Because of this, it is critical that skilled medical professionals be on hand when this drug is administered.* In 1989, when the drug was used predominantly on people with very low (<100) CD4+ cell counts, there were a few deaths possibly related to Compound Q. It is still unclear if these deaths were Q-related, as the deaths occurred after the drug had cleared the system. Nonetheless, people with fewer than 50 CD4+ cells are discouraged from using Compound Q as confounding factors may lead to complications.

Common reaction to the drug is a flu-like symptom and water retention starting 12 to 36 hours after infusion and lasting 2 to 3 days. It is noted on the underground that these effects tend to diminish with subsequent infusions. Because of the potential for painful side effects many people pre-treat prior to infusions with an anti-inflammatory like ibuprofen or Tylenol, and an antihistamine like Benadryl and, perhaps, a steroid like prednisone or decadron. These pre-medications are given to help ameliorate side effects. Some of these pre-treatment drugs may negatively impact the immune system. People considering therapy should discuss this with their health care provider

Due to the potential for life threatening reactions, underground sources will only release Compound Q through a prescribing physician or skilled medical professional. Some of the doctors experienced with administering the drug are willing to guide other physicians. People interested in trying Q should put their physician in contact with doctors experienced with Compound Q. For more information, contact the Project

Early Intervention - 1994

Beginning with the 1993 International AIDS Conference in Berlin, many people and their physicians became confused about the value of early intervention against HIV disease. Most of the confusion stemmed from conflicting reports about the effectiveness of long-term use of AZT in healthy people with CD4+ counts below 500. While there are continuing debates about the validity and implication of recent studies, there is no reason for this debate to cause confusion over the value of early intervention. Early intervention has never meant just using a drug once CD4+ cell counts fall below some predetermined level. Thus, the value of early intervention does not hinge upon the long-term success or failure of any individual drug. Instead, the concept has always referred to a broad spectrum approach of personal responses to HIV infection, an approach which was as valid and helpful in 1984 as it is today. What has perhaps fallen since Berlin, and rightly so, is the notion that there is some simplistic "cookbook" medicine solution to dealing with HIV disease. There will be no "cookbook" solutions until a cure is found. For now, response to HIV disease must always combine a variety of behavioral and medical approaches.



The Early Intervention Model

The Project Inform early intervention model, published in various forms since 1987 is a true expression of a holistic approach to health. Some aspects are meant to apply beginning the first day a person learns he or she is HIV positive. Other aspects, such as an antiviral or opportunistic infection strategy, come into play at various stages of disease progression.

General Health Maintenance

- *Diet, nutrition, exercise*
- *Sleep habits, a reasonable workload*
- *Reduced alcohol and recreational drugs*
- *Health promoting behaviors*

Studies in recent years have emphasized the importance of nutrition and exercise as key steps in HIV disease. Alcohol and drug abuse at the very least have severe indirect affects because they counteract all the other steps in the model.

Supportive Therapy

- *Psychological, emotional, spiritual*
- *Stress management*
- *Empowerment, activism*
- *Balancing medicines (e.g. anti-oxidants)*
- *Philosophy of health / wellness*

No one is prepared through learning or experience to cope with a plague. No one is inherently equipped to casually accept a diagnosis of a life-threatening illness or to see that illness devastate our communities. We all need help. Some find that help in the form of psychological, emotional, or spiritual support. Most seek help in learning how to better manage the stress that is so much a part of HIV disease. Many find great strength and support through the empowerment of taking control of their own health and in taking action against the failure of government and institutions to effectively address the issue of AIDS. Such activism can take many forms, such as demonstrations in the street, volunteering at AIDS service organizations, or writing a check to support groups who take action. Even medicine has its "supportive" approaches, such as the use of anti-oxidant supplements and vitamins to help counteract some of the cellular damage done in HIV disease. Finally, many people find great comfort in exploring philosophies of medicine, such as Traditional Chinese Medicine or ayurvedic healing, or scientism. Such approaches give people a meaningful way of understanding what health is. Ideally, they complement, rather than conflict with each other. Each has something to offer and there is no one single right path for everyone. The greatest benefits come from choosing one's own personal pathway, while respecting the pathways of others.

Antiviral Strategy

- *The virus is active and replicating*
- *Viral load increases as disease progresses and has consequences*
- *The challenge: when , what, how*

The rationale for using antiviral medications is as clear or clearer today than it has ever been. But making decisions about what to use and when to begin are sometimes difficult. For a few years, the official government recommendation suggested that the choice could be made solely on the basis of a CD4+ count under 500. While the interpretation of early intervention studies such as the Concorde and ACTG 019 remain debatable, most scientists are in agreement that simply putting everyone with fewer than 500 CD4+ cells on a single drug, for an indefinite period of time, is not a rational approach. People with such counts differ widely in their needs and status, as well as in their response to therapy. For some, a CD4+ count of 500 is maintained for many years. For them, the argument for intervening with a drug might be modest or weak, since disease progression is less rapid. For others, a count of 500 is a brief stopping point between 600 and 400 or 300. For them, the argument for intervention might be much stronger based on the evidence of decline. In this sense, the t-cell trajectory (stability, improvement or decline) is more meaningful than a simple cell count.

Other factors which might influence the decisions about when or whether to use antiviral medications include mild clinical decline, such as unexplained weight loss or minor symptoms. For some people, understanding one's own general experiences with drug therapy is important. If you generally tolerate drugs well or poorly, this might predict your response to antiviral medications as well, at least on a psychological basis. Personal philosophy likewise plays a role, as some people prefer to confront disease as early as possible, while others might prefer to wait. Project Inform's philosophy is not so much to recommend any particular drug or starting time, but to encourage people to become educated about the choices, the issues, and the risks and benefits. This applies to decisions about when to begin using such drugs, when to switch, when to combine drugs, and perhaps when to give the body a rest.

Decisions about the use of antivirals will become easier over time as better and less toxic drugs become available, and as better diagnostic markers of disease progression are available to guide one's choices.

Opportunistic Infection Strategy

- *Compensate for failing immune response*
- *Goal: maximum prophylaxis with mini-*

mum number of drugs
- *Ultimately limited by drug interaction, tolerance, and resistance*

This part of the model only affects people who have suffered a significant degree of disease progression. The first risk of major opportunistic illness occurs, on average, when CD4+ counts fall below 200 (though there is some modest risk for people with minor symptoms and counts below 300). While it is critical to take action to prevent infections in this stage of progression, there are real limits to our ability to do so. The best approach is one which employs the fewest drugs to prevent the largest number of infections. See the Project Inform Guide to Opportunistic Infections for more information.

Immune System Strategy
- *Logical approach, building on the apparent temporary success of the immune system in combating HIV*
- *Goal is to support or strengthen immunity rather than fight the virus directly*
- *But much easier said than done*

Ideally, HIV disease would be completely controlled through the immune system. Unfortunately, we know that the immune response eventually fails in most people, so we know there are limits. Many approaches have been proposed for utilizing the immune system itself to combat HIV, ranging from therapeutic vaccines and cytokine therapy to magic immune-boosting potions in a bottle. One thing we know for sure is that the immune system is far more complex than anyone had imagined, so simplistic solutions, while common, are almost always misleading. While research pursues the best ways to strengthen or rebalance the immune response, everyone has the power to make the best of their immune response through simple interventions with nutritional support, exercise, and the avoidance of immune-damaging chemicals, such as alcohol and recreational drugs.

Summary

Early intervention is as alive and important today as it ever was. If anything has changed, it is the over-simplistic notion which some gave used to narrowly define early intervention as the use of a single drug. While drugs may indeed play a role in early intervention, they are only likely to help when used as part of a comprehensive life-enhancing strategy, one which understands that the body is more than the sum of its parts.

Gene Therapy

The field of gene therapy has progressed rapidly over the past three years. The first human gene therapy protocol was started in May 1989 and now several dozen protocols are in human studies for a variety of diseases, including HIV. Gene therapy, sometimes referred to *recombinant DNA technology*, is a broad term referring to the use of genetic materials. As this technology moves into clinical trials, it is important to understand the goals of each approach and how they differ.

Gene therapy may be used to alter immune system cells to make them resistant to HIV-infection and perhaps be useful for immune reconstitution. Other gene therapy approaches are antiviral approaches, which disable the virus during its life cycle in order to inhibit viral replication. Gene therapy can be used as a vehicle to deliver drugs, such as interleukin-2, a chemical which has shown encouraging results in studies being conducted through the National Institutes of Health. Gene therapy approaches may also prove useful in preventing or treating opportunistic infections associated with HIV. While gene therapy research is still in its infancy, this technology is quickly moving toward the clinic, with eight human studies in HIV currently being developed, four of which are already underway.

Immunogenetics

Immunogenetics is an effort to insert or modify genes in an effort to stimulate natural immune defenses. Viagene is testing an approach which delivers a new gene to cells which causes them to produce proteins similar to HIV itself, making them act like a vaccine in hopes of strengthening immune response against HIV. Preliminary results demonstrate the therapy to be safe, and further studies are enrolling volunteers in both Northern and Southern California. Perhaps the most important aspect of the Viagene study is that it is testing a method which directly delivers the new gene into body cells and tissue. Most other gene therapy experiments use indirect, or vector-based approaches to delivery, which is more complex.

Immune Reconstitution

A very small pilot study is about to begin at the Howard Hughes Medical Center, University of Michigan, wherein cells are manipulated outside the body with REVM10, a gene which may render them resistant to HIV-infection. If successful, this approach opens new doors to immune reconstitution. The initial study will look at cells drawn from the peripheral blood, to examine the effect of genetic manipulation on cell function and the ability of the cells to express the gene. While the preliminary study will probably not result in clinical benefit, it is ground-breaking work and will lead to valuable insights into direction for this approach to therapy for HIV-disease. Eventually this research will lead to inserting this gene into a cell which is typically found in the bone marrow, called a stem cell. Stem cells are the 'mother of all cells' and can literally mature and differentiate into all of the cells of the immune system. By inserting a gene which renders a cell resistant to HIV-infection into a stem cell, it may be possible to repopulate the immune system with an entire repertoire of cells which cannot be infected by the virus. Stem cells are an attractive target for gene therapy as they may provide the key to true immune reconstitution. Systemix, of Palo Alto, California, is developing stem cell technology as well as conducting research into gene constructs which may be useful in HIV-disease.

Drug Delivery

A unique approach to gene therapy, which combines cell therapy with immunogenetics, is being developed at the University of Washington, in Seattle. Phil Greenberg is developing a method to genetically alter cells to produce interleukin-2 (IL-2). IL-2, also known as *T-Cell Growth Factor,* is an important naturally occurring chemical, which is necessary for T-cell differentiation and development. Preliminary studies of IL-2 in HIV-disease are encouraging and suggest that as we better learn how to use the drug, it may become an important part of the armature to fight HIV. By combining cell therapy with genetic manipulation, Dr. Greenberg hopes to boost HIV immune response as well as repair some of the immune dysfunction.

Dr. Greenberg is looking at manipulating CD8+ cells, which are believed to be very important in controlling HIV. Preliminary studies involve inserting a ganciclovir-sensitive gene, often referred to as a 'suicide gene'. If CD8+ cells, expanded or manipulated outside the body, produced a potent antiviral response when reinfused, the amount of inflammation created by this response could prove dangerous, possibly causing pneumonia or serious swelling of the brain. By inserting a ganciclovir-

sensitive gene into these cells, it is possible to administer ganciclovir to destroy the cells if they create too potent of an immune response. A study of the safety and effectiveness of ganciclovir-sensitive gene insertion has enrolled its first patient in Seattle. Because CD8+ cells rely on the presence of IL-2, which is deficient in HIV-disease, the possibility of delivering a gene which will make these cells produce IL-2 is attractive. Dr. Greenberg has been working on developing IL-2 receptors which could help cells produce this chemical despite whatever immune dysfunction, caused by HIV, is creating an IL-2 deficiency.

Antiviral Approaches

Technologies which are related to gene therapy include antisense and ribozyme technologies. Both antisense and ribozymes target specific viral RNA sequences. However, antisense is being developed as a drug whereas ribozymes require a gene transfer approach. They also 'attack' the viral RNA sequences differently. Antisense drugs bind to the viral RNA whereas ribozymes chop up the viral RNA.

Antisense technology involves arranging short strands of genetic material that are targeted to bind to specific viral RNA sequences. When HIV incorporates into the machinery of a cell, it does so by binding its RNA with the immune cell's DNA, in a fashion that can be likened to a zipper. When the teeth of the zipper come together and close, the viral RNA being one set of teeth, and the cell's DNA being another, the virus is initiating the process of 'transforming' the cell into a factory for new virus. Antisense acts like a piece of gum in that zipper. By binding to one side of the 'teeth', when the zipper comes to close, the antisense has gummed up the binding area and the virus cannot attach, thereby disabling its activity. The first antisense for HIV, being developed by Hybridon, went into humans in Europe last year. Human studies of the Hybridon antisense, called GEM 91, began in spring at University of Alabama, Birmingham. This strategy hold potential for controlling many viral diseases, including those associated with HIV-disease. ISIS Pharmaceuticals recently announced that it is about to begin a Phase I/II study of an antisense for CMV. Unfortunately this entire field of research has been slowed down due to restrictions placed on its development by NIH patenting and licensing agreements.

Ribozymes, which are sometimes referred to as molecular scissors, cut viral RNA strands at selected sites. Ribozymes seek out viral particles and chop them up into bits, hopefully rendering them non-infectious and incapable of replicating. One of the problems with ribozymes is that they lose their specificity in chopping up the RNA. In test tube studies, ribozymes can get sloppy and chop up unspecified RNA, which could result in toxicities and may be dangerous. There are different kinds of ribozymes, the two most common forms being hammerhead and hairpin ribozymes. The names simply refer to the similarity of the structure of these ribozymes to a hammerhead shark and a hairpin. The first human trial of a ribozyme was approved last year, and will be a trial of a hairpin ribozyme, which was developed by Flossie Wong-Staal at the University of California, San Diego. Problems with manufacturing have delayed this study, which is now expected to begin sometime this year in Southern California.

Conclusion

Recombinant DNA technology, or gene therapy, holds great potential as therapy for HIV-disease. The field of recombinant DNA technology is still in its infancy, however, and there are many unanswered questions about its usefulness. Finding a gene construct which efficiently inhibits HIV replication or protects a cell from HIV infection is only half the battle. Getting that gene into human cells, either by injecting the genetic material directly or by packaging the gene in a virus and delivering it to the cells by injection, or infecting cells outside the body, is another challenge to optimizing gene therapy approaches. A number of non-viral delivery mechanisms are being explored in an attempt to decrease the risk of causing harm in delivering the genes to the appropriate cells in the body. How genetically manipulating cells will affect cell function is a concern which only further human experimentation will clarify. There are many unknowns and uncertainties.

Cytokines

The immune system is an intricate network of cells, which communicate through a chemical network called cytokines. Cytokines are messengers, or communicators, produced by immune system cells, and are the general mediators of immune response. Unfortunately, cytokine function is very complicated. When properly functioning, the immune system maintains a delicate balance, where extremely small concentrations of combinations of cytokines are produced by cells in order to turn on immune responses, turn off immune responses or promote the development, maturation or function of certain cell populations. Some combinations of cytokines determine the maturation of cells, while other combinations determine cell's function. It appears that some cytokines have biphasic natures - at low concentrations they produce one immune response, while at high concentrations they produce another.

There are no simple solutions, no "T-cells in a jar," no simple pathways to "boost the immune system." On the contrary, the immune dysfunction in HIV-disease is often contradictory, with some aspects of the immune system suppressed while others are over-active.

Interleukin-2

IL-2, originally called *T-Cell Growth Factor*, has been studied in both HIV and cancer for a number of years. Toxicities associated

with IL-2 include fevers, swollen lymph nodes, flu-like symptoms and increased levels of gamma interferon. Because IL-2 promotes T-cell activation, and HIV can only infect active T-cells, IL-2 also increases viral replication and therefore should be administered with an antiviral. IL-2 has been researched extensively in HIV since the early '80s. One of the earlier studies of IL-2 in HIV demonstrated that after administration of IL-2, CD4+ cell counts rose dramatically, sometimes hundreds of cells, then fell dramatically though slightly above what they had been prior to therapy. More recent study of IL-2 at the National Institutes of Health (NIH), in people with greater than 200 CD4+ cells, demonstrated substantial and sustained CD4+ cell increases in *some* study participants. The difference between the earlier study and the more recent study at the NIH was the dose and schedule of IL-2 administration. Because cells mature and develop in cycles, when IL-2 occurs naturally in the body it might be produced in varying amounts according to some type of natural pattern. Therefore, changing frequency of administering synthetic IL-2 may result in dramatic differences in the outcome of clinical studies. Similarly, in the body, IL-2 is produced in extremely small concentrations at specific locations, by specific cells. Dumping large amounts of IL-2 into a vein may be an extremely crude way to deliver the drug. Changing the dose may also alter the effect, both in toxicity as well as impact on CD4+ count. A number of trials are enrolling across the country, evaluating different doses and administration schedules. Gene therapy approaches to delivering IL-2 are being explored but are not yet in human studies in HIV. It may be possible to insert an IL-2 gene into cells so that the cells themselves are induced to produce IL-2. This may help toward optimizing the delivery and dose of this cytokine.

IL-2 is currently FDA approved for use in certain cancers and some physicians are using the drug in their practice. Because it is not approved for HIV, it may be difficult to get insurance companies to pay for it. IL-2 is also available through a number of studies across the country.

Interleukin-12

IL-12, also called *Natural Killer Cell Growth Factor*, is a cytokine primarily produced by cells called monocytes. IL-12 is has been shown to be important in promoting T-helper type 1 (TH1) immune responses (See February 1993 *PI Perspective*). TH1 cells are responsible for inducing cell-mediated immune responses, while TH2 cells are responsible for inducing antibody responses. IL-12 appears to promote TH1 responses while suppressing TH2 responses. As science seeks to understand HIV-disease and the natural immune response, cellular immune responses are increasingly being viewed as critical toward controlling HIV replication and disease progression. Monocytes and macrophages are a primary reservoir of HIV. IL-12 production might be disrupted because of a general dysfunction in immune response caused by HIV infection of these cell lines. Research into IL-12 is provocative not only because it holds the possibility of bolstering cellular responses against the virus, but also because it may correct a general immune dysfunction caused by the virus. Preliminary studies of IL-12 in animals have been reviewed by the FDA and a small phase I clinical trial is about to start at San Francisco General Hospital. While the drug has not been tested in humans, animal studies suggest there may be some neurotoxicities associated with IL-12. These were more pronounced in female primates, possibly suggesting a hormonal interaction. Women will not be excluded from early Phase I studies of IL-12, and doses studied in the trial are well below those at which they would expect side effects. Potential neurotoxic effects of the drug will be monitored carefully in the study.

Cytokine Inhibitors

While some cytokines may promote or restore immunity, some can accelerate HIV replication and are associated with disease progression. Cytokines associated with inflammation, such as IL-1, IL-6 and TNF-alpha, have been associated with increased viral replication, wasting syndrome and progression of Kaposi's Sarcoma. A number of strategies to inhibit these cytokines are currently in clinical trials. Thalidomide, once a controversial drug which causes severe birth defects if taken during the first trimester of pregnancy, is a selective and potent inhibitor of TNF-alpha. Test tube studies suggest that thalidomide has anti-HIV activity and its inhibitory effect on TNF-alpha may prove useful in managing wasting syndrome. There have been anecdotal reports of success in using thalidomide to treat HIV-related aphthous ulcers. Two studies are currently underway to evaluate the benefit of thalidomide in HIV-disease. One study is examining the antiviral and anti-TNF activity of thalidomide, while the other is examining the use of thalidomide in the treatment of aphthous ulcers. Pentoxifylline, also called Trental, is an approved drug for use in people with clotting disorders and is thought to inhibit IL-1, IL-6 and TNF-alpha. A number of studies evaluating pentoxifylline in HIV-disease are being reviewed by the manufacturer to determine if results are significant enough to warrant further study. This information should be available shortly.

In the mean time, pentoxifylline is an approved drug which can be obtained "off label." Similarly, an antioxidant called NAC may be useful in reducing TNF-alpha levels. NAC can be obtained through many Buyer's Clubs and health food stores.

As knowledge of cytokines and their functions increases, there has been a growing interest in the potential to augment or suppress cytokine production in order to control HIV-disease. The danger in manipulating cytokine response rests in our limited knowledge of the immune system and the pathogenesis of HIV. Because the immune system maintains a delicate balance that is not wholly understood, it is unclear if administering a cytokine which appears to be deficient in HIV-disease will restore an immune response, or further aggravate immune dysfunction. Understanding the best use of cytokines as therapy in terms of both frequency and dose, may be an arduous process of trial and error. An early dose escalating study of gamma-interferon was stopped because it appeared to increase HIV-replication. Subsequent study of gamma-interferon suggests that this cytokine has a biphasic nature. At high doses gamma-interferon increases HIV-replication, while at low doses it appears to inhibit HIV replication. While cytokines as therapy hold great potential in the battle against human disease, there are still many uncertainties which demand caution when manipulating immune re-