PI PERSPECTIVE

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Themes...
The IVth Conference on Human Retroviruses and Opportunistic

The fourth meeting of the Human Retrovirus Conference in Washington, D.C., in late January brought new evidence that the recent advances in AIDS treatment are producing sustained results. The short-term dramatic benefits reported from the use of triple-drug combinations and new classes of drugs have been extended over much longer periods. Similarly, some of the key questions about the depth of response – whether the new drugs effectively suppress virus in lymph tissues and other body sites – were answered positively. Perhaps most importantly, the conference helped to clarify strategies for guiding individual treatment decisions. While many questions remain unanswered, the general direction of treatment strategy has never been clearer. Even where treatment failure exists, as it surely does for many people, its causes are for the most part now understandable. This gives reason to hope that we may yet be able to solve them. The challenge of widening the success of treatment is to get people at all levels – physicians, insurers, government officials, patients and caregivers – to understand the new data and act upon it. Vested financial interests, demands for unattainable forms of evidence, lack of information and the inertia of past practices continue to loom as major obstacles to effective treatment for those with HIV.

The presence of such obstacles is especially frustrating in light of new data that treatment has begun to reduce the rates of hospitalization, new infections and death. Preliminary analysis shows that it has also reduced the overall cost of HIV treatment, despite the high cost of the drugs. This news comes at a time when only a modest percentage of infected people are able to use the new drugs in the most effective manner. The current reductions in death and disease perhaps offer only a hint of what may be possible once effective treatment is available for everyone.

Despite the positive scientific tone of the conference, the meeting was held in an atmosphere of surprisingly intense political division. More than 5000 people attempted to register to attend but only 2400 were permitted entry. Not only were some members of the HIV-infected community denied entry, but also thousands of researchers and practicing clinicians, along with a large number of people from the pharmaceutical industry. In this regard, the meeting was a return to the days when activists and physicians had to fight their way into scientific meetings. The stakes in this debate over the future nature and size of the conference are addressed in *"A Conference on the Verge of Disfunction"* on page 5.

A New Consistency

One of the most encouraging aspects of the meeting was the degree to which new research questions are producing consistent and complimentary answers:

- Reduction in viral load was consistently shown to correlate with clinical benefits – as measured by a reduction in the rate of disease progression and death (see "Virology" on page 6).
- Reduction of viral load below the lowest limit of detection resulted in the longest duration of treatment effect and the greatest suppression of resistance (see "Virology" on page 6).
- Even people with advanced disease appear to have a profound antiviral response to the better therapies.
- Two or more highly active antivirals, used for the first time, have routinely produced viral load reductions to undetectable levels in most volunteers.

In this issue

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- Reduction of viral load in the blood stream results in similar reductions in lymph tissue, vaginal secretions, and semen. These data raise difficult new questions about whether effective HIV suppression may also diminish a person's ability to transmit the virus.
- Finally, the advances make a true difference in the things that matter most – freedom from disease, suffering and death. Reports from both Europe and the United States show that rates of death, new infections and hospitalizations started a downslide beginning in early 1996, just as the new therapies became available.

This wave of consistency gives new confidence that the advances of the last year are not a fluke. It is becoming clearer as to what works and what doesn't, and this confidence should make it easier now to develop therapies that are easier to use, less toxic and less costly.

All this good news, of course, comes against the backdrop of a painful gap between study results and practical outcomes in the real world. An ever-increasing number of people do not have the option of using therapies in the idealized fashion seen in clinical trials. For them, much of the current news tells only of lost opportunities. One ray of hope is the growing understanding of why therapy fails the imminent availability of other new drugs. Armed with this knowledge, people can at least be in a better position to plan future steps along the treatment trail.

Endurance

One of the great fears researchers, physicians and patients have shared since the advent of the new therapies is that the benefits would soon diminish, as happened with the previous drugs. Some have argued that AZT promised similar dramatic benefits and a potential cure, but drug failure and toxicity quickly dashed such hopes. The comparison is deeply flawed since *no one* ever suggested that the benefits of AZT monotherapy were anything but limited and short-lived. No one spoke of "eradication" or undetectable viral load in 1987, or reported the kind of dramatic benefits seen today. The combination therapies today offer viral suppression ten to a thousand times better than those of previous therapies. The new perspective added at the Conference is that the benefits are lasting longer than most expected. While older drugs used as single agents routinely failed to suppress virus for more than a few months, the new combinations seem to be maintaining near zero levels of viral reproduction for a year or more in many people. How long "or more" means remains speculative as few people have been on the drugs for more than 1½ years.

The newest data show little or no drop in effectiveness over time – at least in those who maintain proper use of the drugs. Drugs can still fail for any of three common reasons: (1) unacceptable side effects or discomfort; (2) the daily routine proves untenable; or (3) other factors, such as poor absorption which hampers effective uptake of the drug. Frustrating as they are, such limitations help tell us what needs to be improved in the next generation of drugs. It also tells us that the health care delivery system needs to include support services to increase adherence to the difficult regimens.

Long-term data suggest that it is easier to *keep* viral load below the level of detection than it is to get to that low level in the first place. But once there, the low level of viral activity makes it easier to suppress viral resistance for long periods. One implication of this is that if drugs can be made sufficiently tolerable and easy to use, effective lifetime therapy might be achievable.

Unanswered Questions

Despite these surprisingly positive advances, few well-informed people believe that the AIDS epidemic will be over any time soon. Difficult questions remain in many areas.

One of the most striking areas of uncertainty is the degree of immune restoration people can expect in response to effective antiviral therapy. Ideally, complete suppression of HIV would permit the immune system to heal itself. This may indeed happen for some people. But it is not clear that this is possible for everyone, especially those who have already progressed to serious levels of immune deficiency. Conference reports on this were all over the map:

- Some researchers reported striking evidence of the reappearance of lost cells in the immune system, signaling at least some level of genuine immune restoration.
- Some provided case reports of people suffering from untreatable opportunistic infections which suddenly responded after starting three-drug therapies.
- Others reported the opposite: people with serious immune depression who saw large increases in CD4+ cell counts after treatment, yet experienced major opportunistic infections, suggesting that immune restoration was at best incomplete.

This lack of uniformity in immune response might seem a sign of inconsistency, but analysis suggests it is to be expected. Cell numbers are not the sole measure of the status of the immune system. Scientists talk in terms of cell numbers because they are the only simple measures we have to describe the immune system. Aside from cell numbers, there are critical tissue sites that affect immune function, such as the lymph tissue in lymph nodes, the gastrointestinal tract, the tonsils and the rectal mucosa. We know that the status of the thymus gland and bone marrow, however unmeasurable, almost certainly have a profound effect on the ability to restore normal immune responses. People differ widely in the health of these tissue and organ sites, independent of CD4+ cell counts. It should not be a surprise, then, that immunologic response to antiviral therapy will differ. The question is what to do about it. What forms of immune restoration therapy will have the greatest effect, and when will they be available? Other than continued interest in IL-2, few answers are being offered.

A few other unanswered questions:

- Will the long-term benefits now being seen hold up for another year? Two years? Four?

- Is it possible to create drugs that are easier to use, less expensive and have less long-term toxicity? The fact that we need them doesn't guarantee we can produce them.
- What will be the cost, in body and in spirit, of a lifetime regimen of multi-drug treatments?
- Why does regrowth of CD4+ cells seem to stop short of reaching truly "normal" levels in most people? Why is there so little CD4+ response in some people, despite good antiviral response? The currently popular model of HIV dynamics does not adequately explain either phenomena.
- Even if HIV is effectively controlled for a lifetime, can the immune system be rebuilt?
- When will we be able to build an effective vaccine for HIV disease?

Some of these questions can only be answered by time, while others will require much additional research. Proposed answers today are largely speculative. What is certain though, is that until we answer these and related questions, today's hope of effective therapy will serve more as a model than a reality for many of the people infected with HIV.

Societal Consequences

It is for now an accepted fact that the new advances in HIV therapy have little relevance for impacting the epidemic world-wide. Problems of cost, distribution, compliance and medical infrastructure pose enormous obstacles. Even within the US and other developed nations, optimum therapy is still being employed by a modest subset of those who need it. Additional obstacles include:

Physician and institutional education: achieving results promised by clinical trials doesn't come easily. Physicians must be retrained to think in terms of long-term strategies and to understand how the use of each new drug affects the use of others. Many of the practices considered "state of the art" just a year ago, such as starting people on two-drug nucleoside combinations like AZT plus 3TC, are now believed to be unwise. Most treatment practices still amount to little more than "serial monotherapy" in which patients and physicians leap to add each new drug as soon as it becomes available. Hospitals and medical institutions often lag a year or more behind the current state of knowledge. Institutional formularies for AIDS in managed care often seem to be written by people who don't understand current treatment science.

Patient and community reorientation: years of bad news about past therapies and drug toxicity have left many individuals and many whole communities understandably but unduly skeptical about the hope offered by the new treatments. While such skepticism may have had only modest consequences in an era of weaker drugs, today its cost can be measured in years of life lost. Anti-treatment messages are still common in many communities and cities. Overstatement of the challenges of treatment compliance and lack of support for compliant behaviors can frighten many people away from getting the treatment they need. Newsletter writers, case workers and other service providers can either act as gateways to the new knowledge and its benefits, or gatekeepers who in effect block access to treatment for others because of their own biases and outdated knowledge base. Without changed attitudes and information, vast numbers of people will fail to take advantage of important medications, even when they are technically available to all. This issue is already reaching critical proportions in the increasing volume of treatment information being provided to the patient community. A growing amount is coming from groups who, however well intended, are inexperienced in the subject.

Lack of simpler treatment regimens: while this is partially a matter of better drug formulation, it is also a matter of drug testing. The difficult regimens required today merely reflect the ways the drugs were initially tested. Additional studies, using the same drugs, may find simpler and easier ways to use them.

Inequitable distribution of Federal and State dollars: funds set aside to help pay for treatment are subject to

intense political debate within AIDS-affected communities. As long as the demand for funds to support personal treatment must compete against demand for funds to support organizational needs, support services and bureaucratic structures, some people will be treated with great unfairness.

Our AIDS service organizations and support systems of the last 10 years have largely been built to support people in the process of dying. Today, there is a growing need for services to help those newly able to go on living. The issues for many people today center around re-engaging with life: employment, paying off accumulated debt, childcare, relationships and getting square with the IRS. These can be profound challenges for people whose lives have been turned around by effective treatment. Before we heed calls to simply "downsize" our AIDS service agencies, it may be wiser to first rethink and at least partially reorient their functions.

A related point is the effect of treatment on the *transmission* of HIV. Will some HIV-infected people, invigorated by the success of their own treatment, misread scientific discussions about how this success might affect transmission? What does the phrase "undetectable viral load in semen or vaginal secretions" say to people who have been controlling their sexual practices for the last decade? Most confusing of all will be data, possible in the near future, showing that transmission rates dip in treated populations. If a "statistical reduction in transmission" is interpreted to invite "risk-free unprotected sex," surely the net rate of transmission may rise over the long term, with the added danger of transmission of drug-resistant strains. "Reduced risk" of transmission is not the same as "zero risk". Who will lead – and carry on – the community debates triggered by this imminent phenomenon?

Another risk is that the media will continue to overstate the success of AIDS treatment, leaving the public and the Congress with the view that AIDS is over or fading away. This is hardly a theoretical concern, since any reading of the last six months of the popular media suggests that this is already the case. Some of our leading news periodicals have all but pronounced the end of the epidemic in their headlines, while hiding the details in the small print. This could have disastrous consequences in terms of support for care, prevention and research programs.

In Summary

The IVth Human Retrovirus Conference signaled a consolidation of views and a growing consensus on the status of AIDS research and treatment. In that regard, it was a positive and helpful event. Yet, people are still dying, and will continue to do so. However effective and durable the new treatments are for some, their benefits elude the grasp of others. With each advance and step forward, we are left ever more acutely aware of those being left behind, those who can't pay the price of admission, those who can't tolerate the drugs, and those who are blocked by every wall society puts in their way. This is an odd time for people fighting AIDS, a time of great relief and reassurance in some ways, and a time of new fears, risks and outright danger in other ways. It is not a time to drop our guard or risk the loss of ground already gained. Renewed commitment, courage and determination must moderate whatever euphoria each of us chooses to allow ourselves. There is much work yet to be done.

Project Inform

The Basic Message

- **Get tested**, *anonymously*.
- **Learn your options** and line up your support.
- If positive: **maximize your health**, **get a complete physical, a full immune health workup** and **get *informed*!** (See the PI document *"Day One"*).
- **Get baseline CD4+ and HIV RNA tests, repeat quarterly**. Chart the trends. Women should get "gyn" exams and "pap" tests every six months.
- If the CD4+ trend is downward or already below 500, and HIV RNA above 5,000, **or** if HIV RNA is above 30,000-50,000, regardless of other factors, **optimize nutrition and consider combination antiviral treatment**.
- If viral measures do not decline below the limit of detection or at least below 5000, **consider a more aggressive antiviral regimen.**
- 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 an antiviral regimen** if not already on one and **learn about preventive treatments** against other opportunistic infections. **Learn about drug interactions.**
- If you have begun preventative therapies and your CD4+ count rises as a result of antiviral therapy, **remain on any preventative treatments you have started.**
- If CD4+ count stays below 75, **intensify monitoring,** consider prevention against MAC/MAI and CMV infections. **Learn about preventive therapies.**

A Conference on the Verge of Dysfunction

The IVth Conference on Human Retroviruses and Opportunistic Infections (HRC) was noted not only for its useful scientific content but also for the intense debate it triggered about the nature, size and makeup of the meeting itself. The conference was originally created to fill the gap left when the annual International AIDS Conference became a bi-annual event. This year, planners attempted to address some of the short-comings of the previous meetings: too much product promotion, too many concurrent events, overly large meeting sites and too many people to permit useful scientific discussion. Organizers aggressively limited participation to no more than 2400 people, specifically excluding marketing and public-relations personnel from the pharmaceutical industry and capping the number of community representatives. They argued that this would preserve the "intimate" nature of the conference and permit scientific exchange.

Despite support for some of the changes, many people found the "cure" worse than the problem. Critics, including Project Inform and almost every other interested AIDS organization, argued that there was nothing "intimate" about a meeting of 2400 people and that HIV-affected people had an absolute right to attend. HIV-affected people had not been denied access to any major AIDS meeting for the last several years. Critics were also unanimous in condemning the restrictions that denied access to thousands of practicing physicians and AIDS researchers, including many well-recognized names in science and physicians responsible for the care of tens of thousands of patients. Some also argued it was shortsighted to place severe restrictions on industry, as it alone can turn scientific insights into practical products. By making industry an unwelcome party, many feared that it would discourage participation in AIDS research. Surely, it should be possible to cut down on promotional activities without telling a key partner in AIDS drug development to stay home.

Beneath the debate, which eventually erupted in the form of a raucous protest at the conference site, was a deeper and unspoken question: exactly who is in charge of this conference and who appointed them? It has become one of the most important AIDS meetings in the world, yet it is controlled quite literally by a handful of more or less self-appointed people. While those involved are respected scientists, too much power lay in the hands of far too few people. Despite a modest number of people on a Scientific Advisory Committee and a few non-voting community representatives, four people made all the key decisions. Even their close friends described the leadership of the meeting as an oligarchy. Their preferences, views and outlook impacted every aspect of the conference. This represents a dangerous precedent, as it was clear that there was little room for even slightly dissident voices in the scientific makeup of the meeting.

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Equally troubling was the fact that members of the "Scientific Advisory Committee" were numerically over-represented in the abstracts and papers accepted at the meeting. A disproportionately high percentage of people who had two or more papers accepted were themselves members of the Committee. Another example, and a contradiction of the claimed effort to minimize industry promotion, was the acceptance of no less than eight papers about a new drug under development by Abbott Labs. The drug, at least two years away from practical application, had not yet been tested in a single HIV-infected person and hardly warranted major attention. How could such a drug be so vigorously promoted? Easy - Abbott Labs was the sole pharmaceutical company with a representative on the "Scientific Advisory Committee." In a related example, the same Committee doled out a series of special honorary lectures largely to members or close associates of the Committee itself.

Over the last few years, more and more of the large and small scientific conferences on AIDS have come to be controlled by this same small group of people. Such a trend is not in the best interests of science or the patient community. There is plenty of room for small private conferences that encourage intense scientific discourse. There is also room for large, inclusive conferences. But there should be no room for a major national conference in which a narrow faction of the scientific community overly influences both the program and the makeup of the audience. Project Inform urges that responsibility for managing this important conference be transferred to an independent party, such as the National Institutes of Health or the Institute of Medicine, where at least it will be subject to broad-based oversight and public supervision.

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Viral Load and Progression

The excitement raised by the results from recent protease inhibitor studies have been tempered by the gaps in knowledge on how to best use these therapies as well as concerns about drug resistance. Results from several new studies are slowly filling the gaps in knowledge, sometimes with surprising data.

Viral Load in Plasma and Other Reservoirs

A recent study showed that HIV RNA levels in semen strongly correlate with RNA levels in plasma (blood). Semen viral load was not necessarily higher in people with lower CD4+ counts. This study found that there was no relationship between viral load in semen and disease progression. Both semen and plasma viral load decreased dramatically after starting antiretroviral therapy.

Another study looked at viral load in vaginal secretions and found that HIV RNA levels in vaginal secretions fell in 13 of 14 women who started therapy. Five women who did not take antiretroviral therapies had no reductions in RNA levels in their vaginal secretions. When three of the women stopped their therapies, the RNA levels promptly increased.

Confirming earlier European results, a study at the University of Minnesota showed a correlation in viral load changes in the plasma and lymphoid tissue. Lymphoid tissue was obtained from the tonsils of people who were treated with AZT + 3TC + ritonavir. Participants had a 2.5 to 2.8 log drop in plasma viral load after 24 weeks of therapy. The 10 lymph tissue samples studied so far had an average 3.4 log drop in HIV RNA levels after 24 weeks. Generally, lymphoid tissue has about 2 logs more RNA than plasma.

Another study looking at lymphoid tissue, but from a layer of cells (mucosa) in the rectum, showed similar results. This study found that the number of HIV RNA copies in this kind of lymphoid tissue fell dramatically after one week of potent 3-drug combination therapy. Perhaps most importantly, this study opened a new and perhaps less invasive way to study lymphoid tissue.

Resistance

A retrospective study of people with HIV in Iowa reported that the HIV protease enzyme can develop mutations associated with drug resistance, *even prior to the administration of protease inhibiting drugs*. The study tested blood samples taken between 1993 and 1996 before any of the participants had used protease inhibitors. Nevertheless, 30% had naturally occurring mutations in the protease enzyme. More significantly, 26% had mutations associated with resistance to the protease inhibitors and 23% harbored virus that had multiple mutations in the protease enzyme. This may partially explain why some people get a less durable or no response at all when they start protease inhibitor therapy. Somewhat surprisingly, 10 people who had these naturally occurring mutations in the protease enzyme still had good results on a 3-drug therapy (2 reverse transcriptase inhibitors and one protease inhibitor). Most of the participants had undetectable viral loads after 6 months of therapy.

In Memory

We dedicate this issue of the *PI Perspective* to:

Richard Smith
Tyrone D. Stone
Ron Wilmot

and all the others for whom the system did not move fast enough or try hard enough.

Their memory lives on in the work that remains.

Another study looked at 23 samples from people who had failed indinavir (Crixivan), saquinavir (Invirase) or ritonavir (Norvir) to determine if they would be resistant to nelfinavir (Viracept). Generally, people who had developed only one mutation in the protease enzyme remained sensitive to nelfinavir; but people who had multiple mutations were resistant and did not benefit from the drug. The data, however, suggest that some of the people "failed" the other drugs for reasons other than true resistance, as resistance to ritonavir and indinavir takes more than one mutation (a single mutation, though, may produce resistance to saquinavir). It is uncertain whether people who develop true high-level resistance to ritonavir or indinavir will respond to nelfinavir.

Duration of Therapy Effects

A critical question for most people is how long the effects of protease inhibitors will last. Preliminary results were presented from a study to determine whether viral load can predict the duration of viral suppression during protease inhibitor therapy. The durability of treatment response was defined as the time from starting therapy to the time HIV RNA levels increased by 0.3 log. Surprisingly, the durability of response *was not* predicted by baseline viral load, baseline CD4+ cell counts, magnitude of viral load drop or magnitude of CD4+ cell increase. Instead, only the lowest HIV RNA value (nadir) achieved on therapy could predict the length of response. This study also found that viral levels must be undetectable (less than 200 copies of HIV RNA) to prevent indefinitely or significantly delay the emergence of resistant virus. The specific results showed that people whose viral load did not fall below 1,000 copies of HIV RNA had a response of only 60 (+/- 26) days. People with a lowest level of 200-1,000 copies of HIV RNA had a 102 (+/- 25) day response and people with a lowest level of fewer than 200 copies of HIV RNA had a response of 207 (+/- 81) days. These data answer a critical question faced by patients and physicians who wondered if it was sufficient to simply lower the viral load, or whether it was necessary to suppress it below the limits of detection. The data demonstrate that the effect of treatment will be short lived when therapy fails to fully suppress viral replication. The implication is that therapy should be aggressively applied to whatever degree is necessary for full suppression (within the limits of tolerability). This would require more routine monitoring of HIV RNA levels,

especially for people just starting or switching antiretroviral therapy, so that modifications in their treatment regimens can be made, if necessary. These new results suggest that for some people, four- and possibly five-drug regimens will be necessary to suppress HIV RNA levels below the limit of detection in order to get the maximum benefit from therapy.

These data also suggest that recent guidelines issued on viral load use by the International AIDS Society USA may already be outdated. Those widely cited guidelines suggest that a treatment has failed when viral load returns to or is within 0.3 to 0.5 log of pretreatment levels. This study demonstrates that waiting for 'treatment failure' to occur is too late and modifying or changing treatment regimen should be considered when HIV RNA levels increase by 0.3 log from the lowest level.

A study of 1330 people from seven different ACTG (AIDS Clinical Trials Group) studies show that both HIV RNA levels and CD4+ cell counts are important variables in determining disease progression. Additionally, this study found that HIV RNA level changes and CD4+ cell count changes taken together are a better indication of therapy success than either measure alone. A particularly interesting finding was that the benefit of reductions in HIV RNA levels does not depend on the baseline HIV RNA level. Rather, the benefit of a therapy depends on the amount of reduction, regardless of baseline HIV RNA levels. For example, a one log reduction from 150,000 copies of HIV RNA to 15,000 copies reduces the relative risk of disease progression by the same amount as a one log reduction from 50,000 copies of RNA to 5,000 copies.

ACTG 320: Last of the Body Count Trials?

In what was hopefully the last trial of its type, ACTG 320 was halted early when one of its treatment regimens proved clearly superior to the other. The study concluded that when people with advanced disease and a prior history of antiviral treatment received either AZT + 3TC or AZT + 3TC + indinavir (Crixivan, the Merck protease inhibitor), those who received the 3-drug combination fared better in every way. They lived longer and were less likely to progress to AIDS, at no cost in increased toxicity. The triple therapy resulted in about a 50% reduction in death and progression to AIDS-defining infections over an average 38-week followup time. The study was stopped earlier than planned when analysis showed the advantage for the 3-drug regimen. All 1156 participants started with CD4+ cell counts under 200, (average CD4+ cell count was 89) and 38% had CD4+ cell counts below 50. Eighty-three percent were male, 17% female, 27% black, 19% Latino and all had prior antiviral experience but were new to 3TC and indinavir. Results are shown in **Table 1.**

Table 1: ACTG 320

	AIDS or death			Death		
	All	<50 CD4+	>50 CD4+	All	<50 CD4+	>50 CD4+
AZT+3TC	63 (18%)	44 (34%)	19 (9%)	18 (5%)	13 (9%)	5 (2%)
AZT+3TC+ indinavir	33 (9%)	23 (16%)	10 (4%)	8 (2%)	5 (3%)	3 (1%)

Ethical and Scientific Concerns

The outcome of this study surprised no one, since at the time it was initiated, other studies had already shown the superiority of the 3-drug regimen compared to 2-drug nucleoside combinations. The people receiving the 2-drug regimen were, in the view of many, doomed to an inferior outcome. The question is: why was such a study done? Many activists, researchers, physicians and even employees of the companies involved protested bitterly from the outset that this study would result in an earlier and higher death rate for those receiving AZT + 3TC. Supporters of the study, mostly the FDA and a few medical conservatives who somehow got their way, argued that the clinical and survival benefits of the 3-drug combination had not yet been proven in a randomized, controlled clinical trial. Technically, this is true, but irrelevant to anyone except those who refused to acknowledge earlier studies showing that the triple combination produced dramatically better and longer-lasting reductions in viral load and improved CD4+ counts. Other studies had already shown that improvements of this type were directly associated with major improvements in survival and delayed progression. Unable or unwilling to put the two types of studies together and draw reasonable conclusions, the study's supporters pressed their demand for a body count before they would accept what had become obvious. In the end, the trial was halted when volunteers began leaving in droves and researchers were having nightly pangs of conscience as they saw the body count rise. A hastily called analysis reaffirmed what was already known about the superiority of the triple therapy and the study was halted, albeit with an excess of dead bodies and people who had progressed to AIDS.

Some of the brave but unwitting volunteers who participated paid the price with their lives, while others are left with perhaps irreversible immune suppression. In their honor, we must be certain that neither the FDA's traditions nor the doubts of scientists who cannot reason will ever again be valued over lives of people. The time for studies whose outcome is measured in bodies is over in this epidemic. It has long been over.

Antiviral Update

Reports from the IV Conference on Human Retroviruses and Opportunistic Infections in Washington, DC, in January 1997 continued to present the success of 3-drug combinations for the treatment of HIV. These combinations seem, in some instances, to restore the immune system sufficiently to overcome some infections. These new results also suggest that triple combinations that include a protease inhibitor can suppress viral replication for sustained periods in people with advanced HIV disease. This indicates the vital importance of developing a long-term treatment strategy for the use of these antiretroviral drugs.

Updates from Previously Reported Studies

Results continue to be encouraging from the Merck 035 study. The study enrolled people with CD4+ cell counts ranging from 50 to 400 who had used prior AZT therapy. They received AZT + 3TC, indinavir alone or AZT + 3TC + indinavir. The results for people receiving the 3-drug combination are shown in **Table 1:**

Five people receiving the 3-drug combination had lymph node biopsies to look for viral RNA. Two had fewer than 20 copies of HIV RNA and were HIV antibody negative in peripheral blood and lymph node cultures. But 50-100 copies of HIV RNA were detected in the lymph nodes of two others. This measure, however, remains "below the limit of detection" used in most other studies.

Table 1: AZT + 3TC + Indinavir

Time	% of patients with HIV RNA copies below 500	50	Median viral load drop
24 wks	27 of 30 (90%)	20 of 29 (69%)	2.2 logs
36 wks	23 of 29 (79%)	22 of 29 (76%)	2.0 logs
52 wks	23 of 28 (82%)	21 of 27 (78%)	2.3 logs
68 wks	18 of 21 (86%)	10 of 14 (71%)	N/D

N/D=Not Determined at this time.

Ritonavir + Saquinavir: Similarly, results from a study comparing different doses of ritonavir and saquinavir continue to indicate that this combination may be an option for people who have cycled through the nucleoside analogues. The study enrolled 141 people with CD4+ cell counts between 100 and 500, who had not been on previous protease inhibitor therapy. The results after 24 weeks (20 week results in parentheses) are shown in **Table 2:**

New Drugs and Combinations

DMP-266 + Indinavir: Some encouraging results have been reported on the use of DMP-266 (a non-nucleoside reverse transcriptase inhibitor, or NNRTI) in combination with indinavir (Crixivan). The thirty participants had CD4+ cell counts between 100-500 and HIV RNA levels above 20,000 who had been either previously treated with nucleoside analogue therapy or were naïve to this form of therapy. All received indinavir alone for two weeks and were then assigned to receive either DMP-266 + indinavir or continue on indinavir alone. The laboratory used a very sensitive viral load test that measured down to zero copies of HIV RNA, creating an opportunity for a larger "log reduction" than is reported in most other studies. Therefore, the results were reported in two ways. When the viral load reductions were based on the values reported by the laboratory, people using the combination had a 4.1 log drop after 24 weeks compared to a 2.2 log drop for those on indinavir alone. The other analysis described anyone whose viral load fell below 400 copies of HIV RNA as having an average of 200 copies. This more conservative method reported people using the combination as having a 2.4 log drop after 24 weeks compared to 1.5 log drop for those on indinavir alone. At 24 weeks, 82% of the 21 people on the combination had fewer than 400 copies of HIV RNA compared to 38% of the 9 people using indinavir alone. Both groups had about 100 CD4+ cell increases after 24 weeks. Side effects were mild to moderate, including headache, rash and diarrhea. Using either analysis, this is very impressive data, roughly equal to the best data seen from most 3-drug combinations.

Table 2: Ritonavir + Saquinavir

Group	VL drop	CD4+ gain	% below LD
400 RTV+ 400 SQV*	>3 logs	100	90
600 RTV+ 400 SQV*	>3 logs	110	80
400 RTV+ 400 SQV**	(>3logs)	(120)	(85)
600 RTV+ 600 SQV*	(>3 logs)	(75)	(65)

VL=Viral Load ( )=data at 20 weeks
LD=Limit of detection, 500 copies RNA
* =2x daily ** =3x daily

1592U89: Results with 1592U89, Glaxo Wellcome's nucleoside analogue, continue to show promise. People received 1 of 4 dose regimens of 1592 (200 mg 3x daily, 300 mg 2x daily, 400 mg 3x daily or 600 mg 3x daily). After 4 weeks of receiving 1592 alone, people either continued 1592 alone or added AZT for 8 more weeks. At the end of the initial 4 weeks, people had a 1.5 to 2.2 log drop in HIV RNA and an increase of 79 to 127 CD4+ cells. There were no significant differences between the dose groups, perhaps due to the small number of people using each dose. After 12 weeks, 22% of those using 1592 alone had viral load below the limit of detection (fewer than 400 copies of HIV RNA) compared to 64% of those using the combination. About 60% of the people who received 1592 alone for 12 weeks developed a mutation that may confer resistance to 1592. Only 13% of those on AZT + 1592 developed such a mutation. One interesting observation was that when people with a 1592-associated resistant mutation stopped taking 1592, the mutation disappeared. Whether the resistant mutation is truly "gone" or simply much harder to detect is unclear.

141W94: Some preliminary results show potent antiviral activity from the combination of 141W94 (the Glaxo Wellcome/Vertex protease inhibitor also known as VX 478) and the new Glaxo Wellcome nucleoside analogue

drug 1592. After 4 weeks, the maximum median viral load drop was 2.1 logs and 71% of the participants had a viral load below the limit of detection (fewer than 400 copies of HIV RNA). Additionally, a 60 to 125 CD4+ cell increase was observed. Two factors making the results more impressive than they might sound are that no one knows the ideal dose of either drug, and in most similar studies, the maximum drop in viral load isn't seen until 16-24 weeks.

MKC 422: Triangle Pharmaceuticals' MKC 422, a new nucleoside analogue compound shows good activity. MKC 422 behaves like a non-nucleoside reverse transcriptase inhibitor. Participants on low doses had only a slight drop in HIV RNA levels, which soon rebounded. The highest dose group studied received 500 mg once a day, still a modest dose level compared to most drugs. Participants in this dose group had a maximum 1 log drop in HIV RNA, which is quite impressive given that it was used as a single agent and no one really yet knows what the ideal dose will be. There has been no significant impact on CD4+ cell numbers seen to date. Higher doses of the drug are still being studied.

Hydroxyurea: A study conducted in Switzerland enrolled 142 people with CD4+ counts between 200 and 500 who received ddI + d4T or ddI + d4T + hydroxyurea. Most of the participants had received no previous antiretroviral therapy. Results after 12 weeks are shown in **Table 3:**

Researchers believe that the modest CD4+ cell count increase among people receiving the triple combination is due to the hydroxyurea, which can cause temporary, reversible suppression of lymphocyte production. The impact of the lower CD4+ cell count increases is not known but hydroxyurea may still represent an option for lowering viral load when other approaches fail.

Table 3: ddI + d4T + Hydroxyurea

Group	VL drop	CD4+ gain	% below LD
ddI + d4T	1.8 logs	91	32
ddI+d4T+HU	2.2 logs	10	55

VL=Viral Load
LD=Limit of detection,500 copies HIV RNA

d4T + 3TC: A French study, known as ALTIS, showed that d4T + 3TC may be a very powerful combination and may be useful as part of a 3-drug combination. ALTIS 1 enrolled 42 people who had not been on any prior antiretroviral therapy, while ALTIS 2 enrolled 41 people with prior AZT, ddI and ddC experience but who had never used d4T and 3TC. If participants still had viral load above 3,000 HIV RNA copies after six months, ritonavir was added to their combination. Otherwise, they continued on the d4T + 3TC combination. Results are shown in **Table 4:**

d4T + 3TC did not show the rebound in viral load seen in studies of AZT + 3TC. In ALTIS 1 baseline viral load was the only factor that correlated with response (viral load and CD4+ cell counts). In ALTIS 2, people who had only used single drug therapy fared better than those who had used multiple drugs and combinations. These data suggest that d4T + 3TC is at least as active as AZT + 3TC; good news for people who cannot or do not wish to use AZT. However, most researchers still believe that it makes more sense to initiate therapy with a 3-drug combination, which includes a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. This is because none of the 2-drug nucleoside combinations seems able to reduce viral load below the limit of detection in most users. When such a combination routinely fails to reach this level of suppression, it is bound to fail over time due to the development of resistance, thus wasting the two drugs for only a short-term, limited benefit.

Table 4: ALTIS 1 and 2

Group	Max. VL drop	VL drop @24 wks	Max. CD4+ gain	% below LD
ALTIS1	2 logs	1.66 logs	108	21%
ALTIS2	1.4 logs	0.55 logs	46	5%

VL=Viral Load
LD=Limit of detection, 200 copies HIV RNA

However, when the two drugs are used in 3-drug combinations with a potent protease inhibitor most users see their virus levels fall below the limit of detection, which better protects all three drugs against resistance.

Preliminary results from the AIDS Clinical Trials Group (ACTG) study 193A show that 3-drug combination therapy was better than 2-drug combinations or alternating therapy in delaying disease progression and prolonging survival. One thousand three hundred and fourteen people with fewer than 50 CD4+ cells took part. They received AZT alternating with ddI, AZT + ddC, AZT + ddI or AZT + ddI + nevirapine (Viramune). Results are shown in **Table 5:**

The triple combination was superior to the alternating regimen and AZT + ddC in delaying disease progression and prolonging survival. There was no significant difference between the triple combination and the group that received AZT + ddI.

Table 5: Double vs. Triple Combinations

Group	# deaths	Median survival (wks)
AZT alt. ddI	148	100
AZT + ddC	142	97
AZT + ddI	128	109
AZT + ddC +	118	112

Advanced Disease Studies: A small pilot study conducted in Canada reported encouraging news for people who have been on extensive combination antiretroviral therapy. Twenty-one people with fewer than 50 CD4+ cells, who had been on combination therapy received indinavir + nevirapine + 3TC. After 20 weeks on this 3-drug combination, people had an average 3 log reduction in viral load, 100 CD4+ cell increase and 400 CD8+ cell increase. Perhaps even more encouraging, 60% of the participants had viral load reductions below the limit of detection (fewer than 500 copies of HIV RNA). Fifteen percent had viral load reductions below detection even by the ultra sensitive PCR (polymerase chain reaction test) which measures down to 20

copies of HIV RNA.

Two other studies showed encouraging data for people with advanced disease. The first enrolled 32 people with fewer than 250 CD4+ cells, who had viral loads greater than 5,000 copies or evidence of disease progression despite 4 months of 3-drug therapy (2 nucleoside analogues and a protease inhibitor). They received ritonavir (600 mg twice daily) + saquinavir (400 mg twice daily) + two nucleoside analogues. The results are shown in **Table 6:**

The second study offered more encouraging news. Three hundred and twenty people with fewer than 50 CD4+ cells (the average was 17 CD4+ cells) and who had been on prior nucleoside analogue therapy (except 3TC) received AZT + 3TC, indinavir alone or AZT + 3TC + indinavir. The results after 24 weeks of study are shown in **Table 7:**

Commentary

Table 6: Combination Therapy in Advance Disease

after...	VL drop	CD4+ gain	% below LD
4 wks	1.7 logs	42	53
12 wks	2.2 logs	64	97
16 wks	2.2 logs	72	93

VL=Viral Load
LD=Limit of detection, 400 copies HIV RNA

The encouraging results from these studies in people with advanced disease indicate, more than ever, that 3TC should only be used as part of a 3-drug combination. It should not be 'wasted' as part of a 2-drug combination where there is not sufficient antiviral activity to effectively suppress the virus, resulting in the development of resistant strains. Other results also indicate that 3-drug combinations provide better and more sustained antiviral activity, which also delays the development of resistance.

Table 7: Combination Therapy in Advanced Disease

Group	Median VL drop	Median CD4+ gain	% below LD
AZT + 3TC	0.2 logs	0	0
IND alone	0.15 logs	65	2
3-Drug	2.2 logs	84	65

VL=Viral Load
LD=Limit of detection,500 copies HIV RNA

Other reports show that people who start protease inhibitor therapy with low CD4+ cell counts (fewer than 100 cells) and get good CD4+ cell responses are still at risk of developing opportunistic infections (OIs). Researchers recommend that people in this situation continue to take their OI prophylaxis (preventative) therapies.

The preliminary results on the new generation of nucleoside analogues, non-nucleoside reverse transcriptase inhibitors and protease inhibitors indicate that they offer a significant advantage over the current generation of drugs. Generally, they are significantly more potent, require less frequent dosing, do not have food restrictions and appear to be active against resistant strains of virus. These new therapies will provide new combination options for people who have already used or are intolerant to the currently available therapies. Project Inform is negotiating with the developers of these new therapies to establish expanded access programs.

More on Protease Inhibitor Interactions:

No significant drug interactions between nevirapine and ritonavir have been noted.

Indinavir increases saquinavir (current formulation) levels by 6-fold and the enhanced oral formulation (EOF) of saquinavir by

AZT During Pregnancy

The NIH recently held an independent panel to assess data from two studies of AZT toxicity to mouse fetuses and whether this new data had implications for AZT use in pregnant women. AZT is recommended for use in late stage pregnancy and in newborns because an earlier study showed it reduced the risk of mother-to-child transmission by 2/3. The panel concluded the benefits of AZT in preventing perinatal transmission outweigh any risks of AZT leading to cancer in the child.

A new National Cancer Institute (NCI) study showed that very high daily doses of AZT given in the last trimester, increased in the number of liver, lung and reproductive tumors several-fold over the life of mouse offspring. The AZT dose was very high, the maximum the fetus could survive. A study by AZT's manufacturer, showed other results. This study used clinically relevant doses (1/12 to 1/50 those in the NCI study) and showed no greater rsik of tumors except in one group of offspring receiving AZT over their entire lifetime. Researchers acknowledged that it is unknown if this mouse model can predict carcinogenic effects in humans. There are no reports of such tumors in children.

The panel concluded that the benefits of AZT clearly outweigh its carcinogenic risk. The panel stressed the need to counsel HIV-infected pregnant women on the benefits and risks of AZT and recommended follow-up of children exposed to AZT *in utero* to assess the long-term effects of therapy used during pregnancy.

While the studies provide no basis for alarm about recommendations for AZT use to prevent perinatal transmission, they stress the need for safer, more effective treatment for pregnant women. Project Inform has long noted that if AZT can produce a 2/3 drop in perinatal transmission, then new therapies should be more effective, perhaps stopping transmission altogether. Studies using such combinations should be a high priority for AIDS research.

Nelfinavir At Six Months

Nelfinavir (Viracept) is the newest protease inhibitor, and was approved by the Food and Drug Administration (FDA) in mid-March as long awaited results from a few nelfinavir studies became available. Preliminary results show promising activity for the combination of AZT + 3TC + nelfinavir in treatment-naïve populations. Almost 300 people who had received no prior antiretroviral therapy participated in this study. The study had no CD4+ cell entry criteria and thus allowed people with low CD4+ cell counts and high viral loads to participate. Participants received AZT + 3TC + placebo or AZT + 3TC + nelfinavir (either 500 or 750 mg three times daily). The study allowed people in the placebo group to add nelfinavir if their CD4+ cell counts or viral loads returned to pre-study levels and allowed people receiving nelfinavir to change their other antiviral therapy. The results for all participants after 24 weeks of the study are shown in **Table 1:**

Comparing the 500 and 750 mg nelfinavir groups shows that people who entered the study with HIV RNA levels greater than 100,000 fared better on the higher dose. Of the people with viral levels above 100,000 HIV RNA copies, 80% receiving the combination with the higher nelfinavir dose saw reductions in viral levels below the limit of detection, compared to 45% receiving the triple combination with the lower nelfinavir dose and 5% of people receiving the AZT + 3TC combination. Nelfinavir was generally well tolerated. The major side effect reported was diarrhea, affecting 12% of people on the lower dose and 19% of people on the higher dose.

Table 1: Adding Nelfinavir

Group	VL drop	CD4+ gain	% below LD
AZT + 3TC	1.38 logs	104	20
AZT + 3TC+ 500 NFV	2.32 logs	161	68
AZT + 3TC+ 750 NFV	2.48 logs	151	80

VL=Viral Load
LD=Limit of detection, 500 copies HIV RNA
Represents all HIV RNA levels at entry

Nelfinavir in Children

Preliminary results were reported from a study looking for the appropriate dose of nelfinavir in children. This study found that a 20-30 mg/kg dose, taken three times daily, produced roughly the same nelfinavir blood levels in children as 500-750 mg three times daily in adults. Some very preliminary results show that the children respond well to nelfinavir, with about a 2 log reduction in viral load after 4 weeks of nelfinavir as a single agent therapy. Adult studies show over 50% of people develop resistance when a protease inhibitor is used alone, so this is probably not a wise use of the drug. The sponsor of the drug, Agouron Pharmaceuticals, should be commended for initiating pediatric trials early in the development of this drug and for making the drug available to children on an expanded access basis. In this regard, Agouron has clearly raised the standard above the behavior of other companies developing protease inhibitors and AIDS drugs in general.

Long-Term Strategies

A key question facing physicians and their patients is just when, where and how to use nelfinavir in the overall mix of antiviral therapies. Unfortunately, the limited number of clinical trials with this drug presently makes it almost impossible to answer this question precisely. Nelfinavir has a somewhat different resistance pattern than other protease inhibitors and may be less toxic in some ways. Although its most common side effect, diarrhea, occurs in a relatively high percentage of users (from 15 to 26% in studies), the severity of the side effect is generally modest. This observation, however, must be tempered by the fact that the drug has still only been tested in a relatively small number of people for a modest period of time. As the resistance pattern for nelfinavir seems different from the other protease inhibitors and this might make it possible to switch to ritonavir or indinavir successfully even after acquiring resistance to nelfinavir. Resistance to nelfinavir does not appear to convey automatic cross-resistance to the other drugs. Together, these two properties of moderate side effects and a different pattern of resistance might make nelfinavir a good choice as part of a first-line combination therapy. For now, this is only a theoretical advantage as it has not been tested to any significant degree in a clinical trial.

One possible conflicting characteristic, however, is that nelfinavir might not be as potent as indinavir or ritonavir, at least at the currently recommended doses. Many researchers believe that the most potent drugs should be used first and that nelfinavir would be used as backup if the other drugs cannot be tolerated or fail. But the drugs' possible lack of cross resistance only works one way – when nelfinavir is used first. The most common mutations which lead to high level resistance to the other protease inhibitors are likely to cripple nelfinavir as well. Thus, physicians may have to weigh the possible advantages of a favorable pattern of resistance and toxicity against the disadvantages of a possibly lower dose. Even this point is not clear, however. While the drug is decidedly more potent than the standard version of saquinavir, it may only be slightly less potent than ritonavir and indinavir. The question is – how potent is potent enough? A series of clinical trials comparing nelfinavir to and combining the drug with indinavir and ritonavir are currently in the planning stages and these trials should help answer these questions.

One other advantage of nelfinavir is that it can be taken with food, so it may be easier to use.

Agouron Pharmaceuticals, the developer of nelfinavir, has filed for FDA approval of nelfinavir for children and adults. This is the first time that a developer of an HIV protease inhibitor has sought simultaneous approval for both children and adults and we applaud Agouron for this effort. However, for the first time with any HIV drug, nelfinavir will not be reviewed by the Antiviral Drugs Advisory Committee (ADAC) of the FDA or at one of the committee's public hearings. The FDA believes they have enough data to approve the drug without the input from outside advisers or the public. Project Inform, along with other advocacy groups, feels this is unwise. It sets a bad precedence as the ADAC usually gives useful advice to the FDA, and HIV-affected groups provide an important community perspective during public testimony. Additionally, the hearings provide a useful forum for other companies developing therapies to get a feel of where the FDA and the ADAC is heading. Nelfinavir and should be available in drug stores shortly.

In conclusion, these data help to put nelfinavir into the picture of treatment options. The best dose for adults seems to be 750 mg, 3x daily. The incidence of diarrhea was only slightly higher among those receiving this higher dose and the better potency may be a reasonable tradeoff. We really do not know if this is the optimum dose because so little research has been done on higher doses; a 1000 mg dose might bridge the potency gap. Also, lack of data for long term use makes us wonder if the current doses might lead to resistance. The dose of nelfinavir in children equivalent to the adult dose seems to be 20-30 mg/kg 3x daily.

Nelfinavir and ritonavir were approved by the FDA for children in mid-March. Nelfinavir is also approved for adults.

Nelfinavir is easier to take than either indinavir and ritonavir. Unlike indinavir there are no food restrictions to struggle with, and unlike ritonavir, the drug does not need to be refrigerated and does not have the drug interaction problem associated with ritonavir.

Drug Interactions with Nelfinavir

Some important information on interactions between nelfinavir and other commonly used drugs have recently been made available:

- Nelfinavir increases saquinavir (Invirase) levels by 4-fold and saquinavir increases nelfinavir levels by 18%
- Nelfinavir increases indinavir (Crixivan) levels by 51% and indinavir increase nelfinavir levels by 83%
- Nelfinavir increases ritonavir (Norvir) levels by 9% and ritonavir increases nelfinavir levels by 152%
- Nelfinavir increases rifabutin (Mycobutin) levels by 3-fold and rifabutin decreases nelfinavir levels by 32%
- Rifampin decreases nelfinavir levels by 82% and therefore these two drugs should not be used together
- Ketoconazole increases nelfinavir levels by 35%
- Nelfinavir decreases ethinyl estradiol (oral contraceptives) levels by 50%
- Nelfinavir should not be used in combination with terfenadine (Seldane)

Pediatric Update

Drug development and data on using antiretroviral therapies in children often lags behind that for adults. Data are just now emerging on studies of protease inhibitors in children. The studies still required children to take single drugs for long periods, despite the evidence from adult studies showing this is improper use of these drugs. Many children now have resistance to the drugs, which may result in newer protease inhibitors having less effect for them.

One study looked at AZT + ddI + ritonavir (Norvir) in 40 children aged 6 months to 18 years. It was designed to find the optimal ritonavir dose, and the children received 250, 300, 350 or 400 mg/m^2 of ritonavir oral formula for 12 weeks and then added AZT and ddI. Most of the children had been on previous antiretroviral therapy. There was no significant difference in viral load reduction between the ritonavir doses, with an average peak reduction of 1 to 2 logs. However, the children on the three lower doses saw their viral loads rise back toward pre-study levels at the end of the 12-week monotherapy phase, implying that the lower doses were inviting development of drug resistance. Only those using the highest dose had a drop in viral load at 12 weeks.

Adding AZT + ddI resulted in a temporary small drop in viral load for the children on the 3 lower ritonavir doses. The higher dose group continued to have sustained viral load reductions after starting AZT + ddI. Children on all four ritonavir doses had about a 100 CD4+ cell increase with another small bump after adding AZT + ddI. Intolerance to ritonavir forced four children to leave the study and three had elevated liver enzymes. Based on these data, the recommended dosing schedule for ritonavir in children is to start with 250 mg/m2 twice daily. The dose should then be increased by 50 mg/m2 increments every 2-3 days up to the maximum dose of 400 mg/m2 (or the adult dose of 600 mg 2x daily).

The initial 12-week monotherapy phase seems hard to justify in light of known adult data. It is unfortunate for

Suggestion for minimizing ritonavir taste problems for children...

Before: Give the child peanut butter to coat the mouth, or a lifesaver. The lifesaver appears to 'stun' the taste buds and the kids don't recognize the bad taste as much.

After: Give the child something that tastes good to wash out the aftertaste of the suspension.

the children involved in these studies that the same lessons had to be relearned at the expense of their ability to benefit from the drug and other protease inhibitors. Institutional Review Boards, drug companies, researchers and the FDA - who approved this study - need a few lessons in current antiviral strategy and a review of Ethics 101.

Another study, AIDS Clinical Trials Group (ACTG) study 240, enrolled 216 children who received AZT or d4T. The study started in 1993 and was open to children aged 3 months to 6 years, who had symptoms of HIV disease and less than 6 months of prior antiretroviral therapy. The study showed children using d4T gained more weight and lost fewer CD4+ cells than those using AZT.

One small 3-drug study showed long-term suppression of HIV in two children. Six children received AZT + ddI + nevirapine (Viramune). Five had good viral load reductions, but three of them saw their viral load rise to pre-study levels. The other two children (who were twins) sustained viral loads below the limit of detection (fewer than 400 copies of HIV RNA). One continues to have viral load below detection after 18 months (at most time points, she had fewer than 20 copies of HIV RNA). Both no longer produce HIV antibodies and seem to have lost HIV-specific immune response, suggesting the possibility of true eradication, beyond anything reported in adults. HIV DNA (as opposed to the RNA detected by commercial tests) has been detected in the twins throughout the study, though only at low levels. There is no consensus on what the HIV DNA means. Some researchers think it shows the virus is present and capable of growing; others think that the DNA is debris that cannot generate new infectious virus. Only time and study will answer this question. The other twin, a boy, also had a viral load below the limit of detection (usually fewer than 20 copies of HIV RNA). However, after 16 months he saw a slight viral rise (1000-1700 copies of HIV RNA) and was switched to AZT + 3TC + ritonavir. His viral load has fallen again, and both remain on therapy.

The studies support the belief that children, like adults, should be treated with the most potent combination treatment regimen available. Nelfinavir and ritonavir were approved by the FDA for children in mid-March. Nelfinavir is also approved for adults.

Glaxo 1592: A Call for Access, A Call for Caution

Glaxo Wellcome's new nucleoside drug, GW1592, purports to be the most potent drug of its type. Its most critical role, at least initially, may be to serve as an alternative, new nucleoside for people already failing other new drugs or who need it to make effective use of combination therapy. It is critical that Glaxo make the drug available on expanded access as soon as possible. So far, the company has announced plans for a disappointing and somewhat late program, beginning with release of a liquid formulation for pediatric use in April, followed by a small program for adults sometime "in the summer." The adult program will initially be limited to people with very advanced disease and evidence of failure on existing drugs.

We salute the expanded access for pediatric use since children are so often the last to receive any new drug. But no one is satisfied with the adult program. Project Inform and other activist groups are working to hasten and widen it. The company claims that access is hampered because its first attempt at large scale production failed and engineers have yet to even determine how to solve the problem. We see little reason to doubt the company's story about the production failure since an underground attempt at production ran into the same problem when scale-up was attempted. For now, the company plans to supply clinical trials, as well as the tiny expanded access program, with product made in small scale production batches.

Despite Glaxo's protests, there are a few things they might do to expand the access program. One is to make more of the liquid pediatric formulation for use by adults. There is no claim of a production problem with the liquid formulation. Secondly, the company could establish several parallel small-scale production lines, or contract with other firms to do so. The only question is how quickly either approach could gear up to supplement production and whether the drug would be created quickly enough to speed up the expanded access program. It's hard

to believe that a company with all the resources and skills of Glaxo Wellcome is incapable of creating modest additional quantities of the drug.

A Note of Caution: As 1592 approaches wider availability, people should heed the lessons of past programs and avoid rushing to use the drug just because it is *new*. Optimum use will require starting 1592 along with at least one other potent and previously unused therapy, something that may not be immediately possible for most people. Simply adding it to existing regimens will only continue the harmful cycle of "serial monotherapy" of past years, in which the true potential of many drugs has often been wasted. When more than 30,000 people rushed to get 3TC on expanded access in 1995 led to a high percentage of people inadvertently wasted the opportunity to use it wisely. When they started using a protease inhibitor six months later, few had a fresh two-drug combination of nucleoside drugs to use with it and consequently weren't able to make the best use of the protease inhibitor. No one could have foreseen this problem in 1995, but today the principle is well recognized. Long-term strategies now must guide the use of 1592 - not just the desire for a new drug. For a majority of people, perhaps the best thing to do with 1592 might be to wait until they are able to start it in a new combination with an upcoming protease inhibitor or other new drug. People who are rapidly declining must use it in whatever fashion is possible, but this is probably a small percentage of people. ***If there is one critical lesson learned from the use of protease inhibitors, it is that it is more important to use a new drug CORRECTLY than it is to use it NOW.***

Strategy Update: 2- vs. 3-Drug Initial Combinations

As the strategies for effective long-term use of antiviral drugs become clearer, one issue which still troubles many physicians is whether it is acceptable to use simple 2-drug combinations, like AZT + 3TC or d4T + ddI or 3TC, in people who are just beginning therapy. Some do this merely out of habit because it was once the standard of care, while a few others believe it is a wise way to use the limited number of drugs available. They feel this approach provides sufficient therapy for some time while preserving the use of protease inhibitors, non-nucleoside analogues and triple combinations for later.

While on the surface this may sound reasonable, a careful look at recent discoveries argues against it. ***Here's why initial therapy should not be limited to two nucleoside analogue drugs):***

- New studies show that ***reducing viral load below the limit of detection is essential for long-term treatment strategy***.
- ***Duration of treatment effect*** (how long any treatment effect lasts before being overcome by drug resistance) ***is determined by the nadir, or lowest point, of viral replication achieved*** in response to treatment; ***the lower the level achieved, the longer a treatment will last*** and the longer drug resistance will be suppressed.
- ***When therapy fails to suppress virus to the limit of detection, resistance quickly develops.***
- ***2-drug nucleoside combinations alone, like AZT+3TC, rarely suppress viral replication below the limit of detection;*** even in best cases such as initial treatment in very healthy people, only about 20% reach viral supression below the limit of detection. Few sustain it for more than 24 weeks.
- ***With 3-drug combinations, 50% to 95% reach and sustain viral load below the limit of detection*** (some 2-drug combinations using dual protease inhibitors may also do this).

Use of 2-drug nucleoside combinations runs a very high risk of failure, leading to rapid drug resistance in more than 80% of users. Such strategies do little more than quickly waste the two drugs used, making them poor partners for future combination use. This is particularly wasteful with 3TC, the most potent, but resistance-prone drug of this class. When used incorrectly in a 2-drug combination, resistance to 3TC sets in literally within weeks and its initial high potency is very quickly lost. After that it acts like another weak nucleoside analogue.

In contrast, when nucleosides are used wisely in combination with potent partners like ritonavir, indinavir, or nevirapine, they are protected from resistance and can provide long-term useful contributions to a combination regimen. When 3TC is used in a triple combination, for example, little or no evidence of resistance is seen after a year or more and the drug remains a very potent partner.

It is always hard to abandon past practices because it sometimes makes people feel like they are admitting to a mistake. This is not the case in abandoning 2-drug nucleoside strategies. At one time, they were the best science had to offer and they offered short-term clinical and survival benefits. But things have changed and continued use of 2-drug nucleoside combinations today does little more than waste their potential contribution to true, long-term strategies.

Protease Inhibitors and Beyond

Responses to new antiretroviral therapies have brought new optimism but not all people respond and some have had a less robust and durable response than others. Many researchers believe that the best way to treat HIV will be to use drugs against multiple targets of HIV. They believe this will put the virus at a disadvantage, making it more difficult for virus to mutate and develop resistance. Drugs that act on HIV in a variety of ways are therefore critical to provide new options. A new generation of protease inhibitors is entering studies. Some of these have activity, in the lab, against virus resistant to current protease inhibitors. Several drugs with other mechanisms of action are also in development. The more developed are discussed in *"Antiretroviral Update"* on page 8, but others which have yet to accumulate solid data are also worth being aware of.

Protease Inhibitors

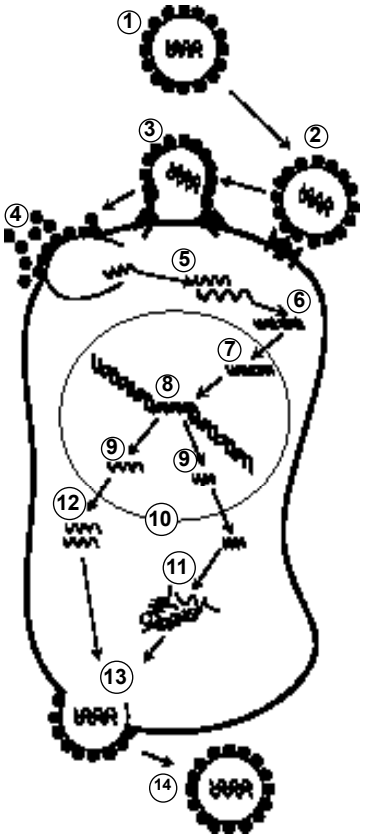
Abbott Laboratories' ABT-378 is beginning clinical studies. The active compound in this drug is very potent but, like saquinavir, is poorly absorbed. Abbott is blending it with about 50 mg of ritonavir, which helps with absorption. The blend of the two compounds will be marketed as a single new drug. ABT-378 has some resistance patterns that overlap those of available protease inhibitors, but Abbott hopes the drug's potency may allow it to work even for resistant virus. Initial animal studies suggest that once- or twice-daily dosing will be possible. As with any drug in an early stage of development, it's not possible to predict how well it will work in humans.

Pharmacia/Upjohn's protease inhibitor, PNU-140690, is just beginning human studies. In a laboratory setting, this compound has a different resistance pattern than the currently approved drugs and so should be active for resistant virus.

RT Inhibitors

Several companies are developing new compounds to inhibit reverse transcriptase (RT) **(Figure 1, step 5)**. Bristol-Myers Squibb is giving priority to developing lobucavir. It is nucleoside analogue like AZT, ddI and 3TC, but it mimics a different amino acid (guanosine) than other drugs of this type and may be active for a wide range

1 Free Virus
2 Attachment
3 Fusion
4 Uncoating
5 Reverse Transcription
6 Viral DNA Synthesis
7 Migration to the Nucleus
8 Integration into Cell DNA
9 RNA Transcription from DNA
10 Migration from the Nucleus
11 Protien Production
12 Viral RNA Production
13 Packaging and Budding
14 Maturing Virus



of viruses, not just HIV. Lobucavir may inhibit HIV, hepatitis B, various herpes viruses and cytomegalovirus (CMV). Phase II/III studies of an oral form of lobucavir will soon begin for treating HIV and CMV.

HBY097, being developed by Hoechst/Bayer, is a non-nucleoside RT inhibitor (like nevirapine and delavirdine) which is in phase I/II studies. Preliminary results show that this drug is quite active (about a 1.5 log reduction in viral levels after 14 days of taking HBY097 alone). Studies combining HBY097 with other antiretroviral therapies are ongoing.

Calanolide A will begin studies soon. It is a naturally occurring chemical from a tree found in the Malaysian rain forests. It has a different resistance pattern from other non-nucleoside RT inhibitors, which may be an important advantage. In laboratory studies, it has greater activity against virus that is resistant to other non-nucleoside RT inhibitors than to "wild type" virus.

Zinc Finger Inhibitors

Several groups are developing compounds to inhibit the "zinc finger" of HIV. Zinc finger activity is common to many viruses, making it a good target. Zinc fingers capture HIV's genetic material and help package it into new virions (a whole virus particle) **(Figure 1, step 13)**. The zinc fingers may also play a role in an earlier stage of the HIV replication process. Parke-Davis' compound, CI-1012, is currently in phase I multiple dose studies at the NIH (National Institutes of Health) and a few other sites. A Dutch company is developing Azodicarbonamide (ADA) which is currently in phase I/II studies for people with advanced stage disease in Europe. Because these drugs operate at a different site, prior resistance or failure with protease inhibitors should not have any effect on their potency.

Fusion Inhibitors

Pentafuside (also known as T-20) is an inhibitor of HIV fusion that is currently in phase I human studies. This type of drug works by attempting to interfere with the ability of HIV to attach to cells **(Figure 1, step 3)**. This drug is given intravenously (into the vein), and based on animal studies it readily penetrates tissue and the lymph nodes. Lack of an oral formulation may hinder development of this product.

Another drug, FP-21399, being developed by Fuji ImmunoPharmaceuticals, appears to work similarly to T-20 and is in phase I studies. FP-21399 seems to interfere with HIV's ability to enter into the CD4+ cell. The drug must be

given intravenously and also seems to penetrate tissue and the lymph nodes.

A third drug, ISIS 5320, from ISIS Pharmaceuticals, works by a similar mechanism of action. Studies have shown that this drug specifically binds to HIV's envelope protein, gp120, and inhibits the binding of both infectious virus and virus-infected cells to both CD4+ expressing and non-CD4+ expressing cells. This drug also blocks cell to cell transmission of the virus in a laboratory setting. ISIS 5320 is expected to begin clinical studies in the near future.

One caution about all three of these drugs is that all previous HIV drugs that attempted to work by blocking viral fusion have failed. It appears that it is fairly easy to create fusion inhibitors that work in isolated laboratory conditions, but very difficult to make them work in the body.

Integrase Inhibitors

A new class of drugs, integrase inhibitors, has attracted attention in the pharmaceutical industry for the last few years. The role of the integrase enzyme **(Figure 1, step 8)** is to integrate HIV's genetic material into the host cell's DNA. Integration is needed for HIV replication and effectively blocking this step would prevent HIV from making new virus. Only one drug of this type, zintevir (AR177) which is being developed by Aronex Pharmaceuticals, is currently in phase I/II studies, but there have been no results released from these studies. Zintevir has to be administered intravenously. Many companies report that they have found making drugs of this type to be extremely difficult.

HIV-Related Weight Loss

Results from a study comparing a testosterone patch (Testoderm) to a placebo patch in 133 men with HIV-related weight loss were recently released. Testoderm is a unique system that delivers testosterone through a patch at low constant levels, mimicking the body's natural patterns of testosterone production. The study showed no differences in weight gain between those using the patch compared to those receiving the placebo. Both groups had slight gains in total weight and body cell mass measures, but the placebo group had slightly higher increases in both of these measures. Surprisingly, while those receiving the testosterone patch had increases in testosterone levels to normal ranges, these increases did not result in improved weight gain. There were no differences between CD4+ cell count and viral levels (HIV RNA) in either group. Other studies of the testosterone patch will be reporting shortly.

Although the Testoderm patch is available for off-label use, data do not support its use for treating HIV-related weight loss. A benefit of the Testoderm patch is that is has fewer side effects than injected testosterone. Testosterone as therapy for HIV-associated weight loss may need to be delivered at higher doses than the body normally produces.

A study of thalidomide for the treatment of HIV-associated weight loss has also recently ended. Preliminary reports from the drug's sponsor suggest the data are encouraging, though no details have been released. Data from the thalidomide study should be available shortly, so interested parties should call the PI Treatment Hotline for an update. Also, results from studies of oxandrolone (Oxandrin), an oral anabolic drug, are expected soon. Currently the only approved therapies for HIV-associated weight loss are:

- megastrol (Megace), a female sex hormone resulting in weight gain, primarily in the form of fat,
- dronabinol (Marinol), a synthetic form of marijuana which stimulates appetite,
- recombinant human growth hormone (Serostim), which has been shown to increase lean body (muscle) mass.

Perhaps the most important aspect of the Testoderm data is that patients and physicians can't make broad assumptions about the value of using anabolics for weight maintenance in HIV. Even though many people report personal results using such products with exercise, each product may produce its own individualized results. Studies of nandrolone (Deca-Durabolin) and oxandrolone are seeking volunteers. Many of these studies offer compensation and incentives to participate. Perhaps the best incentive, however, is to get answers on whether these therapies have any benefit in maintaining or improving weight gain and how to best use them. For more on developing a comprehensive weight maintenance program, call the Hotline at 1-800-822-7422 for the *Weight Loss and Nutrition Fact Sheet.*

IL-2 Update

Interleukin-2 (IL-2) is a chemical produced by immune cells. It is also manufactured and administered as a drug to augment immune response. While anti-HIV drugs interfere with HIV's reproduction, the goal of IL-2 therapy is to preserve or enhance certain immune functions. If administered intermittently, IL-2 stimulates CD4+ cells to reproduce. Current enthusiasm for IL-2 therapy in HIV disease stems from studies using intermittent administration of IL-2, which resulted in dramatic and sustained CD4+ cell increases. However, some researchers and physicians question the value of CD4+ cell increases due to IL-2 therapy. Do these new cells function properly? Will they prevent HIV disease progression? It appears that the cells function at least as well, if not better, than CD4+ cells increased as a result of antiviral therapy. While results from small studies have looked promising, only a large study of IL-2 will answer questions about the effectiveness of this therapy.

IL-2 has long been researched in HIV. Several ways have been tried to administer the drug: injection under the skin (subcutaneous), injection in the abdomen and infusion directly into a vein (intravenous or IV). They have also tried various administration schedules: daily, weekly, monthly and bimonthly. And they have experimented with different doses, from low doses (1 million International Units [IU]) to very high doses (18 million IU). When IL-2 is given daily at low doses, it seems to act differently than when administered at higher, intermittent doses. At low doses, it appears to activate natural killer cells. At high intermittent doses, it seems to be a T-cell growth factor.

When used in people with CD4+ cell counts above 300, IL-2 therapy is associated with large increases in CD4+ cells. In people with more advanced disease, the response is smaller but still impressive when the drug is used in combination with protease inhibitors. For a complete description of IL-2 results, see *PI Perspective #19 and #20*.

Side effects seen with IL-2 are predictable and sometimes severe. Nearly everyone given IL-2 experiences flu-like symptoms during administration; the severity is typically related to the size of the dose used. Treatment with antihistamines and ibuprofen *before* IL-2 therapy may reduce these symptoms. Less common side effects include headache, diarrhea, increases in bilirubin and alkaline phosphatase levels and decreases in phosphorus, calcium, granulocytes, hemoglobin and platelet counts. Also, because IL-2 stimulates the immune system, particularly CD4+ cells where HIV is often harbored, it can also increase HIV replication. However, current studies demonstrate that antiviral drugs can control this viral replication. In these studies, people receiving IL-2 in combination with antivirals showed no lasting increase in HIV RNA levels over their pre-study levels.

If IL-2 can preserve CD4+ cell function as well as numbers, it may play a critical role in combating immune dysfunction.

Do The CD4+ T Cells Work?

No data suggest that the new cells do not work. No one in the studies has experienced opportunistic infections at abnormally high CD4+ cell counts. Current tests to measure cell function leave a lot to be desired. Still, the tests do suggest the new cells work at least as well as new CD4+ cells seen as a product of antiviral therapy.

Because IL-2 results in what is called a "peripheral expansion" of CD4+ cells, it may only cause growth of the cell types that are present when therapy begins. It cannot replace types that may have been destroyed due to HIV infection. In other words, if all the cells necessary for fighting PCP have been destroyed due to HIV infection, it is doubtful that IL-2 will bring back what is gone. If, on the other hand, there are even a few cells left which can fight PCP, IL-2 therapy may increase the number of those cells, preserving and enhancing what remains in the repertoire of immune function. There are no tests that can determine which cells remain in the repertoire, so people with low cell counts who have dramatic increases in CD4+ cells, whether this is due to IL-2 therapy or to antiviral therapy, should remain on preventative therapies for opportunistic infections.

The Next Step in IL-2 Therapy?

Project Inform has followed and encouraged development of IL-2 since the mid-1980s. It is clear that the time is ripe to begin a study large enough to get definitive answers regarding IL-2's effectiveness. One company developing IL-2, Chiron Corporation, has recently committed to the future development of this therapy in HIV. Recently Project Inform attended a meeting convened by the National Institutes of Health (NIH) which included representatives of research institutions from Australia, South Africa, the United Kingdom, the United States, Brazil and Canada. At this meeting, there was a general consensus to proceed with a large study of IL-2, and the US Government was called upon to take leadership in coordinating this effort. No other therapy has produced the sizable CD4+ cell increases seen with IL-2 use. If IL-2 can preserve CD4+ cell function as well as numbers, it may play a critical role in combating immune dysfunction. Over ten years of research on IL-2 in HIV disease has not produced answers because studies have not been designed to prove its effectiveness. It is time the government and research community rise to the challenge of a new era of AIDS by building on the foundation of improved antiviral therapies, and focusing attention on preserving, enhancing and restoring the immune system.

Medicaid: The System and How to Use It

Medicaid is a lifeline to HIV care for roughly half of those living with AIDS and 90% of all children living with AIDS. Seven of ten public dollars spent on AIDS care come from Medicaid. The program pays for inpatient, outpatient, home healthcare, prescription drugs and medical supplies. Over the next four years, Medicaid is one of the programs that will be slated for cuts, "reforms", or inadequate funding as the President and Congress try to balance the federal budget. The danger in budget cuts, particularly to public health and education, is that costs are shifted to the state and local governments which often do not have the money to cover costs or have different spending priorities. The real needs of people then go unmet. At a time when advances in research have renewed optimism about treatment but increased the costs of treating HIV, Medicaid and other important health programs must be enhanced and protected, not targeted for deficit reduction.

Even without cuts or proposed "reforms", people living with HIV/AIDS face challenges within the Medicaid system. Medicaid is a joint program of the states/territories and the federal government. Although it is intended as a healthcare safety net for low-income people, it currently serves only 62% of poor Americans. About half of the 35 million people covered by Medicaid are children, 7.6 million are women, 4.3 million are elderly and 5.4 million are blind or disabled. Many of the regulations and protections in Medicaid are developed by the Healthcare Financing Administration (HCFA). The individual state programs must comply with federal mandates, but they are also allowed a lot of autonomy in deciding who qualifies, what the benefit packages are and how the programs are run.

Working with Medicaid

The application process for Medicaid and other public benefits can be daunting. If you are applying for Medicaid (Medi-Cal in California) you must meet criteria in one of 27 federally defined "categorically needy" groups. Examples include income level, disability requirements, eligibility for other benefits, age (over 65 or under 7), or pregnancy status. The specifics vary state to state, so it is vital to understand what is available. If you are considering moving to another state, make sure the benefits and eligibility are comparable. The Access Project at 1-800-734-7104 can help with state information and contacts.

To begin the application process, collect all written information explaining the program. Pay close attention to eligibility criteria, timelines for filing, waiting periods, disability requirements and financial restrictions. People with HIV/AIDS generally qualify if they are unable to perform "substantial work" due to HIV/AIDS. Therefore, it is important to get copies of your medical records and keep your own health notes. The more information you have, the easier your access to benefits. Keep track of symptoms such as night sweats, fatigue, lack of concentration, eating difficulties, pain, treatment reactions, weight, etc. Request to have your notes entered into your medical records. It is helpful to have someone wade through the benefit information and application procedures with you. If you have access to benefits counselors who are HIV specialists, use their help. Community-based organizations, AIDS service organizations, case managers and eligibility workers can also help.

To reduce the bureaucratic delays, AIDS Benefits Counselors of San Francisco suggests the following:

- Keep a file for each program.
- Make copies of forms and note the date you return them.
- Get a receipt if you return forms in person, otherwise use certified mail and keep the receipts.
- Note the response time limit on any mail you receive from the government; response time generally ranges from 10 - 60 days.
- Keep a log and write down names, titles and phone numbers of government agency personnel; note the date, a summary of your discussion and any promises made.
- If you are uncomfortable with English, find a translator. Government offices may not have a person who speaks your language and procedures can be complicated.
- Expect long waiting lines; you may spend the whole day in the office.

Accessing quality care within the current Medicaid system can require work. Studies show that patients of providers who are experienced with HIV stay healthier and live longer than those whose providers have limited HIV experience. Given the current complex, quickly changing HIV treatment environment, both clinicians and researchers have stressed the importance of HIV knowledgeable care providers. Yet, even for people with private insurance, finding a physician with good HIV treatment skills can be difficult. It is particularly hard to find a care provider who is both knowledgeable and empathetic to women with HIV. Because Medicaid typically pays less than private insurance, Medicaid recipients may find it even harder to access specialists.

In areas hardest hit by the epidemic, there are many HIV specialists who accept Medicaid and/or work in public health clinics. While these clinics generally require longer waits, many have a high standard of HIV care. People in rural or less impacted areas can have a much more difficult time finding a qualified provider. In some states, programs have been developed to drive people to quality care providers. One of the best ways to find an HIV specialist who takes Medicaid patients is to talk to other Medicaid recipients. Support groups, local community-based organizations and people with AIDS coalitions (PWACs) are all good places to exchange information. Many organizations are not able to recommend specific doctors but can provide a list of local HIV providers. The AIDS Clinical Trial Unit (ACTU) and CPCRA (Community Programs for Clinical Research on AIDS) sites nearest to you may also be able to refer you to an HIV-experienced doctor in your area. Contact them by calling

1-800-TRIALS-A.

Drugs and Diagnostic Tests

Another challenge within the Medicaid system can be getting prescription drugs and viral load tests. Not all AIDS drugs are equally effective, and none of them can be used effectively without also using diagnostic measures like the new viral load tests. All Medicaid programs cover some prescription drugs. But not all drugs are available and some require long pre-approval processes. Your state's program may not cover the needed diagnostic tests or the best drugs, or even those minimally required. Also, the amount of money the individual has to pay for a drug may be restrictive. While some states have few limitations on drugs, others place caps on the number of drugs you can get through Medicaid in a month. In some states, there are drugs that require prior approval and do not count toward your limit. It is vital to understand the local regulations on prescription drugs and what is available on the covered list of drugs (formulary). People have circumvented some drug limitations by getting prescriptions 60 or 90 day supplies of some drugs in alternating months. This approach has to be carefully worked out to avoid lapses in drug access. At least one state uses its AIDS Drug Assistance Program (ADAP), an HIV drug delivery program funded through the Ryan White CARE Act, to cover drugs for Medicaid patients hampered by drug limits.

Some state Medicaid programs, including New Jersey, Indiana, New Mexico, Oklahoma, Alabama and Texas, are not covering viral load tests. People in such states may be able to access the tests through patient assistance programs. For more information on such programs, call the Project Inform hotline. It is also important to educate state officials as to why access to viral load is necessary and to advocate for reimbursement through Medicaid.

Medicaid and Managed Care

Although the cost of funding Medicaid has slowed dramatically in the past year (a trend that is likely to continue), Medicaid expenditures in previous years were growing at alarming rates. Working on the theory that managed care, particularly the tightly controlled Health Maintenance Organization (HMO) system, can help reduce Medicaid costs, many states have been moving quickly into Medicaid managed care. As of April 1995, 44 states contracted with managed care organizations to provide services to Medicaid recipients. As of February 1996, 17 states have implemented managed care programs for disabled Medicaid beneficiaries, and six of the programs are mandatory for most or all disabled individuals. There will be continued movement into managed care in the future.

Managed care brings another set of hurdles for Medicaid recipients in terms of access to both adequate care and prescription drug services. Many managed care systems work with "capitated" payments; rather than paying for each service rendered, the insurer (the Medicaid program) pays a set fee for an individual regardless of the amount of care provided. Under capitated systems, there is incentive for the doctor or medical group to limit care, because they will receive the same amount of money regardless of how much care they provide.

In order for states to move into managed care they must file a waiver with HCFA outlining their intent for implementation. Advocates should watch this process closely, as safeguards for people living with HIV can be detailed in this waiver. Another major challenge for people living with HIV, their advocates and public health officials is to ensure that each individual entering the system gets enough information to effectively evaluate the managed care plans offered. Getting the level of information necessary to determine if a managed care plan will meet an individual's needs is difficult even with private insurance. A good model for information dissemination has not yet been developed in the move to Medicaid managed care.

Most managed care organizations, particularly HMOs, have not demonstrated an ability to fully meet the needs of people with chronic or life-threatening disease. Areas of concern include access to specialty providers, access to appropriate treatment, and access to cutting edge treatment information. A major challenge will be to ensure that HMOs are ready to care for HIV-positive individuals and that Medicaid recipients with HIV have sufficient information to choose a plan wisely.

Meanwhile, President Clinton has suggested a $22 billion cut over five years in federal Medicaid funding, including a cap or limit on payment per beneficiary. In a system that already has restrictions and challenges for people living with HIV, this proposal will almost certainly deepen existing problems. HIV, when treated effectively, is one of many higher cost illnesses. Unless

states have the willingness and the necessary funding to pick up the extra cost, financial caps are likely to result in broader restrictions on high cost prescription drugs and monitoring assays. Reduced payments may make it more difficult for experienced HIV doctors to accept new Medicaid patients. People with higher cost chronic and life-threatening illnesses would likely suffer disproportionately under such a proposal. Recent encouraging news that the new treatments have reduced the overall cost of healthcare for people with HIV/AIDS might sound helpful, but it is unclear whether this cost reduction will be maintained over longer periods. For now, all it means is that the new drugs have prevented expensive hospital visits for a substantial number of people. But when the high cost of the drugs is added up for many years of treatment, the apparent short-term cost savings might evaporate.

Medicaid is still the most important AIDS care program and must not only be maintained at its current funding level but also enhanced to better serve people with chronic and life-threatening illnesses. Additionally, movement into Medicaid managed care must be closely monitored on the local, state and federal level to ensure protections for people living with HIV/AIDS. For more information on how you can help monitor Medicaid and let President Clinton and Congress know that this program is important to you and people you know, please join the Treatment Action Network or call PI at 415-558-8669.

Join The Treatment Action Network!

After the 1994 elections radically changed the composition of the U.S. Congress, advocates had to alter their strategy for influencing decision-makers. No longer could a handful of D.C.-based lobbyists represent people with HIV/AIDS to obtain funding and fight harmful legislation. Advocacy organizations began developing and strengthening their grassroots networks so that people across the country could personally communicate their concerns to their representatives.

Project Inform has mobilized a strong grassroots response to HIV/AIDS research, treatment and funding legislative issues since 1991, when a volunteer founded the Treatment Action Network (TAN). The idea was to give people affected by the epidemic the tools to influence policy decisions affecting their lives.

Grassroots work will be even more crucial in 1997, especially given the growing perception that AIDS is all but conquered. This view could be used to cut support for AIDS issues. Access to new drugs is uneven, especially in the face of President Clinton's proposal to cut Medicaid by $22 million. There is a pressing need to ensure that new options are developed for those who are not benefiting from existing drugs. Your help will strengthen TAN's position as the only grassroots network focusing on treatment development and access issues. TAN members will focus on key issues such as pressing pharmaceutical companies for expanded access to drugs that haven't yet received FDA approval.

Obtaining adequate funding for Medicaid and AIDS-specific programs will be difficult this year. President Clinton's 1998 budget proposes very modest increases for HIV/AIDS research, care/treatment, prevention and housing programs. He is requesting only 4% more Ryan White funds and 2.6% more for research. The increases don't even match inflation; they are a step backward.

The President is not asking for any additional funding for the AIDS Drug Assistance Program (ADAP, see *PI Perspective #19*, Access in Crisis). Last year, after a very strong grassroots response, funding for ADAPs grew from $0 to $167 million. TAN members played a critical role in that effort. Some members even organized a meeting with key staff from Senator Hatfield's (R-Oregon) office and others spoke at a press conference and Congressional briefing.

A stronger grassroots effort will be needed this year to build on past victories. We must communicate with our elected officials and make sure they understand that AIDS isn't over. It makes no sense to retreat in this war the first time we gain the an advantage; now is the time for intensifying the government's response to the epidemic.

Your help is needed to make this happen. There are 1,500 TAN members across the country who receive monthly Action Alerts and legislative updates. They write, call, and meet with their elected officials about treatment and research policy issues. They also contact leaders of pharmaceutical companies to challenge exorbitant prices and to press for expanded access and patient support programs for specific treatments. They use their personal stories and experiences to influence the decisions of those in power.

If you are willing to spend a few minutes every month contacting decision-makers and making a real difference in the course of the epidemic, empower yourself by joining Project Inform's Treatment Action Network. There is great strength in numbers. You will receive all of the information and tools necessary to communicate effectively. Call Project Inform at 1-800-822-7422 and ask for an introductory TAN packet, or send your name and address to Project Inform/TAN, 1965 Market Street #220, San Francisco, CA 94103, FAX 415-558-0684 or e-mail rclary@projinf.org. With your help, we will continue make a difference this year.