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Four New Concepts for Combatting HIV Infection
... and Why They Won't Be Tried Anytime Soon

The new generation of antiviral drugs and the widespread availability of the PCR tests for measuring viral load have opened new pathways in the treatment of HIV disease. While protease inhibitors look very promising, HIV-infected people may benefit as much from new insights about the nature of the disease provided by the drugs and diagnostic tests. We now have a far better understanding of how quickly the virus replicates, where it is reproduced, and how it responds to treatment. This is suggesting new strategies that go beyond mere viral suppression. AIDS research is on the threshold of approaches in which the process - the way we *use* the drugs - may be at least as important as the products themselves.

In theory this may allow us to reach new thresholds of effectiveness in combating HIV infection. The critical question now is whether anyone will exercise the leadership and foresight necessary to do the needed work. Since these new approaches focus on strategies and processes rather than products, the usual cast of sponsors is unlikely to show much interest.

Concept #1: Strategic use of antiviral combinations.

The almost universal practice of medicine today is product oriented. Doctors and patients alike tend to think in product terms: use (or don't use) AZT; switch from AZT to ddI, etc. Once a person begins taking a drug, conventional practice keeps the person on it until there is evidence of failure or intolerance. If people stay on a drug long enough, it is almost certain that their virus will become resistant to it.

One way to delay or avoid the problems of resistance and toxicity is to assume from the beginning that it will be necessary to change therapy on a routine basis. A new generation of "strategy" trials will soon begin testing various ways to do this. In this approach, study volunteers (or individuals acting with their doctors) will begin therapy using an agreed upon first step, probably a well-understood combination such as AZT + 3TC. If a drug or combination doesn't result in a significant reduction in HIV levels within a month, it probably never will. Thus, physicians can reach a decision point within 30 days to either continue the therapy or switch to something else. Afterwards, viral load (PCR) and CD4+ cell testing will give additional guidance about what to do next. There are at least three possible long-term strategies:

A. ***Change to a different drug or combination on a timed basis***, such as every six months. In this approach, the "signal-to-switch" is based on data from previous trials showing how quickly resistance develops, on average, to this drug or combination. One likely limitation of this approach is that the "average" time to resistance may not apply to every individual situation. Thus some people using this approach might stay on a therapy longer than they should, while others may abandon it too quickly, shortening the duration of benefit they might have received. However, even with these risks, this approach seems likely to work better than simply waiting for people to fail on the drug.

B. ***Change to a different drug or combination when the viral load increases significantly***. This approach relies upon viral load testing (PCR) to give the "signal to switch" therapies. Many scientists favor this approach since the viral load test is the most direct measure of viral activity generally available. In this sense, viral load is not a "surrogate" marker but a direct measure of an antiviral drug's

In this issue

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effect on its intended target.

___One possible weakness of this shows up with protease inhibitor drugs. Recent studies have demonstrated that these drugs appear to provide sustained improvements in CD4+ cells even after PCR testing shows that viral load has begun to increase. It is not clear whether this says something about the limitations of PCR testing, or whether virus produced after using a protease inhibitor is somehow weakened and less likely to cause damage to the immune system. Whatever the answer, this approach seems to offer the most precise way to determine the value of a therapy used for suppressing virus levels. Additional studies already underway will help answer the question.

C. ***Change to a different drug or combination when CD4+ cell levels begin to fall significantly, but before clinical changes occur***. While CD4+ tests are only one measure of the health of the immune system, they correlate well with clinical symptoms and the risk of opportunistic infections. The main risk of using this approach, however, is that it may not give the "signal-to-switch" until after the damage is done and a significant and perhaps irretrievable loss of CD4+ cells has occurred.

It is not clear which "switching" strategy will produce the best clinical and survival benefits. Any of them are likely to be superior to remaining on a drug or combination until clinical signs of failure become evident. Any of them will diminish the risk of developing long-term, cumulative side effects from the individual drugs or combinations. A likely fourth strategy will simply be to take all 3 points into consideration and make a reasonable judgment call about when to switch therapies.

Using any of these strategies will require careful monitoring and access to a wide array of drugs. Fortunately, this is finally becoming possible. There are now four approved antivirals (AZT, ddI, ddC, d4T,3TC), and one available drug targeted at cellular activity (hydroxyurea). Several important drugs are waiting just offstage for approval over the next several months, including nevirapine, delavirdine, and three protease inhibitors (saquinavir, indinavir sulfate, and ritonavir).

Practical considerations: Unfortunately, physicians and their patients are largely on their own when trying to figure out how best to employ such strategies. The goal of studying these approaches will be to determine standards of care, not to meet FDA licensing requirements. Consequently, drug manufacturers have little interest in paying for them. The responsibility for this type of testing falls to the federal government's AIDS research establishment. But at the moment, the federal program is reducing the amount of funding devoted to clinical trials, so prospects there look bleak. At a time when there is a rapidly growing backlog of critically needed clinical trials which can only be done by the federal government, there is less money being allocated to fund them.

Concept #2: Activate the dormantly infected compartments of the immune system.

No matter how good antiviral drugs become, it seems unrealistic to hope that it will be possible to use them for a person's entire normal lifespan. Even the best therapies may still encounter problems with long-term toxicity, tolerance, and resistance. An ideal solution to HIV infection, like any other disease, would be to end the battle between virus and the immune system conclusively. This is not necessarily an unreachable goal. Short of reaching that goal, it might at least be possible to greatly reduce the total body burden of HIV in hopes of adding many years to life expectancy. The key question might be determining the best time and way to use the available drugs to make the greatest possible impact.

Today's best combinations are, in some people, doing an excellent job shutting down virus reproduction in the "fast-acting" compartment of the immune system. This compartment is made up of activated, infected cells which are rapidly producing virus and which are quickly dying and being replaced by new cells. Recent data from the Aaron Diamond Research Center and the University of Alabama demonstrate that most of the infected cells producing new virus are newly formed every 48 hours. It is precisely because this compartment is so highly active that it makes a good target for antiviral drugs (and for the immune system itself).

New studies show that even when drugs stop virus production from this compartment, a trickle of virus production continues from elsewhere. Scientists believe it is coming from the "slow-acting compartments," probably including follicular dendritic cells, macrophages and monocytes, and infected but inactive CD4+ cells (latently infected cells). In contrast to the fast-acting cells, these produce a small amount of virus but the cells live long, slow lives. This makes them very difficult to deal with, either by a drug or by the immune system.

The problem of these cells is insidious. Well before all of these cells finally become active and visible targets, a drug has usually been in use for so long that the virus from the fast-acting compartments is starting to become resistant. Thus, the first target is getting out of control again before the second target becomes accessible.

One proposal is to try to simultaneously activate *all* or most of the slow-acting infected cells while fighting back intensely with antivirals, supportive therapies, and the immune system itself. Once activated, cells become visible targets for the immune system while the drugs should be capable of coping with any new virus they attempt to produce. In theory, this might make it possible to "burn out" the HIV infection much as the body does other acute infections. Failing this lofty goal, the strategy might at least "set the clock back" by several years by greatly reducing the level of underlying, slow-acting infected cells. Overall, this approach would seek to turn HIV infection from a slow, chronic infection into an acute infectious state.

The strategy would invite an all out war between HIV infection and the immune system. Many people experience a period of acute infection very early in the course

Continued, next page...

Benefits of Combination Therapy Confirmed

by Ben Cheng

Long awaited results from two large studies comparing single drug antiviral treatment to combination therapy have been released. Both studies confirm that combination therapy is superior to AZT alone.

Beginning in 1992, the AIDS Clinical Trials Group (ACTG) study 175 enrolled 2467 people with CD4+ cell counts between 200 and 500, who had no major opportunistic infections (1067 of whom had never taken antivirals previously). People received either AZT alone, ddI alone, AZT + ddI or AZT + ddC. The doses used were 600 mg/day of AZT, 400 mg/day of ddI and 2.25 mg/day of ddC. During the trial, anyone experiencing a 50% or greater drop in CD4+ counts or developing an opportunistic infection was reassigned to a different therapy. Those receiving monotherapy were switched to a combination, while those already on a combination were assigned to the alternate combination. This innovative approach was the first step toward a true "management strategy trial" as described in PI Perspective #16. It protected volunteers from the possible harm caused by staying on a therapy after it had begun to fail.

Researchers evaluated the impact of treatment on three possible outcomes:

- *treatment failure:* a 50% or greater drop in CD4+ cell counts, development of an opportunistic infection or death;
- *clinical progression:* development of an opportunistic infection or death;
- *survival*: an outcome based solely on death.

The treatment failure analysis showed that ddI alone, AZT + ddI and AZT + ddC were all superior to AZT alone. This was true for all study participants, regardless of whether or not they had previously taken antiviral therapy. The clinical progression analysis showed that overall, people receiving ddI alone or AZT + ddI were significantly less likely to progress to AIDS. People who had never taken antivirals previously received greater benefit from the AZT + ddC combination while those who had previously taken AZT benefited most from either AZT + ddI or ddI alone. In the survival analysis, overall there were significantly fewer deaths among people receiving either AZT + ddI or ddI alone. While there was no difference in survival between the four treatments for people who had never previously taken antivirals prior to the study, trends favored people who were on AZT + ddC. For people who were AZT-experienced, there were significantly fewer deaths among people receiving ddI alone or the AZT + ddI combination. These results are summarized in Tables

continued, next page ...

...Four New Concepts... *Continued from page 2*

of the disease, before HIV becomes a slow, chronic infection. Even then, the body almost, but not quite, wins the battle, greatly suppressing the virus for many years to come. Rerunning that battle with the help of antiviral therapies and supportive measures might rid the body of the infection once and forever or at least greatly curb its spread.

This process-oriented approach would best be tested in a hospital setting to assure safety. Researchers would first treat the patient to maximize suppression of HIV with the most potent available combination of antiviral drugs, possibly one or more protease inhibitors and one or more RT inhibitor drugs (AZT, ddI, ddC, d4T, 3TC, nevirapine and delavirdine). Since the duration of the process would be brief, it might be feasible to use the drugs at higher than normal doses. Hospital admission would occur at the peak of viral suppression. The patient would be monitored daily for all signs of HIV activity as well as general health. At the chosen moment, physicians would systemically administer one or more of several agents known to activate dormant and slow-acting cells. As with interleukin-2 therapy, there would likely be a brief increase in viral load which should be contained by the antivirals. Supportive therapies could be used to suppress harmful cytokine release and oxidative stress.

No one knows how long this scenario should continue or whether it would need

continued on page 13

1 through 3.

Preliminary virologic data were collected on 348 participants using the PCR test. Initial analysis indicate that viral levels concur with the clinical results, further supporting the use of the PCR test as a tool for measuring the effectiveness of drugs. More PCR data will be available in the near future. Other virologic data will report on the levels and effects of AZT-associated resistance and the syncitium-inducing (SI) type of HIV (a viral type which may lead to more rapid disease progression).

There were no significant differences in toxicity between the groups, although for people who had never taken antivirals previously, there appeared to be more toxicity among those on AZT alone.

Overall there was no difference in clinical progression and death rates between those who immediately began combination therapy and those who failed on single agent therapy and were reassigned to one of the combination arms of the study. There was a trend, however, (32% reduction in risk of disease progression or death) toward improved outcomes for those who received immediate combination therapy who had never previously taken antivirals. Part of this result may be due to the fact that ddI was significantly superior to AZT and comparable with the combination therapies in most analyses, and therefore reduced the power in detecting a difference between immediate and delayed combination therapy.

A week after the results of ACTG 175 were announced, a similar European/ Australian study known as the Delta trial reported its results. Delta enrolled 3214 people with CD4+ cell counts between 50 and 350 (2131 of whom had never taken antivirals previously). People received either AZT alone, AZT + ddI or AZT + ddC, using the same doses as in ACTG 175. The major difference between Delta and ACTG 175 is that Delta allowed people with a previous opportunistic infection to participate. The trial consisted of two parts: Delta 1 included only people who had never taken antivirals previously and Delta 2 included only people who had used AZT for at least 3 months.

The combined results of Delta 1 and Delta 2 show a 25% reduction in death rates for those on combination therapy. Delta was stopped when people on combination therapy showed a significant survival advantage. Of those on AZT alone, 17% died compared to 10% on AZT + ddI and 12% on AZT + ddC. Similarly, 28% on AZT alone had disease progression compared to 18% on AZT + ddI and 23% on AZT + ddC. Preliminary analysis of Delta 2 (people previously treated with AZT) shows no difference between monotherapy and combination therapy in delaying disease progression or death. Of those on AZT alone, 26% died compared to 23% on AZT + ddI and 26% on AZT + ddC. Thirty-nine percent on AZT alone had disease progression compared to 38% on both AZT + ddI and AZT + ddC. There were no significant differences in side effects between the treatment regimens, although people on AZT + ddI had more gastrointestinal problems.

Results from these studies will likely change the standard of care for people with asymptomatic HIV infection and a recommendation has already been made in Europe to this effect. These are the first large studies to show that combination therapy can delay disease progression and prolong survival. People who have never taken antivirals previously may want to consider starting with combination therapy or ddI alone instead of AZT alone. The superiority of ddI alone compared to AZT alone contradicts an earlier study, ACTG 116A, which involved people with more advanced disease, but is consistent with the interim results of a pediatrics study, ACTG 152 (see May 1995 issue of the *PI Perspective*). Because of this contradiction, some may see the superiority of ddI over AZT monotherapy to be less conclusive. The debate may be moot since most researchers seem convinced that combination therapy, of one form or another, is ultimately superior. For AZT-experienced individuals, switching to or adding ddI is superior to remaining on AZT alone.

Further analyses of these studies will provide more information on how to best use these therapies and possible explanations on why therapies lose their effectiveness. These results cannot be directly compared to other combination therapies such as AZT + 3TC or those involving the protease inhibitors. However, as confidence builds in the predictive value of PCR tests, it may be possible to compare these data to other combinations on the basis of their effect on viral levels. Using this parameter, existing data would suggest that the AZT + 3TC combination, as well as some of the combinations using protease inhibitors, may be superior to the AZT + ddI or AZT + ddC combinations tested here. For now, the most important finding of ACTG 175 and Delta is that there is now hard evidence that combination therapies are superior to AZT monotherapy, and that the reign of AZT monotherapy as the conservative "standard of practice" should quickly come to an end. This is little news to readers of *PI Perspective*, as Project Inform has been recommending the use of combination therapy over monotherapy since the late 1980s.

ACTG 175 - Outcomes
(larger type = statistically significant)

Table 1: All study volunteers combined:

Therapy	cd4 $^{50\%}_{\downarrow}$ / AIDS /death	AIDS/death	Death
AZT	196 (32%)	96 (16%)	54 (9%
AZT+ddI	**113 (18%**	**65 (11%)**	**31 (5%)**
AZT+ddC	**120 (20%)**	76 (12%)	40 (7%)
ddI	**136 (22%)**	**71 (11%)**	**29 (5%)**

Table 2: People without prior antiviral use:

Therapy	cd4 $^{50\%}_{\downarrow}$ / AIDS /death	AIDS/death	Death
AZT	63 (23%)	32 (12%)	18 (7%)
AZT+ddI	**37 (14%)**	20 (8%)	11 (4%)
AZT+ddC	**27 (10%)**	**16 (6%)**	9 (3%)
ddI	**46 (17%)**	23 (9%)	11 (4%)

Table 3: People with prior antiviral use:

Therapy	cd4 $^{50\%}_{\downarrow}$ / AIDS /death	AIDS/death	Death
AZT	133 (38%)	64 (18%)	36 (10%)
AZT+ddI	**76 (22%)**	**45 (13%)**	**20 (6%)**
AZT+ddC	**93 (27%)**	60 (17%)	31 (9%)
ddI	**90 (26%)**	48 (14%)	**28 (5%)**

Advances in Protease Inhibitor Development

by Ben Cheng

The widespread availability of protease inhibitors is now a few months away and, for some people, it is already here. On November 7, the FDA Antiviral Advisory Committee recommended accelerated approval for saquinavir in combination with currently available antiviral drugs for people with advanced disease. This should put the drug in pharmacies in as little as three months. At the same time, new or enlarged expanded access programs have been announced for some of the other protease inhibitors.

Results from several studies continue to show impressive anti-HIV activity of this family of compounds. These results show that it may be possible to slow the development of resistance to these drugs by using them in combinations. Additionally, data makes it clear that people who achieve consistently higher drug levels in the blood have better antiviral activity and greater CD4+ cell count increases. It is therefore important to take these drugs so that their absorption will be maximized - for ritonavir (formerly ABT-538) and saquinavir this means taking them with food, but on an empty stomach with indinavir (formerly MK-639). It is also important to take these drugs at designated times to ensure adequate drug levels. If drug levels get too low, there is an increased risk of developing resistance to that drug.

Indinavir Sulfate *(also known as MK-639 and Crixivan® from Merck)*

Merck is currently supplying indinavir to about 1400 people in an expanded access program which might be enlarged after the first of the year. The company expects to file for FDA accelerated approval in early 1996.

One recently reported study compared indinavir alone to either AZT alone or the two drugs combined. Results of this first combination study show the clear superiority of indinavir to AZT, but also that combining them may lead to a more sustained suppression of virus than indinavir alone, suggesting that the combination may be slowing the development of resistance. The study enrolled 73 people who had less than two weeks prior AZT use and with CD4+ counts below 500 and HIV RNA counts above 20,000. Volunteers received AZT alone (200 mg. three times daily), indinavir alone (600 mg. four times daily), or the combination. As might be predicted, people on AZT alone had only a slight decrease in HIV RNA which returned to original levels after 24 weeks. People receiving either indinavir alone or the combination had an average 2.5 log drop in HIV RNA after 12 weeks of therapy. Interestingly, people on indinavir alone sustained a 1.5 log drop in HIV RNA at 24 weeks whereas people on the combination had a sustained 2.5 log drop, suggesting that the combination may be able to delay drug resistance. Additionally, people on the combination had slightly greater increases in CD4+ cell counts (averaging about 75 after 24 weeks) compared to people on indinavir alone (about 50 after 24 weeks). However, the overall level of CD4+ cell increase seems surprisingly modest compared to reports from earlier indinavir studies.

A second study, testing revised doses of indinavir, enrolled people with CD4+ counts between 150 and 500 and HIV RNA counts over 20,000. Volunteers received either 800 mg. every 8 hours, 1000 mg. every 8 hours or 800 mg. every 6 hours of MK-639. People on all three doses had similar antiviral and CD4+ cell responses. The median maximum HIV RNA drop was about 2 logs and after 24 weeks there was still a 1.5 to 2 log decrease. There was also an average increase of about 100 CD4+ cells at 24 weeks on all three doses. No previously unreported toxicities were seen in the study. As a result of this study, Merck decided to use the 800 mg. every 8 hours dosing schedule for their phase III studies.

The only one known drug interaction with indinavir and is with rifabutin. Indinavir significantly increases rifabutin levels in the blood and the dose of rifabutin should be cut in half if the drugs are used simultaneously. It is also very likely that there will be an interaction with rifampin, astemizole (Hismanal), terfenadine (Seldane) and loratadine (Claritin).

Ritonavir *(previously known as ABT-538, from Abbott Laboratories)*

Abbott Labs expects to file for FDA accelerated approval of ritonavir in early 1996. Abbott will initiate a compassionate use program for about 1500 people in December, 1995 or January, 1996 (call the Project Inform Hotline for more information). Additionally, a new softgel capsule is likely to be introduced in November 1995 with high hopes of making the drug more palatable. In the meantime there are several recommendations to better cope with the foul taste of the current liquid formulation. Salty foods seem to mask the taste and fatty foods (like chocolates) may help to better dissolve the drug. To get rid of the aftertaste, users might try rinsing with a mouthwash or wine.

A small French study gave ritonavir to 25 people with CD4+ counts below 250 who had never been on antiviral therapy. Volunteers received ritonavir alone for two weeks and then added AZT + ddC. After 4 months, there was an average decrease in HIV RNA of 2.5 logs, with one third of the group now having undetectable amounts of virus. The group averaged an increase of about 125 CD4+ cells. Perhaps even more important, there was a substantial decrease in the number of infectious cells detected in blood after 16 weeks.

Another recent finding by Abbott Labs is that the combination of ritonavir and saquinavir (the Roche protease inhibitor), have a powerful drug interaction which might be either beneficial or harmful depending on how it is managed. In animals, when ritonavir and saquinavir were given together, the amount of saquinavir detected in blood accumulates rapidly over a few days, eventually reaching a level as much as 300 times that normally found. The interaction does not affect the blood levels of ritonavir. While it is still not known whether the same degree of interaction will occur in humans, there is a strong likelihood that it will be similar, although the degree may vary widely in different people. This might make the two drugs a very potent combination, especially if the effect is consistent, but it also brings a greatly increased risk of severe toxicity, especially at the currently used doses. Because of the many unknowns here, people are strongly discouraged from experimenting with the combination on their own until more is learned. The same process which causes this interaction results in several other known interactions between ritonavir and other drugs. When used with clarithromycin,

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The Basic Message

- **Get tested**, *anonymously*.
- **Learn your options** and line up your support.
- If positive: **maximize your health**, **get a complete physical** and **a full immune health workup** and get educated! (See the PI document *"Day One"*).
- **Get baseline CD4+ and PCR tests, repeat quarterly**, charting the trends. Women should also get "gyn" exams and "pap" tests every six months.
- If the CD4+ trend is downward or consistently below 500, or PCR above 100,000, **optimize nutrition and consider antivirals** (a combination!).
- If PCR doesn't decline at least 3 fold, or rises, start or change to a different antiviral regimen.
- If the CD4+ trend stays below 300, **consider or use preventive treatment against PCP** (oral drugs if possible). If the count continues to fall below 200, reconsider antiviral therapy if not already on and consider preventive treatments against other opportunistic infections. Learn about drug interactions.
- If CD4+ count stays below 75, **intensify monitoring,** consider preventive action against MAC/MAI and CMV infections. Learn about other preventive therapies.

clarithromycin levels are significantly increased; with fluconazole, ritonavir levels are increased by about 15%. Other interactions are likely with rifabutin, rifampin and itraconazole. Ritonavir should also not be taken with the antiarthritis drug piroxicam (Feldene), the antiulcer drug cimetidine (Tagamet), the antihistamines terfenadine (Seldane), astemizole (Hismanal) and loratadine (Claritin), the antidepressant paroxetine hydrochloride (Paxil), the sedatives codeine, meperidine (Demerol and Mepergan), diazepam (valium), midazolam (Versed) alprazolam (Xanax) and triazolam (Halcion), the antifungals clotrimazole (Lotrimin and Mycelex), miconazole IV (Monistat IV) and ketoconazole (Nizoral) and the heart drugs bepridil hydrochloride (Vascor), encainide (Enkaid), flecainide (Tambocor) propafenone hydrochloride (Rythmol), and amiodarone (Cordarone).

This somewhat bewildering list of possible drug interactions suggest that although ritonavir may be highly desirable for its anti-HIV activity, it will create many problems in common use and require great care on the part of physicians.

AG1343 *(also known as Viracept®, from Agouron)*

AG1343 is in an earlier stage of development than saquinavir, indinavir or ritonavir and consequently, less is known about its effects. A British study of AG1343 enrolled 20 people with CD4+ counts between 200 to 500, more than 20,000 copies of HIV RNA and who had either never been on antivirals or had discontinued other antivirals for at least one year. People received either 300 mg or 600 mg of AG1343 three times a day. After 28 days, people who had a greater than a one log drop in HIV RNA were allowed to continue on AG1343. Two people in the low dose group and 4 people in the high dose group had greater than a one log drop, but surprisingly people on the lower dose had better CD4+ cell responses. Because of the small numbers of people treated, it is difficult to know what, if anything, these results mean, except that a small number of those treated had substantial reductions in HIV RNA.

A second study enrolled 30 people with CD4+ counts above 200, more than 20,000 copies of HIV RNA and who had either never been on antivirals or had discontinued antivirals for at least one year. Volunteers received either 500 mg, 600 mg, or 750 mg of AG1343 twice a day and like the British study, people who had at least a one log drop in HIV RNA after 28 days of therapy were allowed to continue on an extension phase. The logic of a design which denies treatment to people whose response falls below an arbitrary threshold is uncertain. Some people think the approach might be in the patients' best interests, while others think the opposite. Twenty-one of the thirty people enrolled qualified for the extension phase with people on the three different doses having similar HIV RNA responses (about a 1.5 log maximum decrease). As might be expected, people who achieved higher drug levels in their blood had better antiviral responses, but these were not necessarily the people who received the highest doses of the drug. Side effects noted from both studies were diarrhea (especially on the higher dose), fatigue, nausea and headache - very similar to the list reported for saquinavir.

Based on these studies, there is little clarity about the optimum dose of this drug. All doses show some level of antiviral activity, but the response does not seem clearly dose-related, as is usually the case. Since the level of antiviral activity is still somewhat below that reported for indinavir and ritonavir, it may be that higher doses will be required. It will be critical for the sponsor to identify an optimal dose before proceeding with efficacy studies.

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Medicaid Cuts Threaten Care for People with AIDS

by Anne Donnelly

The 104th Congress has called for cuts in Medicaid, one of the most critical lifelines for people with HIV/AIDS. Both the US Senate and the House of Representatives have proposed a $170 billion cut to Medicaid over the next seven years as part of the Congressional budget resolution. This is a 30% reduction from projected spending under current law.

These spending reductions are, in part, being used to fund a $245 billion tax cut, also included in the Budget Reconciliation bill, which will disproportionately benefit corporations and wealthy Americans. In addition, Congress has proposed eliminating the present guarantee that all people who meet state and federal eligibility guidelines will receive health care coverage. President Clinton, who has promised to veto this bill, has also proposed cuts to the program, totaling $54 billion over ten years.

One of the arguments used to support this "reform" of both Medicare and Medicaid is that the proposed cuts are the only way to ensure that the programs will not go bankrupt in the future. However, to reduce funding for this program without addressing the underlying causes of increasing health care costs will result in weaker health services for people with AIDS, other people with disabilities, and low income people. It will also lead to more use of inadequate and costly emergency care services.

To achieve the goal of the Republican budget reconciliation proposal, 53% of the proposed $894 billion in federal reductions comes from health and human services programs.

What is Medicaid?

Medicaid is government health insurance for low income persons. Currently, 36 million people, or one in eight Americans, receive Medicaid. Over half of Medicaid recipients are children, 15% are people with disabilities, and 12% are elderly. It is an entitlement program financed by federal and state governments and administrated by the states. The federal government finances 50-80% of the program, depending on the state's per capita income. In some states, Medicaid is given a different name, such as MediCal in California. Many states augment the federal program; for example, in California, Medi-Cal offers prescription drugs as a benefit.

People with HIV/AIDS depend heavily on this program, which provides $3 billion annually to HIV-positive individuals. Medicaid provides basic health care services to 90% of all children with HIV and for at least 40% of adults with AIDS. Medicaid has become the only form of health care coverage available to many people living with HIV/AIDS because of discrimination, preexisting conditions, decreased income, lifetime coverage limits, and other practices by private insurance companies.

Medicaid and Block Grants

The Senate and the House have proposed shifting Medicaid funds into block grants to give states more flexibility and responsibility for their Medicaid programs. Block grants convert program funding into a set pot of money which is given to each state to cover program expenses. Historically, when programs are block granted, less federal money is allocated towards the programs. This is in part because of the incorrect assumption that state administrative expenses will be less than federal administrative expenses. In light of both the proposed cuts and the initiation of a block grant mechanism, state Medicaid programs would receive less overall funding, undermining the only "safety net" for health care coverage.

This mechanism would also remove the "entitlement" status of the program, meaning that all those eligible may not receive coverage. For example, if a state used up the allotted block grant funding and still had people in need of coverage, there would be no additional funding. Consumers Union estimates that 12 million Americans will lose their health insurance coverage under the current proposal. In addition, because the federal government typically attaches few requirements to block grants, the comprehensiveness, accessibility, quality, affordability, or cultural competency of services is not ensured.

Supporters of the block grant approach say that Medicaid is more wasteful than other health care programs and that it has been a major cause of health care inflation. In reality, the major increases in Medicaid spending are largely attributable to two factors: 1) an increase in the number of persons eligible to receive Medicaid due to losing other insurance coverage, and 2) disproportionate share payments. These payments support health care facilities serving large numbers of uninsured persons. For example, San Francisco General Hospital receives 77% of its funding to provide services to the poor and indigent through Medicaid and Medicare, reflecting in part disproportionate share payments. When the two factors outlined above are excluded, the rate of growth for Medicaid is comparable to increases in other forms of medical spending.

Effects of Medicaid Cuts

People with HIV/AIDS will be severely hurt by current Medicaid "reform" proposals. Cuts in Medicaid would worsen the health of people with HIV/AIDS by taking away their guarantee to essential services, such as preventive care, prenatal care and prescription medications that treat and prevent a whole variety of secondary infections. Studies have shown that, when looking at a cross-section of people living with HIV, access to quality health care appears to be the primary factor in the delay of disease progression. People with HIV/AIDS who lose their Medicaid health coverage will ultimately be forced to delay accessing health care services until a crisis occurs. They would be forced to seek care in hospital emergency rooms. Hospitals and state taxpayers would ultimately bear the burden of this high-cost care.

Action is Needed

Now is the time to demand that the President veto the Budget Reconciliation Bill. The President has repeatedly promised to veto this bill, but we need to flood the White House with calls and letters asking him to insist on a compromise with Congress that provides adequate federal funding for Medicaid and maintains the entitlements status of the program. You can call the White House at (202) 456-1414 or write to the President at The White House, 1600 Pennsylvania Avenue NW, Washington, DC 20500. Please call Project Inform's Public Policy Department at (415) 558-8669 for a sample letter or if you need more information about Medicaid reform.

HIV Infection and "Managed Care"

by Anne Donnelly

Despite the failure of the Clinton administration's health care reform initiative, the managed care movement is creating sweeping changes in the way health care is delivered. "Managed care" is not a new concept (California's Kaiser Permanente Health Management Organization [HMO] has been around for 50 years), but millions of Americans who have never considered managed care an option are suddenly being presented with HMOs or Preferred Provider Organizations (PPOs) as their *only* choice.

Whether you are working and receive health care coverage from your employer or are covered by the Medicare or Medicaid programs, you may have to deal with managed care in the near future. Most employees are already covered by managed care plans. Many Medicaid recipients are being transferred from independent providers (private practices) to managed care and Congress is looking at doing the same with Medicare patients.

By definition, managed care is a method by which a patient's care is "managed" to control costs and/or improve continuity of care. However, depending on whom you talk to, you will hear very different visions of reality. Proponents of managed care describe it as a health care system that manages an individual's, family's, or community's overall health, rather than simply treating illness or accidents as they arise. Such definitions make managed care sound like a holistic health care model that places as great an emphasis on prevention and good health education as it does on treating illness. Presumably, the cost of prevention and education will be offset by reducing money spent on expensive problems and hospitalization. Your personal physician serves as a "gatekeeper" to the extended health care system, overseeing your needs and referring you when necessary to medical specialists, dentists, psychologists, and even nutritionists or chemical dependency programs. Such a system, implemented with quality care, can be more efficient and cost effective than the "fee-for-service" model in which patients see a physician when a problem occurs and insurance pays for it.

Managed care's critics see profit-seeking as the ruling principle in many managed care systems. The traditional American fee-for-service health care model can be wasteful and inefficient. Nothing prevents a doctor from ordering expensive, unnecessary procedures or from prescribing costly medications when generics will do. Instead, malpractice suits encourage doctors to protect themselves by doing everything, rather than just what's needed. Also, some doctors profit from their referrals and excessive use of tests. Managed care was designed to eliminate these abuses and save money. Virginia Betts, President of the American Nurses Association points out, "When managed care is used entirely as a cost-cutting measure instead of a system to provide efficiently organized, quality care for a continuum of patient needs, patient care suffers. Too many hospitals are using capitated payment under managed care as a reason to cut back on patient safety and quality of care."

"Capitated payment" (from "per capita or "per head") is central to managed care. When you join an HMO, you or your employer agree to pay a monthly fee determined by the size of the group and the makeup of the HMO. If the care provided costs less than the capitated rate, the HMO makes money. If the care costs more, it loses: the less care provided, the more money made. Profit minded executives control your care rather than *you,* your doctor or hospital. Jane Orient, MD, and Director of the Association of American Physicians and Surgeons, describes managed care as a corporate dream in which patients become commodities and physicians must choose between the patients' and the company' interests.

Most Americans belong to HMOs or PPOs. An HMO can contract with independent medical groups (Independent Provider Associations [IPAs]) which provide care to HMO patients for a capitated fee, or they can employ their own staff who are exclusive to that HMO. "Point of Service" HMO plans have the benefit of letting patients seek care from non-HMO physicians, but these plans have larger premiums. A PPO is a network of independent physicians affiliated with the plan. If your physician is a member of a plan, the plan pays most or all of the costs; if not, you pay a much larger portion of the bill. The physicians get plenty of patients but are paid less for each visit and procedure.

Carol Siporen, an Oakland, CA woman living with AIDS recently wrote in the WORLD newsletter about her experiences with Kaiser. Carol found Kaiser adequate for normal family care: "Kaiser was cheap, one-stop shopping. The prescriptions and doctor visits through my work plan were only a dollar." When she learned of her HIV status the picture changed. Her doctor would not be an HIV specialist and she would have to wait two months to get blood tests. Many of Kaiser's specialists (gynecologists, etc.) had no HIV experience; some were even reluctant to treat her. Services such as psychological consultations and home care had spending caps and, after a set amount of service, she had to stop. Carol fought back. She insisted on seeing HIV sensitive doctors, and managed to find a sympathetic social worker to help her. Her tenacity got her the care she expected, but used time and energy that she could have spent in other aspects of her life. Kaiser finally recognized her hard earned expertise by appointing her to their Patient Advocacy Committee and Standards of Care Committee.

Carol's experience is typical of many peo-

ple with chronic or life-threatening illnesses. If you have the energy to fight for what you need and supportive friends, family, social workers, and physicians, you can squeeze quality out of an HMO, but not easily. If you can't or won't fight, you may have to settle for what you get. Managed care plans look good on paper, but many of the real issues are not addressed in the advertising.

People we interviewed stressed that their prime concern for a plan was the physicians list. Some had built a relationship with a physician and chose a plan because the doctor was a member. Many physicians belong to several plans, but it is possible to lose a personal physician if the physician leaves your plan. People choosing an HMO should research the doctors and managed care plans in their area. Physicians with HIV experience will be more comfortable with their patients (and vice versa). HMOs without HIV-experienced doctors should be pressured to add them and/or allow enrollees to seek care outside of the group at no extra cost.

Most of the important information is hidden behind the plan's advertising so be aware that many plans require providers to sign an agreement not to speak badly of the plan. Many providers will be candid, but you will likely receive varying degrees of information. In addition, administrators may not be aware of all the providers and specialists who are signed up with their plan. Your research time is always well spent.

The managed care revolution is changing the face of health care in America. Particularly in urban areas, physician group practices are consolidating and joining managed care, hospitals are downsizing and closing, and patients are working harder and waiting longer to get quality health care. Because new types of health care institutions are rapidly replacing old ones, there are currently few consumer protection regulations. However, H.R. 2400 (the "Family Health Care Fairness Act of 1995") was brought to Congress on September 27, 1995 by Reps. Charles Norwood (R-GA) and Bill Brewster (D-OK.) It is supported by the Coalition for Health Care Choice and Accountability and many other advocacy groups. At first review, this bill looks supportable. Its bipartisan introduction will be important as it goes through the Congressional process.

The current anti-regulatory atmosphere in American politics will likely mean consumer protection in managed care faces a long, difficult battle. Meanwhile, people living with HIV/AIDS and other life-threatening illnesses will need to fight to ensure quality health care is accessible. Large HMOs should have patient advocacy groups, which can be started by people who share an HMO and similar concerns (don't expect the HMO to do it for you). Even as an individual, you can affect the quality of your managed care. Do careful research before choosing a plan, know how the grievance procedure works, ask questions and question decisions that do not seem right to you. Stay current on your treatment options by utilizing Project Inform and other treatment information services. Don't be afraid to advocate for yourself. Remember that your doctor can be a partner in this process; if he or she refuses consider changing physicians. If you are uncomfortable advocating in a medical setting ask a friend or family member to go to doctor visits with you. Be aware of any agency that regulates your plan, and inform them of your problems or concerns.

When real concern for quality of care governs the policies of a managed care plan, managed care can work well for people living with HIV/AIDS or other chronic conditions. When profits are the bottom line and policy is set by administrators and not doctors, patients will have to struggle for quality care.

Informed and empowered patients will be essential partners in the delivery of health care services.

If you are interested in ensuring increased patient protection and access to care in the managed care environment, please contact the Project Inform Policy Department at (415)558-8669 and/or the Coalition for Health Care Choice and Accountability at (202)347-4350.

Resource Notes:

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

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

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

AIDS Treatment News	1-800-873-2812
Treatment Issues (Gay Men's Health Crisis, New York)	1-212-337-1950
Test Positive Aware (Chicago)	1-312-472-6397
BETA (San Francisco AIDS Foundation)	1-415-863-2437

FDA Committee Recommends Approval of Three New Drugs

The FDA Antiviral Drugs Advisory Committee met in early November and recommended that 3TC (also known as lamivudine and Epivir®) and saquinavir (also known as Invirase®, the Roche protease inhibitor) be approved under the accelerated approval guidelines. The Advisory Committee also recommended d4T (also known as stavudine and Zerit) for full approval based on the superiority of d4T over AZT in delaying progression to AIDS (see *PI Perspective # 16* for results).

The Committee recommended that 3TC be approved for use in combination with AZT both for people who have or have not previously used antiviral drugs. They also recommended approval for use in the pediatric population, despite the fact that pancreatis was seen in some children. Taken together, these are the broadest approval indications yet given for any antiviral drug under the accelerated approval guidelines. The required confirmatory trials are being conducted in people with advanced disease, but not in people with higher CD4+ cell counts, leading to complaints from some that the drug would be sold to people in whom it's clinical benefit would not be confirmed. However, the Committee was convinced of the need to make the drug more widely available because of the 3TC combination's powerful impact on surrogate makers. The combination's increase in CD4+ cells and reduction in viral load (by PCR testing) was substantially better and longer sustained than in any previous antiviral drug trial. In defending its lack of a confirmatory trial in people with higher CD4+ counts, the sponsor argued that it would be difficult or impossible to recruit and keep people with higher CD4+ counts in a such a trial. Proving the clinical superiority of the combination in this population would require putting half the treatment group on what most people feel would be an inferior or at least less active single drug or combination. Moreover, with new and even more active combinations including protease inhibitors likely to be available very soon, it seemed unlikely that people would be willing to stay on the AZT+3TC combination for the two or more years required by such a trial.

A key question left unanswered by this and other recent trials is "What is the best time to begin this or any other antiviral therapy?" Earlier studies had argued that therapy was appropriate anytime a person's CD4+ count fell below 500, but this view is now widely considered unproven. Many people with 500 or lower CD4+ counts seem stable and perhaps in little need of therapy, while some others with counts above 500 experience rapid decline and could possibly benefit from earlier intervention. But this is a question about the use of any antiviral drug and not an issue unique to the use of AZT + 3TC. The issue is being examined in a number of other studies about to get underway, testing whether high viral load (PCR) levels are a better indicator of when to start treatment, independent of CD4+ counts.

On November 7, the Advisory Committee also recommended that the Roche protease inhibitor saquinavir (600 mg. three times a day) be approved for use in combination with any of the approved nucleoside analogues in people with advanced HIV disease (people with fewer than 300 CD4+ cells) who are failing other therapies. Data presented by the FDA showed that people who took saquinavir with a nucleoside analogue or combination of nucleoside analogues that they had not taken previously received greater antiviral effect compared to people who just added saquinavir to their current nucleoside analogue regimen or who stayed on the original regimen. Citing lack of data, the Advisory Committee rejected the sponsor's request to also approve the drug for use as monotherapy for people with advanced HIV-disease who are intolerant to existing therapies.

One concern raised by many people at the meeting was the admission that only a very small amount, less than 4% of the amount taken, of the current version of saquinavir was being sustained in the blood. This is because a liver enzyme very rapidly clears the drug from the blood. In this formulation, the drug is only mildly active. Some people feared that using it might lead to rapid development of resistance which might affect other protease inhibitors as well (see the related article *"Project Inform Resistance Meeting"* on page 18 of this issue). An improved version of saquinavir is already in clinical trials and should be made available sometime during 1996. Many observers concluded that people who had run out of other therapeutic options need not be concerned by this issue and should go ahead and use the drug if they need to. Those not in immediate need of better or changed therapy might be better off waiting for the arrival of the improved formulation or one of the other two protease inhibitors expected to be approved in early 1996.

On November 8, the Advisory Committee recommended that d4T be granted full approval based on the results of a confirmatory study which showed d4T to be superior to AZT for people with between 50 and 500 CD4+ cells and who have had at least 6 months prior AZT therapy. d4T was granted accelerated approval in June, 1994. The confirmatory results for d4T, which correspond with the drug's impact on surrogate markers such as CD4+ cells, should give clinicians more comfort in prescribing this drug as there is now clear cut benefit over continued AZT use.

The FDA must now act on the Committee's recommendations in order for saquinavir to be available in pharmacies and this is expected within the next two months. 3TC was approved as the *PI Perspective* was in production and should be in pharmacies by the time you read this. Saquinavir access might take a little longer, perhaps reaching pharmacies early in 1996.

Advances in Prevention and Treatment of MAC

by Ben Cheng

Several new studies are now helping to optimize the prevention and treatment of MAC (mycobacterium avium complex), a serious infection common in advanced AIDS. Recent information suggests either clarithromycin or azithromycin alone, or in combination with rifabutin, may be more effective at preventing MAC than rifabutin alone. For treatment of MAC, new data show that a 3-drug combination using clarithromycin is superior to 2-drug or 4-drug combinations. These results will certainly define new standards of prevention and treatment for MAC.

The California Collaborative Treatment Group (CCTG) has provided Project Inform with preliminary results from their recent MAC prevention study. We would like to thank the CCTG for this information and applaud their decision to allow us to disseminate it prior to presentation at a scientific meeting. The study enrolled 693 people with fewer than 100 CD4+ cells, who received either azithromycin (1200 mg. once a week), rifabutin (300 mg. daily) or the combination. The study suggests azithromycin is a good alternative, and possibly superior, to rifabutin in preventing MAC (an important consideration because of possible drug interactions) but the combination is better still.

About 10% of people who developed MAC while receiving azithromycin developed resistance to both azithromycin and clarithromycin, and later could not use either drug for MAC treatment. Both drugs are similar and are considered to be the most potent therapies against MAC. Each should be used in combination with other anti-MAC drugs. People receiving azithromycin or rifabutin alone had similar side effects, while those receiving the combination had a slightly higher incidence of side effects. Another recent study showed that clarithromycin was also a good alternative to rifabutin.

A recent French study enrolled 132 people with MAC who received clarithromycin + clofazimine or clarithromycin + rifabutin + ethambutol. The doses used in this study were 450 mg. of rifabutin daily and 1200 mg. daily of ethambutol. For the first two months the clarithromycin dosage was 2000 mg. daily and the clofazimine dosage was 200 mg. daily; after two months both dosages were halved to 1000 mg. daily, and 100 mg. daily respectively. People on the three drug combination were much less likely to develop resistance to clarithromycin, suggesting the combination will be effective longer. There was no difference shown between the two treatments in prolonging survival, decreasing fever or in clearing MAC from the blood. However this may be because the study may have been too small to clearly show such benefits.

A Canadian study enrolled 229 people with MAC who received a 3-drug combination (clarithromycin + rifabutin + ethambutol) or a 4-drug combination (ciprofloxacin + ethambutol + rifampin + clofazimine). The doses used were 1000 mg. twice daily of clarithromycin, 600 mg. daily of rifabutin, 15 mg/kg daily of ethambutol, 750 mg. twice daily of ciprofloxacin, 100 mg. of clofazimine daily and 600 mg. of rifampin daily. The rifabutin dosage was cut in half when almost half the people receiving the 600 mg. developed uveitis, a painful inflammation in the eye. People on the 3-drug combination were more likely to clear MAC from their blood than those on the 4-drug combination. Most importantly, people receiving the 3-drug combination survived longer than people receiving the 4-drug combination. Additionally, people using the 3-drug combination were more likely to clear MAC from their blood while receiving the original 600 mg. dose of rifabutin than those who received the lower dose, even though the higher dose was associated with serious eye inflammation.

A CCTG MAC treatment study enrolled 95 people with MAC who received clarithromycin + clofazimine or the two drugs plus ethambutol. The doses used were 2000 mg/day of clarithromycin, 100 mg/day of clofazimine and 800 mg/day of ethambutol. There was no difference between the two groups in clearing MAC from the blood, but the 3-drug combination may delay resistance to clarith-romycin.

The results of these studies show that a combination containing clarithromycin is probably the best treatment against MAC infection and that a 3-drug combination which includes clarithromycin may delay the emergence of clarithromycin resistant organisms.

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Opportunistic Infection Update

by Ben Cheng

Results from several new studies on preventing and treating opportunistic infections (OIs) should reduce the uncertainty around managing some OIs, but other results have sparked debate and controversy.

CMV (Cytomegalovirus)

In recent years preventing CMV disease has become a focus of research, and results from two new CMV prevention studies will further fuel the debate on the benefits and costs of prophylaxis. An oral ganciclovir study showed no prevention of CMV disease, while a study of valaciclovir showed benefit to using the drug at the cost of increased side effects and mortality. It now appears that people who are CMV culture positive (have CMV detected in their urine or semen) are at higher risk of developing CMV disease.

A recent study, CPCRA (Clinical Program for Clinical Research on AIDS) study number 023, comparing oral ganciclovir (GCV) to placebo (a dummy pill) for the prevention of CMV indicates that oral ganciclovir does not prevent or delay CMV. This contradicts an earlier study which showed a 50% reduction of CMV for people on oral GCV (for full results of the earlier study, please refer to *PI Perspective* number 16) and which led the FDA to approve oral GCV for CMV disease prevention. The new study, CPCRA 023, enrolled 994 people with fewer than 100 CD4+ cells who received oral GCV (1000 mg three times a day) or placebo. The results have caused great controversy because people on CPCRA 023 were not routinely examined by an eye doctor, unlike the earlier study. They were given full eye exams only when their physicians recognized symptoms and the physicians were not necessarily eye specialists. Although CPCRA 023 was designed to "mimic" the real world scenario, many physicians claim that routine professional eye exams are a standard of care, and that the study did not reflect the way most physicians treat people with HIV. Also, people were not examined for CMV before they enrolled, and they may already have had CMV disease before entering the study (approximately 15% of people with fewer than 50 CD4+ cells will have CMV retinitis upon screening). The results of this study will remain controversial and people with HIV and their physicians should carefully discuss whether to try oral GCV to prevent CMV.

AIDS Clinical Trials Group (ACTG) study 204 enrolled 1227 people with fewer than 100 CD4+ cells who received valaciclovir (2 grams four times a day), high dose acyclovir (800 mg four times a day) or low dose acyclovir (400 mg twice

a day). It found people receiving valaciclovir were 30% less likely to develop CMV than those receiving either dose of acyclovir. However, there were more deaths among people receiving valaciclovir than those who received low dose acyclovir. Even people using high dose acyclovir tended to survive longer than those receiving valaciclovir. People using valaciclovir also had more side effects, primarily gastrointestinal, which resulted in people discontinuing therapy. However, a lower dose of valaciclovir may be shown to prevent CMV disease with fewer side effects. Ongoing analysis may also show whether acyclovir is able to prevent other viral infections which valaciclovir can not.

Results from a study of a CMV antisense drug, ISIS 2922, should give hope to people with advanced CMV retinitis. Twenty-two people (28 eyes) with CMV retinitis who had failed all other anti-CMV therapies were given different doses of ISIS 2922 by direct injection into the eye. Doses used were 83, 165, 330 and 495 micrograms once weekly for three weeks, followed by a 330 microgram maintenance dose every other week. People receiving the higher initial doses had better responses, however the one person who was on the 495 microgram dose had severe side effects in the eye. Other side effects were eye inflammation which responded to topical steroids. Some people had their retinitis remain stable for over 50 weeks. New options are always welcome and these results are especially encouraging for people who have failed previous therapies. But the results are not directly comparable to those of larger studies using other approaches, and it is too early to know how ISIS 2922 will fit into the larger picture of CMV treatment.

Fungal Infections

In the first phase of ACTG study 159, 381 people with acute cryptococcal meningitis received intravenous ampho-tericin B (0.7 mg/kg daily) or ampho- tericin B with flucytosine (25 mg/kg daily) for two weeks. In the second phase, they received fluconazole (400 mg daily) or itraconazole (200 mg twice daily) for eight weeks. Results from phase one indicate adding flucytosine does not significantly reduce symptoms (fever and headaches), mortality or the amount of cryptococcal antigen in the cerebral spinal fluid (CSF). It also appears that flucytosine did not increase the incidence of side effects. Results from the second phase of the study indicate that people on fluconazole are more likely to remain cryptococcal antigen negative. However, there was no difference between the two therapies in reducing symptoms.

A study by the Mycoses Study Group (MSG) enrolled 107 people with stable cryptococcal meningitis and no detectable cryptococcal antigen in their CSF. They received fluconazole (200 mg daily) or itraconazole (200 mg daily). Significantly more people receiving itraconazole relapsed and became antigen positive than those people receiving fluconazole. Side effects were similar between the two groups.

The two trial designs differed. ACTG 159 looked at the number of relapses (antigen positivity) after 10 weeks of therapy while the MSG study measured time to relapse. Based on the results of these two studies, fluconazole appears better for maintenance treatment of cryptococcal meningitis, supporting past experience with both drugs.

Four New Concepts

... continued from page 3

to be repeated. Only a few days of activation might be required, since most or all the infected cells should quickly die and be replaced within a matter of days. The immune system itself should quickly target and destroy any cells which begin to express HIV. This strategy might either eliminate virtually all infected cells and free virus, or cause a dramatic, lasting reduction in the threshold levels of virus produced in the body.

When first proposed in 1990, many scientists rejected this strategy out of fear that the available antivirals would not control viral replication during the procedure. With protease inhibitors, more effective combinations, and extremely powerful but short-lived single agents like nevirapine, this is no longer the case. Today, we have better tools and the knowledge to experiment in this fashion. The key will be initiating the activation scenario while the patient is still sensitive to the drugs. The biggest unknown is how much damage will be incurred in the battle, and this question troubles many scientists. Others, however, argue that the total body burden of HIV, on a relative scale, is still fairly small compared to some other diseases from which the body recovers.

Practical Considerations: The main obstacles to testing an "activation: strategy are politics and money. Since the experiment is not about any particular product or drug, it will not find a ready commercial sponsor. Government or academia must take the initiative, though neither is quick to take on high-risk / high-gain clinical experiments. However, there is little magic about this approach. Any competent hospital and research team could develop and implement the necessary protocol.

Concept #3: Fight drug resistance by creating a steadier level of drug activity.

One possible factor in the rapid development of resistance to antiviral drugs is that their effective potency may vary widely over the course of the day. To be truly effective, a drug needs to be present in the blood stream at a certain level. If the level goes too high, the risk of toxicity grows; if the level falls too low, even briefly, inadequate suppression of virus occurs. Drugs levels in the blood rise to high peaks shortly after a drug is taken but fall to troughs before it is time to take the next dose. Recent studies have shown the large of amounts of new virus are literally made every few hours, so it is likely that the rate of viral production fluctuates each day as a person cycles through a daily dosing regimen. The trough level between doses may provide an ideal opportunity for the development of resistant virus since it permits replication in the presence of inadequate levels of a drug. This unfortunate balance of drug vs. virus occurs every few hours in between daily dosing.

There are several possible ways to correct this problem. One might be readily available to individual patients, at least those using two and three drug combinations. Someone taking three drugs might stagger the doses rather than taking all three drugs together. This might provide a steadier level of virus suppression than a fixed dosing regimen. Exactly how this should be done is unclear and will likely vary depending on the combination. Some elements of a combination might still be best taken together because of a desired synergistic interaction, such as AZT + 3TC or ddI plus hydroxyurea. But if a third or fourth drug is added to this scenario, a greater benefit might be achieved by taking it in between the doses of the other two drugs.

Practical Considerations: Relatively simple laboratory or animal studies could quickly test this approach. Some of the necessary data might already exist in the pharmacokinetic profiles of the drugs. If such data were promising, it would then be necessary to conduct small human studies. A positive outcome could lead either to changing the instructions to patients on how to use existing drugs in combination, or to the development of time-release formulations designed to produce steadier blood levels of the drugs throughout the day. This would be a relatively simple task for the pharmaceutical industry.

Concept #4: Shift the reservoir of infected cells out of the lymph system and into the blood stream.

Researchers seem to agree that a key component sustaining chronic HIV infection is the presence of reserves of virally infected cells and free virus trapped in the lymph nodes and other lymphoid tissues. Over time, the chronic infection seems to overwhelm the lymph nodes and the tissue is critically damaged. Conventional wisdom holds that it's a good thing all that virus is tied up in the lymph nodes since that keeps it from spreading elsewhere. A contrary view argues that this chronic entrapment of cells in the lymph system might be one of the reasons the immune system fails to cope the infection. And most people would agree that the eventual resulting destruction of the lymph system by chronic infection is not a good thing. As CD4+ cells are brought into use by the body, they circulate through the lymph system and may become infected while there. A further problem is that there is some evidence that our current drugs are not as effective in fighting viral reproduction in the lymph system as they are in the blood stream (though this is far from certain). Finally, there is great concern that the eventual breakdown of the lymph system due to long-term HIV infection render the system useless.

What if there were a way to drive all those infected cells out of the lymph system and into the blood steam? What if the infection could be kept out of the lymph system before it destroys it? While it might temporarily increase the virus levels in the blood, in theory it might also render the infected cells and entrapped virus more vulnerable to existing therapies. And giving the lymph system a rest, even if a temporary one, might permit the system to heal itself rather than proceed to its inevitable destruction.

In 1992, researchers at the National Cancer Institute proposed to rid the lymph system of virus by destroying the lymph nodes altogether, using a process called "total nodal irradiation." No human experiment was ever done for fear of the many unknowns that might result, even though this approach is sometimes used in cancer treatment. It might be possible to achieve the same goal without destroying anything and without the dangers inherent in radiation treatment. Researchers at one university have been testing this controversial theory for nearly two years in an animal model. A potent well known toxin (pertussis toxin) was applied in a minuscule dose (100 micrograms) to a monkey in an advanced stage of SIV-infection, the equivalent of human AIDS. The pertussis toxin is known

to generate an immunologic "shock" to the lymph system, causing it to restructure itself to deal with the toxin and block entry to the lymph system by other infectious agents – perhaps a defensive trick the body learned somewhere in the course of evolution. Even ntiviral drugs, this apparently resulted in without dramatic, lasting drop in viral load in the first animal tested, as well as a substantial weight gain and return to normal clinical condition. Later experiments, not yet published, have repeated the process in five additional animals who were compared to five controls (similar but untreated monkeys). This time, the treated animals were given lower dose injections of the toxin every two months but still no antiviral drugs. None suffered any detectable side effects. Four of the five control animals were dead after 8 months, while four of the five treated animals were alive with improved clinical condition. The one treated animal which died did so in the earliest weeks of the study, suggesting that it was perhaps too ill at baseline to benefit from treatment.

Practical Considerations: There is no clear sponsor or drug manufacturer who wants to try developing a dangerous toxin as a medicine. The scientists involved are applying for Investigational New Drug status for the toxin which will permit human testing, but getting approval will take up to year. Many scientists and physicians will be wary of giving a toxin to immune-suppressed people. But the animal studies show no signs of harm and it is the clinical data, not the theories, which count most.

Other researchers point out that there may be several other possible ways to break up the clustering of infected cells and virus in the lymph nodes. If so, all the better. They should all be tested.

Commentary

While promising, these are not the only strategies or process-oriented approaches worth attention. Others, like a long-standing and important proposal to suppress some aspects of immune function, have remained untested for half a decade or more. Like other new approaches, these strategies carry some risk with their potential benefit. No one can guarantee that they will not harm a volunteer or that they will produce better results than conventional therapy. We know the risks and benefits of current therapy, and both are limited. To make the next major advances against HIV infection, research may have to step outside the boundaries of conventional thinking and product-oriented research. All of these approaches are based on reasonable, if not fully understood, scientific concepts and it's fairly certain that the experiments could be done with FDA approval. With a little more determination, researchers could bring these and many similar experiments into human clinical testing within a matter of months.

The greatest obstacle faced by all these strategies is that they come at a time when the NIH Office of AIDS Research — not the Congress — is reducing the dollars spent on clinical research. Many clinical research sites around the country are preparing to shut their doors. The AIDS research budget planning process is operating on assumptions about the balance of basic vs. clinical science that are now two years out of date. The only thing that can change this is the volume of the outcry from people with AIDS and their supporters.

New Treatment for ITP

by David Wood

In March of 1995 the FDA approved Rh Pharmaceuticals, Inc.'s "WinRho SDTM," a new form of Intravenous Immunoglobulin (IVIG), for treatment of HIV-related Idiopathic Thrombocytopenia Purpura (ITP.)

ITP is a condition in which the body destroys its platelets prematurely, probably because clusters of HIV fragments and associated antibodies bind to the platelets marking them for destruction by the spleen and other parts of the immune system. Platelets are a key factor in the body's ability to form blood clots. ITP can cause excessive bruising, difficulty scabbing and even spontaneous internal bleeding; increasing the chance of infection and reducing the body's ability to control blood loss.

Many treatments have been tested on ITP. IVIG has been one of the more successful and is thought to reduce the ability of the antibody-fragment clusters to bind to the platelets. Immunoglobulin (Ig) is harvested from the blood plasma of human donors, creating two problems with older forms of Ig; large quantities are required so treatment is expensive- three to four thousand dollars per infusion- and there is a slight chance of a donor passing on a viral infection. Infusions are required every several weeks, making standard IVIG prohibitively expensive and somewhat dangerous for long-term therapy.

WinRho SD donors are stimulated to produce Ig with especially high levels of specific antibodies so a smaller amount of the product is required. This reduces the cost per infusion by about half. Also, WinRho SD has been treated to inactivate any viral contamination, making it safer to use. On the down side, because the WinRho SD antibodies are so specific, it is not effective against ITP in people who are Rho negative, and may not be suitable for some pregnant women.

In the trials the FDA reviewed, WinRho SD was effective both in people who were on AZT and those who were not, and effectiveness had not decreased after six infusions. Side effects developed following 4% of the infusions, and included headaches, chills, and fever. Because of the specific antibodies that the product uses, anemia caused by hemolysis (destruction of red blood cells) can also be a problem and RBC levels should be monitored, especially in people with low hemoglobin. Suggested dosing is set at 250 IU (50mg/kg bodyweight), and the infusions take about three to five minutes, as opposed to the several hours required for other forms of IVIG.

Univax Biologics, Inc. markets the product in the United States with a hotline to provide information on third party coverage, state guidelines and possible individual financial assistance. The hotline number is (800) 789-2099.

Comparing RNA PCR Tests

by Ben Cheng

Tests which measure viral burden (HIV RNA levels in blood) are a sensitive new tool for examining the effect of HIV therapies. As they become widely available, it becomes important for people to know which tests they are getting and how test results compare from one version to another. The most commonly used tests are: Q-PCR: (quantitative polymerase chain reaction, or the Roche PCR); bDNA (branched-chain DNA); and NASBA: (nucleic acid sequence-based amplification). NASBA is commonly used in Europe and is beginning to show up in the U.S. Different laboratories may use different methods of detecting viral burden including their own home brew test.

Studies suggest the tests give similar results, although NASBA may produce slightly higher HIV RNA copy numbers. The bDNA test is generally more consistently reproducible than Q-PCR or NASBA with very little difference between these two. The ACTG virology laboratories found Q-PCR and bDNA comparable in direct comparisons.

The tests have different ranges in which they measure HIV RNA levels. The bDNA test is most sensitive in the 10,000 to 1,000,000 HIV RNA copy range, NASBA is most sensitive between 1,000 to 10,000,000 copies, and Q-PCR between 200 to 1,000,000. A test may be more or less appropriate depending on the stage of HIV disease. Those with high CD4+ cell counts may only have detectable virus load on the Q-PCR test. Also, different amounts of plasma are needed for the tests - bDNA uses 2 ml of plasma (several tablespoons) while NASBA and Q-PCR use 100 and 200 microliters respectively (much less). This may be important when these tests are also used to detect other organisms which cause disease in people with HIV such as cytomegalovirus (CMV) and mycobacterium avium complex (MAC) and therefore requiring large amounts of blood for the tests.

Talk to your physician to find out what test is being used, how sensitive it is,

What's All This Stuff about "Logs?"

The Low-Down on Reading the PCR Test

Users of the new PCR diagnostic test which measures the level of viral activity in the blood have had to learn or relearn a few words not often heard since high school math classes. While the test reports back its results in fairly simple numbers, ranging from 200 upwards to many millions, discussion of how to interpret the test and the effect of antiviral drugs leads to the discussion of changes in the test. The simplest way to express the large changes in PCR numbers needed for a meaningful result relies upon scientific terminology, specifically a logarithmic scale. Hence the discussion of the phrase "LOGS" of change, as in: "a 2 log drop in viral load." The use of logarithmic scales is commonly employed in science and mathematics as a simple way to express large numbers. The log scale is a form of shorthand.

On a simple linear scale like a ruler, each major step up (inches) on the ruler or scale is exactly the same size as the preceding step - or the next step. The distance between the second and third inch is the same as the distance between the first and second inch, or the third and the fourth. While such linear scales are simple and easy to comprehend, they're not very good at expressing large numbers because the scale builds at such a slow rate.

In a logarithmic scale, each step up the scale, say from two logs to three logs, or three to four, represents a distance or amount ten times higher that the last log step. A two log step is not twice as much as one log, but ten times as much, and three logs is ten times as much as two logs or 100 times as much as one log.

Applying this to the PCR test is fairly simple. If a test result shows 500,000 copies of virus, a one log reduction reduces this to 50,000, while a one log increase would result in 5,000,000. A "one log reduction" is another way of saying "one tenth as much" or "reduced by a factor of 10" or a "tenfold reduction." A two log reduction brings the number of viral copies down to 5,000, (a hundred fold reduction or one-hundredth as much). A 3 log reduction would reduce it 500 (a thousand fold reduction or one-thousandth as much). In this case, we can't tell if it's possible to get a 4 log reduction, since this would require reducing the number to 50, well below the tests lower limit of 200.

Understanding this is important for interpreting PCR results. A few examples are provided below:

	Reductions			Increases	
PCR number (HIV RNA copies)	**-2 log** (100 fold)	**-1 log** (10 fold)	**- ½ log** (~3 fold)	**+½ log** (~3 fold)	**+1 log** (10 fold)
5,000	UD	500	~1,600	~15,000	50,000
20,000	200	2,000	~6,600	~60,000	200,000
50,000	500	5,000	~16,600	~150,000	500,000
100,000	1,000	10,000	~33,500	~300,000	1,000,000

UD = Undetectable (below the measurable limit, but not necessarily zero)

A few points to remember:

- The smallest change considered to be accurately measurable is ½ log or a 3 fold change. Any change smaller than this *might* simply be due to normal variances in the test. Repeated tests showing this kind of small change, however, increases confidence that the change is real.
- Several studies have now suggested that test results above 100,000 are generally associated with disease progression, while numbers below this are not. It is not clear, however, whether a result of 1,000,000 or even 10,000,000 implies a greater risk of disease progression than 100,000. At the other

extreme, there is no certainty that a result of 1,000 implies any greater freedom from progression than 10,000 or 50,000.

- The clinical significance of these numbers is probably not constant, but varies depending on the size of the number. For example, with an initial test result of 5,000, the entire range of changes on the chart on the previous page from minus 2 logs (undetectable) up to an increase of 1 log (50,000) may be insignificant since the total viral load never reaches the threshold associated with disease progression. However, it might still demonstrate the activity of a drug.
- At the other end, starting with larger numbers, it is easy to see that even ½ log or 1 log changes might be capable of moving a patient into a category associated with disease progression.

These figures suggest that none of the currently available nucleoside analogue drugs provides adequate suppression of virus when used alone. Even when used in two-drug combinations, they seem unable to match the performance of the best protease inhibitors, though preliminary data on d4T + ddI looks promising. Non-nucleoside RT inhibitors such as nevirapine must always be used in combinations to prevent the rapid development of resistance. The principal advantage of using combinations with protease inhibitors is also to extend the time before the development of resistance.

How do current drugs perform on the RNA PCR test?

Reported Peak Average Reductions in HIV RNA

Drug or Combo	Log reduction, copies of virus
(Nucleosides)	
AZT alone	.5 log (3 fold) reduction
ddI alone	.5 to .6 log reduction
ddC alone	<.5 log reduction
AZT+ddI	.6 to .8 log reduction
AZT+3TC	1 to 1.5 log reduction
d4T alone	no data
d4T + ddI	> 2 log reduction *
(Protease Inhibitors)	
Indinavir (alone or combination)	2 to 3 log reduction
Ritonavir (alone or combination)	2 to 3 log reduction
Saquinavir (alone)	<.5 log reduction **
Saquinavir (combination)	.5 to 1 log reduction
Saquinavir high dose	1 to 1.5 log reduction *
(Non-Nucleoside RT Inhibitors)	
Nevirapine	>2 logs reduction ***
Delavirdine	>2 logs reduction ***

* very preliminary data
** improved formulation expected by 6/96

The field of immune-based therapies is moving forward, with new therapies in the clinic and a number of technologies now in large scale trials. Despite the number of new clinical strategies, there remains uncertainty over how to interpret results from these types of trials, because it may be unrealistic to evaluate these new approaches in the same way that traditional antiviral approaches are assessed. For example, if the goal of an immune-based approach is to augment or heighten immune function, immediate responses on viral load or CD4+ cell number may not be dramatic but a long-term clinical benefit may still be realized.

Large trials of longer duration may be necessary to determine if some of these strategies are useful in the management of HIV-disease. A number of presentations from the Interscience Conference on Antimicrobial Agents Chemotherapy (ICAAC), recently held in San Francisco, summarize recent results of several approaches to modulating immune responses in HIV. These include studies of:

- HIV-IT, a gene therapy approach to augmenting the body's anti-HIV responses,
- interferon-alpha n3, a new formulation of alpha interferon with less toxicities,
- transfer of immune responses from one individual to another, also called passive immune therapy,
- transfer of antibodies engineered to target cytomegalovirus (CMV),
- interleukin-2 (IL-2) in combination with a protease inhibitor.

Two abstracts on studies of HIV-IT, an experimental immune-based strategy, may provide a new piece in the puzzle of understanding immune response in HIV-disease. HIV-IT, which is genetic material resembling HIV, was the subject of a *48 Hours* episode resulting in increased community attention to the technology. This approach, in development at Viagene of Southern California, can be likened to a gene therapy method of delivering a therapeutic vaccine. The strategy is to offer the body a fragment of material resembling HIV, in hopes that the body will mount an immune response and begin recognizing and destroying HIV or HIV-infected cells more efficiently. One study evaluated different schedules of administering the injection, using varying quantities of the material and increasing the number of injection sites. By increasing the dose and number of injection sites, cellular responses against HIV could be increased. The second study affirmed that by administering HIV-IT, there appeared to be increases in the cellular immune response against HIV proteins. Interestingly, however, these improvements or broadening of immune responses against important HIV proteins had no affect on either viral load (HIV RNA or DNA) or on CD4+ cell counts. HIV-IT appears to be safe, with toxicities primarily limited to pain at the site of injection. It is unclear if heightening these immune responses will result in any measurable benefit. Because this is a first generation therapy, it may be that the impact of HIV-IT on

cellular responses is not strong enough to have a measurable affect on the virus or CD4+ counts, or it may be that the particular cellular responses which are generated as a result of HIV-IT therapy are not key immune responses necessary to control HIV replication. Only further study will help shed light on the utility of this approach.

One interesting abstract on a new form of alpha interferon renews interest in this class of drugs as a therapy for HIV-disease. Early studies of interferon-alpha were mixed, with some studies suggesting that increases in certain forms of naturally occurring interferon-alpha were correlated with disease progression and others suggesting that the administration of manufactured alpha interferon may be beneficial. Studies conducted through the National Institutes of Health seemed to suggest that interferon-alpha may benefit people with HIV-disease, but toxicities were a limiting factor in the utility of this approach, with approximately 35% of people suffering from flu-like symptoms resulting in discontinuation of therapy. A company based in New Jersey, Interferon Sciences, Inc., has identified a form of the chemical which appears to have greater anti-HIV effect than the currently available product, interferon-alpha 2b, in test tube studies. The Interferon Sciences' product, interferon-alpha n3, does not appear to have the same toxicities as the currently approved and available product. A small study shows that people receiving the interferon-alpha n3 did not experience the typical flu-like syndrome seen with interferon-alpha 2b, there were no documented liver, kidney or bone marrow toxicities and there appeared to be an antiviral benefit from the therapy. Interferon-alpha is a naturally occurring chemical, produced by immune cells, which is potently antiviral. Synthetic forms of interferon-alpha appear to decrease HIV replication in CD4+ (T-cells) cells by interfering with the production of certain key viral proteins, notably, gp120, which the virus needs in order to infect CD4+ cells. Moreover, interferon-alpha, in test tubes, completely blocks HIV infection of macrophages, another important immune system cell which is also impaired by HIV infection. The new form of interferon-alpha is being studied at Walter Reed Army Institute.

Another immune-based strategy, passive immune therapy, has been the focus of study for many years. Passive immune therapy involves taking plasma from people who are healthy, HIV+ and have high CD4+ counts, and giving it to people who have lower CD4+ counts, or are experiencing symptoms of HIV-disease. The thinking behind this approach is that there may be antibody responses which are beneficial in keeping HIV and perhaps even opportunistic infections in check which, as the immune system is disabled over the course of disease, are no longer as resilient. Rather than trying to 'actively' induce the body to mount an immune response, as is being attempted with HIV-IT, researchers are 'passively' transferring immune responses from people who are healthy to people who are more advanced in disease. Passive immune therapy has been successful in treating other diseases, including viral diseases, but data on its utility in HIV-disease have ranged from dubious to downright confusing. Some studies suggest that passive immune therapy may delay the development of opportunistic infections and have a positive impact on CD4+ count, while other studies show that it has no impact on HIV-disease whatsoever. Some researchers believe that the reason why these data are so mixed is because the level or amount of antibodies (called the antibody titer) being used in passive immune therapy approaches in HIV is far too low to have an impact on the disease process. These researchers cite other diseases where passive immune therapy has been effective and note that the amount of antibody used in those setting were many times higher than what is being applied in HIV. An abstract from the ICAAC meeting may support this claim. Certain antibody titers were measured prior to delivering passive immune therapy to people with AIDS. Two weeks after administering therapy people who received plasma with titers less than 1000 had undetectable levels of the transferred antibody. In contrast, people who received concentrations of antibody titers over 3000 had detectable antibodies after two weeks. This suggests that more frequent therapy, or much higher titers of antibodies, need to be included in strategies for passive immune therapy against HIV-disease. Until this happens the field, while still in limbo, at least will have a direction.

Preliminary data on another passive immune therapy approach, involving the use of monoclonal antibodies (engineered antibodies which target certain pathogens) were discussed at length at the ICAAC meeting. Monoclonal antibodies to HIV, CMV and hepatitis are all being explored in clinical trials. Data from a study of MSL 109, a CMV monoclonal antibody, suggest that the antibody is well tolerated and further studies will explore the potential benefit of MSL 109 with standard CMV treatment. Research into the hepatitis B monoclonal antibody is still in very early stages of human testing and preliminary reports suggest that higher doses may impact the level of detectable hepatitis virus. Further studies will be necessary to see if these approaches will be useful in fighting infections common among people living with HIV. If this technology pans out, less toxic alternatives to managing CMV, and new approaches to managing hepatitis could improve the quality life of people living with HIV.

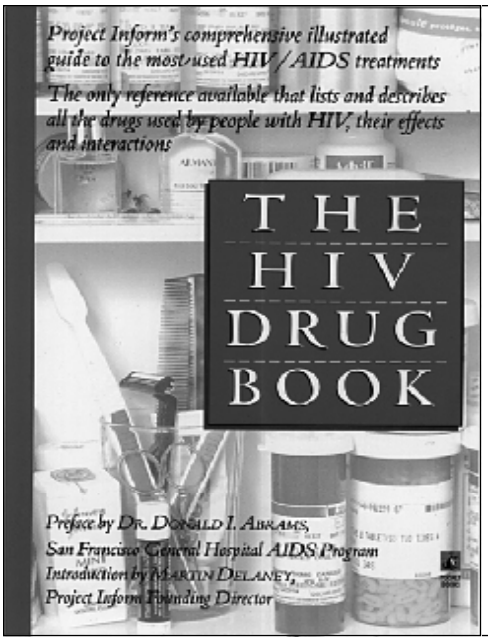
Perhaps the most interesting presentation on immune-based therapies were data from a study sponsored by the National Institutes of Health which looked at interleukin-2 and the Merck protease inhibitor, indinavir. The study involved people who had volunteered for previous IL-2 studies at the NIH, who either did not have a CD4+ benefit from previous

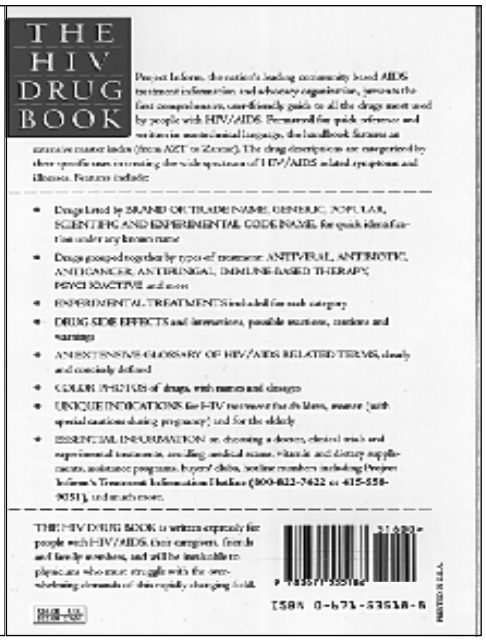
IL-2 therapy or who were part of the control arm and had CD4+ counts less than 300. The study involved 36 volunteers who received IL-2 + continuous indinavir, IL-2 + inidinavir administered only during the 10 days of the IL-2 infusion cycles, or continuous protease inhibitor alone. People receiving either IL-2 + continuous protease or continuous protease inhibitor alone had better CD4+ responses than those who received IL-2 with intermittent antiviral therapy. One participant, who had been on previous IL-2 ther-apy and experienced no CD4+ benefit, when given the Merck protease inhibitor (indinavir) with IL-2 had CD4+ increases from 226 to 1022. Another volunteer, on indinavir alone saw CD4+ rises from 185 to 1085. Because the CD4+ increases in both the indinavir alone as well as the indinavir + IL-2 arms were similar, CD4+ rises were attributed to the addition of indinavir. There was a trend toward greater increases in CD4+ in the IL-2 + continuous indinavir group, however. After 14 weeks on study, the mean CD4+ increase of the IL-2 + indinavir group was 185, and 83 in the indinavir alone group. By week 25 the mean CD4+ increase in the combination group was 200 and in the protease alone group it was 175. Increases in HIV RNA accompanied the infusion of IL-2, but after 14 weeks, viral load appeared stable, with the peak antiviral affect of indinavir occurring early, after one week on therapy. Side effects were predominantly attributable to IL-2 therapy, and included flu-like symptoms. The most common side effect of IL-2 was increased bilirubin. Another study, looking at sixty people with HIV whose CD4+ counts were greater than 200, compared IL-2 + antivirals (AZT, ddI, ddC and/or d4T) to antiviral therapy alone. The mean CD4+ count in each group was approximately 400. At month 10, the mean CD4+ count in the IL-2 treated group was 1000, by week 14 it had fallen to 800. After 16 months, there was a mean increase in CD4+ cells in the IL-2 group of 37, versus a decrease of 5 cells in the antiviral alone group. Future studies will look at IL-2 in combination with protease inhibitors and TNF-inhibitors, in hopes of controlling IL-2-related toxicities.

Antiviral Drug Resistance

On November 5, Project Inform and the Gay Men's Health Crisis of New York sponsored a meeting on resistance and cross resistance to protease inhibitors. The goal was to publicly discuss the potential development of cross resistance to protease inhibitors in light of expected approval of saquinavir and availability of indinavir and ritonavir through compassionate use programs. Representatives from pharmaceutical companies, the National Institutes of Health (NIH), the Department of Defense, the FDA, the Antiviral Drugs Advisory Committee to the FDA and independent scientists were invited.

Jon Condra and Emilio Emini of Merck described their findings on cross resistance between protease drugs. They defined "resistance" as a minimum fourfold loss of sensitivity to a drug. They related their experience with indinavir, showing that early use of the drug at low doses led to inadequate anti-HIV activity which was not entirely corrected by subsequent increased doses. From their results they argued that use of a less potent protease drug might make people unable to get the full benefit of a subsequent, stronger inhibitor. They also showed that resistance to indinavir is due to at least three mutations in nearly random





combination. Several mutation sites can contribute to resistance with indinavir, and one of the mutations found in some resistant isolates was also found to cause saquinavir resistance. Saquinavir may also produce this mutation, raising concern that prior use of saquinavir may predispose a patient to cross resistance or more rapid resistance with later use of indinavir.

Noel Roberts of Hoffman-La Roche summarized data from studies with saquinavir. Genotypic resistance to saquinavir was defined as any isolate having a mutation at the 48 or 90 codon of HIV protease. No other mutation sites seem associated with saquinavir resistance. In this regard, the drug is different from indinavir. Phenotypic resistance was defined as any isolate with a tenfold reduction in sensitivity from baseline, and is clinically more relevant than genotypic mutation because it measures susceptiblity of the virus to a drug. Genotypic resistance only indicates a specific mutation has occurred, not whether the mutation led to changes in virus' sensitivity to a given drug. Saquinavir has shown evidence of genotypic mutation after one year in 36% of people treated; about 60% are due to a change at the 90 site. Roberts argued genotypic resistance does not necessarily correlate with treatment failure. Isolates with genotypic resistance to saquinavir did not show significantly greater indinavir or ritonavir sensitivity. Some in the audience suggested that saquinavir's low bioavailability, and corresponding low antiviral effect, might result in less selective pressure on the virus to mutate. However, Dr. Roberts showed data from studies conducted by Thomas Merigan at Stanford using higher doses of saquinavir which produced greater antiviral effects. In these studies, there was no more or less evidence of resistance due to treatment, suggesting that differences in selective pressure did not play a role in saquinavir resistance.

An extensive discussion followed among the participants, summarized by the points below:

- If there is a clear bottom line, it is that we have more to learn about protease inhibitor drug resistance and its clinical implications. At this stage, the unknowns outweigh the knowns and no single point of view carries the weight of consensus.
- Current knowledge has been unable to clearly correlate genotypic and phenotypic resistance to protease inhibitors with clinical drug failure. There is even some evidence that drug resistance does not automatically lead to drug failure; some people treated with indinavir showed a sustained increase in CD4+ even though they had a return to high levels of viral production.
- Initial treatment with saquinavir may not produce resistance to subsequent drugs like indinavir. All that is known is that in some people, pretreatment with saquinavir may lead to development of one of several mutation sites needed for indinavir or ritonavir resistance. Conversely, someone who develops resistance to indinavir, is likely to be highly resistant to ritonavir and have a moderately resistant to saquinavir.
- In laboratory studies of the various protease inhibitors, saquinavir seems least affected by indinavir resistance, but the level of resistance is still high enough to pose a problem.
- For people with immediate need for new therapy, concerns and uncertainties about resistance do not now warrant withholding the use of an available drug. However, for those who are stable and not in immediate need of new therapy, it might be wise to wait for the development of further information and additional therapy options before taking a protease inhibitor.
- It is unclear whether people who start on the current formulation of saquinavir who then switch to the more bioavailable formulation in development will receive any additional antiviral benefit.

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