

The Coming Sunset on AIDS Funding Programs

At the heart of all the overheated discussion of recent advances in AIDS therapy lies a simple but profound change in the way we deal with the disease. For the first time, it has become possible (and necessary) to think of treatment as a long-term, planned strategy aimed at getting us through many years, rather than a few months. The previous decade's approach had largely been one of stumbling from one short-term crisis to the next, reacting to unforeseen infections and hoping that the latest new drug would provide another few months of respite from a relentless demon. Today's long-term treatment strategies make us think about how and when to use various drugs, how to combine them and how to anticipate the future consequences of each choice that we make. This approach has begun to offer the prospect of sustainable, long-term solutions. Having cleared this important hurdle in the science of AIDS, it is now time to address it in the politics of AIDS.

Sadly, the political thinking of AIDS activism has not yet undergone a similar, but equally necessary revolution. Today's debates, both federally and locally, focus on how to refine and expand existing care, prevention, and treatment support programs on a year by year basis. Each year, a new round of battles begin with the Administration, Congress and State legislatures as advocates seek to find additional funding for the AIDS Drug Assistance Program (ADAP—the program which pays for drugs for people who fall between the cracks of private insurance, managed health care and Medicaid).

Skirmishes flare up between the various groups funded by the Ryan White Care Act, often pitting individual patients, support services and agencies and prevention activities against each other in an ugly fight over increasingly inadequate resources. Each budget year brings a new and increasingly critical debate about the adequacy of funding for Medicaid and how the funds are distributed by the states. Similarly, battle-weary treatment activists continue to launch drug-by-drug, company-by-company struggles over the makeup of patient assistance programs, drug prices and expanded access programs.

While all these battles are sincerely waged in the interests of people with AIDS, all of them miss the point. All are doomed to long-term political failure. The complex plethora of services and support mechanisms created in the name of AIDS is heading for near certain future disaster if we continue to engage in the short-term thinking which presently dominates the debate. Historically, most these programs have been modeled after one form or another of "disaster relief" efforts, the kind of quick-fix mechanisms applied to clean up after hurricanes, floods and earthquakes. A fundamental characteristic of such programs is that they have a beginning, a middle and an end. Another characteristic is that they exist at the political whim of whoever is in power. When Congress tires of dolling out billions of dollars in a particularly disaster-prone year, it can simply say there is no money left and let the next group of hurricane or flood victims fend for themselves. This is not an effective model for what is likely to be an increasingly predictable, decades-long fight against a killer disease.

With each passing year, it's increasingly unclear whether the patchwork of AIDS funding can be sustained for another year. Consider, for example, the fact that the President's recent budget agreement with Congress has quietly and without fanfare eliminated AIDS, as well as the National Institutes of Health, from the list of domestic spending priorities. What is this telling us? How should we expect the public react to the endless stream of overstatement about the recent success of AIDS treatment? How much longer

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can special programs be maintained for AIDS which are not available for people with other devastating life-threatening illnesses?

Ask any seasoned AIDS activists, lobbyists or support people what they are working on these days and the answer will almost always be some immediate crisis or problem. All of our present support programs have been created to resolve a short-term crisis—a shortage of funding, the sudden unexpected availability of a new drug or diagnostic tool, an obvious unmet service need. But all the mechanisms we have created are little more than a complex series of Band-Aids, not real solutions to the underlying problem. Everything has been created to address fundamental gaps in the American health care and welfare systems. How long can a seriously ill patient live on Band-Aids? Not much longer at all. For a quick test of this question, ask any of the people presently fighting to shore up the ADAP program: do you plan to keep doing this yearly for the next 30 or 40 years? Or ask the same question of people fighting to support any Ryan White funded program: do you expect to succeed getting refunded from the next 30 or 40 Congresses? The next 10 administrations? Of course not! Few people even relish the prospects of success next year, let alone next decade.

Another rapidly growing threat is the very success of such programs. Nothing like them has ever existed for people with other life-threatening illnesses, and the public has begun to notice this. For the first time, advocates for other disease-interest groups have begun to rise up and challenge various aspects of AIDS funding in the Congress. We may have a lot of arguments why such comparison are inappropriate or unfair, but the sheer numbers do not favor the long-term success of the political view that AIDS is special and deserves special treatment. The problems faced by people with AIDS, while substantial and severe, are not totally unique. The same inequities and failures of the profit-driven health care system affect millions of people facing other life-threatening illnesses for which no special pro-

grams exist. They are beginning to ask, “Where are the Ryan White Care Act primary care programs for cancer? The ‘ADAP’ supplemental funding for heart disease or multiple sclerosis?” There are plenty of people with other life threatening illnesses who look with great envy upon the framework of support services offered for people with AIDS. Sooner or later, we must accept the fact that it is not unfair for them to ask for equal treatment from government, whether or not their advocates are as well-organized and persuasive as those for AIDS.

In short, unless there are sweeping changes, we are heading toward a future in which there will be no such thing as an ADAP program, a Ryan White Care Act or any other kind of special medical or social support program for AIDS. Such programs will not and cannot be sustained by sheer political will for decades on end. At the risk of causing utter hysteria among our fellow AIDS activists, perhaps it really is time that we ourselves start talking about shutting down such programs as ADAP, patient assistance programs, and Ryan White-funded health care services. Whether we like it or not, all such programs are going to wind up on the chopping block over the next several years.

It is time for us to end our reliance on short-term solutions and to get focused on the true solution—repairing or replacing the American health care system. The US remains the only wealthy “first world” country with a third world health care system for tens of millions of its people. The needs of people with AIDS should be routinely and automatically met by a fair and balanced national health care system. No such system is in sight, and no one even seems willing to talk about it, let alone work on it. All discussion ended with the demise of the efforts made by Hilary Clinton in the early years of the first Clinton administration. Whatever one’s feelings about the methods or proposals put forward at that time, at least the debate was in the national spotlight where it belongs.

It takes only a little honest introspection to realize the degree to which we as AIDS

advocates and our communities may have been diverted, if not “bought off” by the special programs and funding erected in response to our crisis-driven advocacy. While such programs may meet the individual needs of people in crisis, they do not solve the underlying problems that made AIDS such a crisis in the health care system. AIDS put the deficiencies of the system in the spotlight. But instead of fixing the system, we ended up settling for a literal side-show of programs, while leaving the system as deficient as ever. We may have gotten the basics of what was needed for some people with AIDS, but lost the opportunity to solve the problems on a larger scale. Today, we continue taking this short-term view and no longer are making national health care reform a major goal. We took our money and our jobs and we dropped out of the national debate. In the early days of the Clinton administration, most of our major AIDS service organizations were active players in the effort for health care reform. Today, no one mentions the issue, while we go about fighting for our annual program allowances. The communities affected by AIDS should be playing a leading role in the fight for healthcare reform because no other disease interest group is as well organized or politically savvy. But like Hilary and the Clinton administration, we folded up and went away when the powerful forces of the insurance industry, factions of the medical establishment, the pharmaceutical industry and other corporate interests banded together to mislead the public about the implications of national health care. We gave up when an incredible bill of false goods was effectively sold to the American people.

In future months when the competition for dollars heats up with other disease interest groups, we need to avoid going to war against them and instead invite them to join together with us in a massive coalition to reform the health care system. We must learn to be as concerned with the needs of their constituents as we are with our own. It is the only way we will achieve a lasting solution.

Make no mistake about it. The problems faced by people with AIDS should and must eventually be “mainstreamed” into the health care system. There is no other way to address these problems for the long haul. Such a transition will not be painless, however, since it almost guarantees that not all of our agencies, jobs, and buildings will survive. But that’s not what matters—it never did. The outcome will ultimately be good for people with AIDS, and it will be

good for the American public as we take what has been learned in the fight against AIDS and make it applicable to all life-threatening illnesses. Obviously, we must continue to meet the immediate needs of our constituents with existing, short term solutions. We must also begin to devote a significant portion of our political energy to developing the long-term strategies for dealing with AIDS as an expensive, life-long chronic illness that may soon be fully man-

ageable but perhaps not ultimately curable. We need to make sure that we take responsibility ourselves for engineering a graduated sunset on such programs as ADAP and Ryan White-funded health care and not leave it up to the whims of our political enemies. This time, we need to create solutions which can last a lifetime and which don’t leave people with AIDS forever sitting on the fragile political limb of special, annually renewed programs and services.

New Federal Guidelines for the Use of Antiretroviral Agents

Approximately one and a half years after the approval of the first protease inhibitor, the U.S. Department of Health and Human Services has issued its first new set of guidelines for the treatment of HIV disease in several years. While it may be easy to criticize the Guidelines as being late, it is equally important to note that they are as comprehensive and complete as the science allows. They reflect all that has been learned over the last several years of the epidemic.

Perhaps their greatest significance is that they should finally provide physicians throughout the nation with a reference standard for assessing their own prescription of the available therapies. In this regard, the Guidelines should help prevent many of the innocent yet harmful mistakes that are made by physicians or patients who operate without clear direction or solely at the direction of drug company sales personnel. Additionally, the new guidelines should help end the many debates about personal treatment strategies and preferences that have evolved among physicians in the absence of expert guidance. Conversely, the greatest limitation of the Guidelines is that they reflect the many legitimate uncertainties remaining about the use of the current therapies. Several key questions, such as when to start therapy, remain matters of professional opinion rather than proven fact. These and other uncertainties serve as a reminder that these Guidelines are a “work in progress” that will continue to be revised in future

years as additional information comes to light. The panel that created the Guidelines is scheduled to remain intact for at least three years to make sure that new information is routinely and quickly incorporated.

For regular readers of PI Perspective and other Project Inform publications, the new Guidelines offer no surprises. The Guidelines mimic, often word for word, the strategies that have appeared in PI publications for the last year and half. They underscore and support all the key points made in earlier PI strategy recommendations, including:

- The need to achieve “undetectable” viral load as the measurable objective of antiviral therapy;
- The use of triple combination therapy as the minimum baseline for all antiviral treatment, regardless of the stage of disease;
- Discouragement of the use of the standard formulation and dosing of saquinavir, recognizing that the available version of the drug lacks the potency of other protease inhibitors;

- The need to change two or more elements of a combination therapy when treatment fails;
- The recognition that science does not at any one moment have all the answers to the most difficult individual questions such as “when is best time to start therapy?” People must learn to make reasonable choices, acknowledging the uncertainties, risks and benefits and not expect to find rigid cookbook solutions.

History of the Guidelines

Long before data about the first protease inhibitors were submitted to the Food and Drug Administration (FDA), community groups called upon the various federal agencies to convene a task force to address the issues this new class of drugs was likely to raise. Studies had made it clear as early as 1994 that the new drugs offered an unprecedented level of hope but also triggered a new set of problems. Although a Task Force was convened that united community representatives, researchers, government regulators, physicians and pharmaceutical companies, the Department of Health and Human Services never acted upon the group’s recommendations. Early in 1996 when the promise of aggressive combination therapy was clearly proven, Project Inform and others called upon Secretary of Health and Human Services Donna Shalala to prepare physicians to use the new drugs wisely. Her office initially assigned the task to the new Office of AIDS Research (OAR). An initial OAR effort using an outside contractor failed, leading to creation of a committee in the fall of 1996.

By then Secretary Shalala had already initiated a second, independent process to accomplish the same task, headed by Dr. Eric Goosby of the National AIDS Office and co-chaired by Dr. Anthony Fauci of the National Institute of Allergy and Infectious Diseases. In the end, the OAR committee wrote a document describing the general principles of therapy, while the Goosby/Fauci panel wrote the specific recommendations. Both reflect the input of a wide range of experts in AIDS research, community activists, clinicians and other health care providers. To the credit of the government people working on the project, they did a fine job incorporating the many different views into a single, coherent document.

Nuts and Bolts of the Guidelines

The complete Guidelines will be distributed to physicians nationwide and will be available from Project Inform, government offices, websites and many AIDS service organizations. Much of the content of the Guidelines can be summarized in a few points:

- The pace of HIV disease progression is tightly linked to a patient's individual level of HIV replication.
- For now, the evidence makes it clear that HIV disease is best treated by suppressing HIV replication to the lowest level possible, ideally below the limit of detection on the available assays (RT-PCR and bDNA tests).
- HIV RNA levels (viral load) and CD4+ cell counts should be used to determine the timing, course and effectiveness of therapy.
- At any stage of disease, treatment should be based on a powerful 3-drug combination with a high likelihood of achieving undetectable viral load. This now discourages the use of previously recommended 2-drug regimens, such as AZT plus 3TC even early in the course of disease.

Who Should be Treated?

The Guidelines make a fairly strong assertion that most people who are HIV infected should make use of the new antiviral drugs. However, they acknowledge that several fac-

tors must be considered when deciding to initiate therapy, including personal preferences and willingness to commit to what might be a difficult treatment regimen. Other factors to consider, in addition to lab data, include side effects, the long-term course of therapy and the need to extend the use of available drugs over many years. Specifically, the Guidelines suggest that physicians offer treatment as the recommended option for:

- All people with symptoms of HIV infection;
- All people with CD4+ counts consistently below 500;
- People with CD4+ counts above 500 who have significantly detectable viral load

(above 10,000 copies on the bDNA test or 20,000 copies on RT-PCR).

The only time the Guidelines recommend “observing” rather than “treating” a patient is when people have CD4+ cell counts above 500 and viral load below 10,000 copies on the bDNA test or below 20,000 on the RT-PCR test. By “observe” the Guidelines mean to repeat CD4+ and viral load testing at 3 to 4 month intervals. The Guidelines also acknowledge that some physicians may choose to treat even this group, based on observations about the constant rate of HIV replication regardless of disease stage.

A broader description of the treatment recommendations is found in Table 1.

The Guidelines recommend that physicians also consider the relative risk of disease progression over time as a factor in determining when to initiate therapy, particularly regarding asymptomatic people with CD4+ counts above 500. Table 2 represents data from the Multicenter AIDS Cohort Study (MACS) and indicates the relative levels of risk for three groups based on CD4+ cell counts and HIV viral loads. Consideration of these data may give physicians and their patients a sense of the relative risks associated with delaying treatment decisions. These figures represent a change from previously published data, primarily a correction for the age of the stored samples used. Earlier versions of this data showed the same outcomes over time, but associated them with lower levels of viral load, based on errors in the testing process caused by use of older, stored blood samples. Researchers recently conducted new studies to determine how long-term storage had affected the blood samples. The new study found that storage of the blood samples caused the viral load levels to shrink somewhat as the blood sample aged. Thus, the real viral load level associated with a particular outcome, using fresh blood samples, would be somewhat higher than the numbers reported earlier. In addition to this important observation, the new study also showed that the aging of blood samples affected the two most commonly available PCR tests (bDNA and RT-PCR) quite differently. Thus, two sets of numbers are given—one which is relevant for people using the bDNA test and the other for those using the RT-PCR.

Table 1: Recommendations Based on Stage of Disease

Advanced Stage Disease

All people with AIDS should be treated. When initiating therapy for opportunistic infections at the same time as initiating antiviral therapy, special care should be taken to avoid drug interactions. When a patient experiences an opportunistic infection, he or she should not normally be taken off of antiviral therapy.

Persons with symptomatic disease, regardless of CD4+ counts

All should be treated after consideration of the issues affecting treatment choices.

Asymptomatic (i.e., no symptoms) with CD4+ counts below 500

All should be treated after consideration of the issues affecting treatment choices.

Asymptomatic with CD4+ counts above 500

There are two unproven approaches to treatment in early, asymptomatic people: aggressive and conservative. For people with CD4+ cell counts above 500 and a low viral load (typically under 10,000 to 20,000), there is no available data to suggest which approach results in longer survival. Very early, aggressive treatment might lead to longer life. Or, conversely, it might lead to using up the limited supply of therapies too early in the course of disease by triggering the development of viral resistance earlier than necessary. In addition to the general principles and patient preferences, the Guidelines recommend that physicians take into account the relative risk of disease progression people face based on their viral load (see Table 2).

Acute Infection (people who are determined to be infected very early in the course of disease, typically the first few months.)

If infection is suspected, test for HIV viral load. Many, but not all, experts recommend treatment if the test is positive, even at low levels. They believe this offers the chance of changing the entire later course of HIV disease in the person. However, people should be made aware of all the potential risks and benefits of such early treatment. The true long-term effect of immediate treatment is unknown because current studies are not yet complete. Some experts also recommend treatment for all people who were infected within the previous six months. Similarly, immediate treatment is recommended for people with suspected exposure due to accidents in the healthcare setting.

Treatment of HIV-infected pregnant women

Guidelines include the same considerations given anyone else at similar stages of disease. However, due to concerns about the effect of powerful antiviral drugs on the early developing fetus, some researchers recommend delaying initiation of antiviral treatment until after the 14th week of pregnancy. For those already on therapy, some recommend temporarily stopping therapy. These views are based on theoretical but currently unproven concerns.

The Basic Message

- Learn about HIV testing options and choose one that fits your needs! Be sure your privacy is protected!
- If you're positive, don't panic. If you make your health a priority, chances are you will be reasonably healthy for many years.
- Learn about your healthcare options and local support services.
- Get a complete physical and blood tests for CD4+ cell count and HIV level. Repeat quarterly and watch for trends. Women should get GYN exams and Pap tests every six months, more often if abnormal.
- Work with a doctor to develop a long-term strategy for managing HIV disease.
- If the CD4+ cell count is below 350 or falling rapidly, consider starting anti-HIV therapy. Test at least twice before taking action.
- If anti-HIV therapy fails to reduce your HIV level below the "limit of detection" or below 5,000 copies within 3–6 months, consider a different or more aggressive therapy.
- If the CD4+ count trend stays below 300, consider treatment for preventing PCP. If it stays below 200, start treatment for preventing PCP (if you haven't already done so) and reconsider anti-HIV therapy if not on one. Learn about drug interactions and preventive treatments for opportunistic infections.
- If you started preventive therapies and your CD4+ cell count rises in response to anti-HIV therapy, ask your doctor whether it might be safe to stop certain preventive therapies.
- If your CD4+ cell count stays below 75, consider more frequent blood work—perhaps monthly. Consider therapies for preventing MAC/MAI and CMV.
- Regularly seek support for your personal, spiritual and emotional needs. It takes more than medicines to keep you well.

**Table 2: Multicenter AIDS Cohort Study
Progression Rates by CD4 and Viral Load Category**

Group 1: CD4+ = <350					
Viral Load*		% developing AIDS over time			
bDNA	RT-PCR	N	3 years	6 years	9 years
<1,000	<2,000	3	0	0	0
1,001–6,000	2,001–12,000	30	0	18.8	30.6
6,001–20,000	12,001–40,000	51	8.0	42.2	65.6
20,001–60,000	40,001–120,000	73	40.1	72.9	86.2
>60,000	>120,000	174	72.9	92.7	95.6

Group 2: CD4+ = 351–500					
Viral Load*		% developing AIDS over time			
bDNA	RT-PCR	N	3 years	6 years	9 years
<1,000	<2,000	NA**	NA	NA	NA
1,001–6,000	2,001–12,000	47	4.4	22.1	46.9
6,001–20,000	12,001–40,000	105	5.9	39.8	60.7
20,001–60,000	40,001–120,000	121	15.1	57.2	78.6
>60,000	>120,000	121	47.9	77.7	94.4

Group 3: CD4 = >500					
Viral Load*		% developing AIDS over time			
bDNA	RT-PCR	N	3 years	6 years	9 years
<1,000	<2,000	110	1.0	5.0	10.7
1,001–6,000	2,001–12,000	180	2.3	14.9	33.2
6,001–20,000	12,001–40,000	237	7.2	25.9	50.3
20,001–60,000	40,001–120,000	202	14.6	47.7	70.6
>60,000	>120,000	141	32.6	66.8	76.3

* Values given are adjusted from the original MACS data to correct for the presence of heparin and the effects of prolonged storage.** NA= not available. N= number of people in the group in the MACS study

Table 3: Putting Together an Effective Combination Therapy

Choose one drug from Column A and one combination from Column B	
Column A	Column B
Indinavir	AZT + ddl
Nelfinavir	D4T + ddl
Ritonavir	AZT + ddC
	AZT + 3TC
	D4T + 3TC

Certain combinations are not recommended, based either on evidence from clinical trials, toxicity, or the resistance characteristics of the drugs. The combinations specifically not recommended include AZT + d4T; ddC + ddl; ddC + d4T; ddI + 3TC and ddC + 3TC.

What to Use in Treatment

In all instances, whenever treatment is initiated, the Guidelines suggest that it should employ a triple drug combination using one of the highly active protease inhibitors (indinavir, nelfinavir, or ritonavir) and two nucleoside analogues as described in Table 3. For the most potent results, all three drugs should be new to the patient (not previously used). Saquinavir in its current, hard-gel formulation is not recommended as a first-line protease inhibitor because of its poor retention in the blood stream. Recent studies suggest that people would need to use 8 to 9 times the current standard dosage of saquinavir to achieve antiviral activity equivalent to the other protease inhibitors. Some researchers believe that triple combinations employing nevirapine, rather than a protease inhibitor may be a reasonable choice in some situations as an alternative to the protease inhibitor. They argue, correctly, that there is insufficient data from clinical trials to prove that a protease inhibitor always makes for a more potent combination. No specific mention is made of the role of other drugs in the same class as nevirapine.

There is insufficient data at this time to recommend any one of the three main protease inhibitors or any of the various combinations of reverse transcriptase inhibitors over any others. Each drug, however, has highly individual characteristics that will impact people in different ways. Individuals and their physicians should study the options and choose according to specific needs and preferences.

When to Change Therapy

The Guidelines suggest six criteria that may signal the need to change therapy. These include:

1. Failure to achieve at least a 1 log (10 fold) reduction in HIV RNA within 4 weeks of initiating a new treatment regimen. (Though not mentioned in the Guidelines, Project Inform recommends caution in applying this point to people with advanced disease, who sometimes show a slower response to therapy due to concurrent conditions or other factors).
2. Failure to suppress HIV RNA to undetectable levels within 4–6 months after initiating therapy. This is a general but not an absolute requirement, since some people may start with such high viral loads that it is almost impossible to achieve undetectable levels. Physician judgment is required in implementing this point.
3. Return to detectable levels of HIV RNA after they had become undetectable, indicating the development of drug resistance. (This should be determined by repeated tests, not a single test result, since any single test might be misleading). Return to very low viral load levels, such as 5,000, may not always warrant changing therapy, but should signal a need for close observation and more frequent viral load testing to determine whether resistance is beginning to develop.
4. Any reproducible (by repeated tests) increase of HIV RNA of 3-fold or greater above the lowest level achieved. Care must be taken, however, to be sure that such an increase is not due to other causes, such as concurrent on-going infections, use of vaccines or changing test methods, such as switching from bDNA to RT-PCR versions of the viral load test.
5. Persistently declining CD4+ count, as measured on at least 2 occasions.
6. Clinical deterioration, unless the person was already severely immuno-compromised prior to initiating the antiviral therapy.

While any of these conditions may indicate at least the beginning of antiviral treatment failure, they are often not the only factor to

consider when deciding to change therapy. The Guidelines remind physicians that patients do not have an unlimited list of antiviral drugs from which to choose. Thus, the present and future available options must also be considered in making the decision to change treatment. In some cases, no optimal choice may be available for an individual at the moment but one might be on the near horizon as new drugs move toward FDA approval. In such cases, it may be wise to delay changing treatment until the better regimen becomes available.

What to Change to

Very little data are currently available to guide physicians and patients in making decisions about what to do when a triple combination therapy fails. No clinical trials have yet been completed for this situation, although some are just getting underway. Therefore, the Guidelines offer only “expert opinion” on this issue. “Expert opinion” in this context may almost be translated as “try whatever is left,” as there is very little data to support any of these recommendations.

Commentary

Many recommendations from these new Guidelines are sound and well supported by clinical trial data. This is particularly true for the more general points, such as the need to strive to suppress HIV below the limit of detection and the need to initiate therapy with three drugs instead of two. The data about specific drugs, however, are less certain. While a few points are clearly established, such as the inferiority of the current hard-gel version of saquinavir, there is little hard substance to many of the other recommendations made about specific drugs. For example, most of the impressive data about triple combination therapy comes from studies which matched a highly active protease inhibitor with AZT and 3TC, yet the Guidelines seem to imply that any two nucleoside analogue drugs will do just as well. This is very likely not the case. The importance of 3TC is probably underplayed here. At least when a person first begins to use it, it is the most potent of the approved nucleoside drugs and it likely is a

critical factor in achieving high rates of success. But, since it is prone to early development of resistance, it must be used for the first time in a triple combination in order to preserve its potency.

The Guidelines are equally fuzzy about the use of nevirapine. People on the committee responsible for the Guidelines were divided on the use of this drug. Some felt it had not been shown to be an adequately effective partner as a replacement for a protease inhibitor in a three-drug combination. Others felt it had clearly distinguished itself. The problem behind such debates is that few of the studies done for any of these drugs are directly comparable to the studies done for any others. It is difficult to determine the relative contributions of each drug except when one is dramatically weaker, such as saquinavir. This lack of comparability in clinical trials also affects the ability to evaluate the relative potency of nelfinavir, and will soon have a similar effect regarding the new, improved version of saquinavir.

In a broad sense, the general thrust of the Guidelines that treatment must always include a protease inhibitor plus two nucleoside analogues is an overstatement. This is largely an artifact of the way recent studies have been done, not a broad comparison to all the other possible strategies. There is no data to suggest that there is any magic to such combinations or that they are inherently more effective than other possible combinations, such as two protease inhibitors or a protease inhibitor plus one each of the two different kinds of reverse transcriptase inhibitors. The Guidelines favor “one protease plus two nucleosides” only because such combinations have been proven more effective than two-drug nucleoside combinations such as AZT plus 3TC. But there is already growing evidence that dual protease therapy, such as the ritonavir/saquinavir combination, can be at least as effective and durable as any triple combination therapy. It is likely that, as more data accumulates, we will find that what matters most is the total potency of the individual drugs used and their patterns of resistance. The more potent the drugs and the less sensitive they are to resistance, the fewer will be needed.

For now, it is best to view these guidelines as strong generalities, but not as the final word on individual therapies. The text sections, not reprinted here, address these and many other issues. Interested parties should read the entire document.

Project Inform will continue to conduct its own assessment of present and future clinical trial results in the interests of building upon and extending the knowledge presented here. Earlier work allowed PI to accurately present the strategies for antiviral

treatment more than a year before government was able to achieve consensus. We had previously urged the use of combination therapy at least five years before it became the standard-of-care. We hope to maintain a similar lead in future developments.

Update on Antivirals

Recent information about the potential for cross-resistance between protease inhibitors underscores the importance of making wise choices when a person first begins using this class of drug. Early studies had shown that starting on lower, inadequate doses of a protease inhibitor damaged a person’s ability to benefit later from the recommended dose. This led Project Inform and several researchers to caution about using the current version of saquinavir (Invirase) because it is poorly absorbed by the body and therefore has little chance of producing adequate antiviral activity.

Data from new studies, described below, demonstrate that people who initiated therapy using the original, flawed version of saquinavir received little or no benefit from later switching to indinavir or to a new, improved version of saquinavir. Now, Hoffman-La Roche, manufacturer of saquinavir has released data from its own studies of its new, improved formulation of the drug. These studies demonstrate how severe the problem was with the older version, concluding that when used as prescribed, the drug produced only about 1/8 of the dose necessary to achieve effective suppression of HIV. These results strongly confirm the admonition of Project Inform that the standard version of saquinavir is not an appropriate protease inhibitor to use as part of one’s first anti-HIV regimen. It should only be used in combination with a second protease inhibitor, particularly with ritonavir (Norvir). However, the new formulation of saquinavir, has much better antiviral activity than the currently available formulation, and may be an option for first-line therapy in the future. The new version is not expected to receive FDA approval until fall of 1997.

New Soft Gel Capsule Formulation of Saquinavir
Results from studies of the soft gel formulation (SGC) of saquinavir (also sometimes referred to as the enhanced oral formulation (EOF)) show far better activity than the available hard gel formulation (HGC). Although the studies conducted so far make it impossible to make a direct comparison to other protease inhibitors, it is safe to say that the new version is far more potent than the earlier one and warrants classification as a highly active antiviral. However, these results also indicate that people who have previously used HGC saquinavir will get little additional benefit when they switch to the soft gel formulation.

The first study describing activity of the new formulation was an independent AIDS Clinical Trials Group trial (ACTG study

333). It enrolled 76 people who had been on long-term HGC saquinavir therapy (an average of 112 weeks) and had never taken other protease inhibitors. They received either indinavir (Crixivan), SGC saquinavir or continued on HGC saquinavir. Participants in the study had an average of 222 CD4+ cells and a viral load of about 21,000 copies. All people only switched their protease inhibitor and did not switch or add other drugs in their regimen. The results are reported in Table 1 below.

This study was stopped after 8 weeks because none of the therapies met the study criteria for effectiveness, which stated that a therapy had to decrease viral load by at least 0.7 logs to be considered effective. Clearly none of the therapies were able to achieve this goal after a person had used the earlier version of saquinavir. Among the people who were switched to indinavir, 25% had at least a 1 log drop in viral load, 25% had no viral load change at all and 50% had a reduction that was half a log or less. This is significantly less than the 1.5 to 2 log drops that have been observed in the indinavir single-drug therapy studies among people who had not taken prior protease therapy.

The first of two studies conducted by Hoffman-La Roche was designed to determine the optimal dose of the drug. This study enrolled 88 who received three different doses, ranging from 400 mg to 1,200 mg three times daily were evaluated. Antiviral activity was far superior in the 1,200

Table 1: ACTG 333, Saquinavir Formulations

	Viral load@ week 8	CD4+ cell gain@ week 8	% below LD
HGC SQV	No Change	No Change	9%
SGC SQV	0.23 logs	37	10%
IDV	0.58 logs	23	37%

LD = 200 copies HIV RNA; SQV = saquinavir; IDV = indinavir

mg three times daily group (1.43 log reduction in viral levels by week 8) than any of the lower doses studied. This dose (3,600 mg daily) of the SGC saquinavir results in blood levels of the drug that are 8 to 10 times higher than the currently approved dose of the HGC saquinavir, as well as far greater suppression of viral load.

Although the new version delivers about 4 times as much drug to the bloodstream as the older one, this study concluded that this alone was insufficient to achieve adequate potency. It is clear that a high level of antiviral activity was only achieved when the total daily dose of the drug was increased over the previously recommended dosage as well. Combining both the greater potency and the new higher dose, the 1,200 mg three times a day dose of SGC saquinavir (3600 mg daily) achieves blood levels that are 8–10 times higher than that of the currently approved 600 mg three times a day dose of HGC saquinavir.

A second study by the manufacturer enrolled 442 people to receive soft gel saquinavir at the new double dosing level (1,200 mg three times a day) in combination with nucleoside analogue reverse transcriptase inhibitor drugs (NRTIs), such as AZT, ddI, ddC, d4T and 3TC. There was no CD4+ cell count or HIV RNA entry criteria required to participate in this study. Participants had an average CD4+ cell count of 200 and HIV RNA level of 18,000 copies. The majority

merely added the SGC saquinavir to their existing treatment regimen without switching or adding other new therapies. Only 54 of the 442 people added one new nucleoside analogue drug when starting SGC saquinavir and only 23 people added two new nucleoside analogue drugs. Seventy-nine of the participants had been on a previous combination which included a protease inhibitor (71 of the 79 were on HGC saquinavir). The results from this study at week 24 are reported in Table 2 below.

These results again confirm that people with prior use of protease inhibitors (most here had previously used HGC saquinavir) are less likely to get a significant benefit from the new drug. They also appear to confirm the importance of starting at least two if not three new drugs at the same time, rather than simply adding a new one. None of the results are particularly impressive, nor do they compare well to studies in which two or more new drugs were used. This is probably not a reflection on the new saquinavir as it is on the way the drug was used in this study.

These studies collectively show that HGC saquinavir should not be used as first line therapy as this will likely result in little benefit from subsequent protease inhibitor use.

Side effects that have been reported in the studies of SGC saquinavir include diarrhea, nausea, fatigue, headache and abdominal discomfort.

Indinavir Study in Brazil (Protocol 028)

Results from a highly controversial indinavir (Crixivan) study conducted by Merck in Brazil were recently released. The study enrolled 996 people who had between 50–250 CD4+ cells and no prior antiviral therapy. They received AZT alone, indinavir alone or AZT + indinavir. The study was conducted largely to satisfy FDA requirements to show proof of clinical efficacy from the drug. A study like this would never have been permitted in the U.S., since it employed substandard care as the control arm or point of comparison in the study. During the study and in response to political pressure, however, people receiving AZT alone or AZT + indinavir had 3TC added to their regimen. The results at 58 weeks are reported in Table 3 below.

The study was stopped early when it showed a dramatic difference in the percentage of people developing AIDS in either of the groups receiving indinavir compared to the group receiving AZT alone. This study found that people receiving AZT + indinavir were 70% less likely to progress compared to people receiving AZT alone. Similarly, people receiving indinavir alone were 61% less likely to progress compared to those receiving AZT alone.

Results from this study are not unexpected. AZT alone is not a particularly potent anti-HIV drug and will only have modest antiviral activity. Therefore, many people believed that giving people AZT alone, when information on the benefits of triple combination therapy stands for itself, was unethical and that the outcome was already a forgone conclusion. This type of study, which relied on making comparisons to older treatment regimens known to be ineffective, should never again be permitted, either in the U.S. or other countries.

Intravenous PMPA

Results from a small, short-term study of intravenous (IV) PMPA show that the drug has potent anti-HIV activity. PMPA is a new nucleotide analogue reverse transcriptase

Table 2: Saquinavir Formulations Open Label Study

	VL drop	>CD4+ increase	% below LD
Overall	0.9 logs	60	42
PI naïve	0.97 logs	73	46
PI experienced	0.46 logs	48	28

LD = 400 copies HIV RNA PI = Protease Inhibitor

Table 3: Brazilian Indinavir Study

	VL drop	CD4+ increase	% below LD	# progressing to AIDS
AZT	0.25 logs	21	9%	61 (18%)
IDV	0.76 logs	103	34%	26 (7.8%)
AZT + IDV	1.03 logs	112	42%	20 (6%)

LD = 500 copies of HIV RNA IDV = indinavir

inhibitor, which means that like the nucleoside analogues, AZT, ddI, 3TC etc., PMPA targets the reverse transcriptase enzymes of HIV. The major difference between a nucleoside and a nucleotide analogue is that the nucleoside analogues have to become 'activated' in order to be effective, whereas nucleotides are already activated. Twenty people with CD4+ cell counts greater than 200 and detectable viral loads participated. There were no limitations as to whether they had used prior antiviral therapies. Participants were put in three groups receiving 1.0mg/kg of PMPA, 3 mg/kg of PMPA or placebo. Over the 14 days of study, participants were given one dose on the first day followed by a 6 day period of no therapy. After that, doses were given once a day for 7 more days. After the seventh day of daily therapy, people receiving the 1.0mg/kg dose had a median viral load drop of 0.6 logs and those receiving the 3.0mg/kg dose had a median viral load drop of 1.1 logs. These results are impressive because it usually takes around 16 weeks of therapy to reach the maximal response (lowest viral load level). The few reported side effects included headaches, fatigue and dizziness and were generally mild to moderate in nature. Gilead Sciences, the developer of PMPA, has developed an oral formulation which is now being studied in clinical trials. Preliminary results from studies of PMPA are quite encouraging and indicate that it may be a new highly active agent to consider as part of a potent anti-HIV regimen. Advantages of PMPA are that it may require less frequent dosing than currently available therapies (only once daily or perhaps even less in a combination) and appears to active against forms of HIV that have become resistant to other anti-HIV therapies, including protease resistant strains of HIV.

Commentary

We still have only limited knowledge on how to best use protease inhibitors, and as a result many physicians have begun to 'experiment' with some of these therapies, often without the benefit of information from clinical trials. Certain drugs are now being used to boost levels of the antiviral

drugs to enhance potency or to create a more user-friendly dosing schedule, such as changing three times daily dosing to twice daily dosing. Unfortunately, very little information is available to know if this is a viable approach. In some instances, this has already proven futile. For example, new data suggests that no amount of fiddling with the dose of the standard saquinavir, nor efforts to boost its potency by adding grapefruit juice or ketoconazole, were capable of achieving the 8 to 9 fold increase in potency needed. Additionally, this technique may result in increasing levels of other drugs, resulting in added side effects. Moreover, changing the dose frequency raises the pos-

sibility that drug levels become so low between doses that the virus is able to mutate and become resistant to the drug.

Some of the drugs being used to boost other drug levels include ritonavir (Norvir), delavirdine (Rescriptor) and ketoconazole (Nizoral). Perhaps the only proven example of this technique has been the effort to combine ritonavir + HGC saquinavir. Ritonavir dramatically increases saquinavir levels (over 20-fold) and is thus also able change the dosing frequency of saquinavir from three times daily to twice daily. Other clinical studies employing some of these strategies are now ongoing with some results expected by the end of this year.

Saquinavir: Many Issues, Few Answers

While it is important that an adequate formulation and proper dosage have now been determined for saquinavir (Invirase), these changes create several major dilemmas.

How will the drug be priced? Will the net price be twice as high, since twice the dosage is being used?

If the new dosage is correct, this means that the current version is delivering only 1/8 or 1/9 the proper dose. How much harm has already been done by the dramatic under-dosing of this drug? Even people who thought they were solving the problems of the old formulation by taking double or triple doses, or taking secondary drugs to improve its bioavailability, now know that their efforts were likely futile.

The improved drug won't be available for several more months. Is there any ethical basis for continuing the sale or promotion of the existing drug? Would anyone permit the sale or promotion of 1/8 or 1/9 doses of indinavir, ritonavir, or nelfinavir?

Who's obligation is it now to quickly inform physicians and patients—at least those who weren't listening to Project Inform and a few other voices on the subject—not to use the current standard version of the drug? Shouldn't the FDA demand that physician

warning letters be sent out immediately?

What's to prevent problems like this from happening again? Why was the company permitted to continue marketing the drug without warning labels when most of the facts about inadequate dosing have been well known since early 1996?

Who is responsible for the harm done by the aggressive marketing of saquinavir which has taken place world-wide over the last year and half?

Project Inform and other activist groups have asked the sponsor to withdraw their current advertising campaign, which aggressively promotes the drug to HIV infected people without the slightest mention of the well-known problems. The company has attempted to comply and in most instances, the ads have been withdrawn. However, a few vendors who have demonstrated that they value their advertising revenue over the interests of people with HIV disease have held the company to earlier contractual arrangements and have been unwilling to pull the ads. All ads will disappear by

mid-summer and the ad campaigns will switch to the new formulation as soon as the FDA permits. In our view, these ads should never have been permitted by the FDA in the first place and we urge all those publications which ran them to rethink their policies for evaluating ad placement on such sensitive, life-threatening matters.

Finally, we urge the FDA to call for an immediate warning campaign to physicians, advising them of the now well-proven deficiencies of the currently available drug and discouraging its use except in partnership with a second protease inhibitor.

The most frightening aspect of this story is that everything the sponsor did was tech-

nically in compliance with the law. In fact, compliance with the law in some ways interfered in the ability of the company to provide alternative information about dosing. Surely, something is wrong when the system produces such a bizarre outcome

Controlling Diarrhea

Diarrhea is a common problem for many people living with HIV. It occurs when bowel movements are loose (unformed) or watery. Diarrhea can be dangerous as it can result in severe dehydration, weight loss, weakness and malnutrition. It can also result in poor absorption of drugs, leading to decreased blood levels. This results in the same effect as taking too small a dose of drug, which hastens the development of drug resistance. Since many different factors can contribute to diarrhea, it is crucial that the causes be properly identified and treated and that plenty of fluids are taken right away to avoid dehydration.

Severe (acute) diarrhea that has just started may have different causes than diarrhea that has persisted for some time (chronic). A number of steps can be taken right away to help manage the diarrhea.

Step 1: Start drinking more fluids to prevent dehydration.

Diarrhea can result in significant water loss and dehydration. It is very important that fluids are restored immediately. Drinking Gatorade or other electrolyte-rich fluids can help restore nutrient levels and replace lost water. This may be particularly important for people using indinavir (Crixivan), since inadequate hydration when using the drug can lead to painful kidney stones.

Step 2: Determine the cause.

There are many potential causes of diarrhea, and several may be occurring at once. It's important to identify all the causes and treat them appropriately. These may include infections in the gut (e.g. parasitic, bacterial, fungal and viral infections), side effects of medications, lactose intolerance, diet and/

or HIV itself. The following questions may help pinpoint the problem.

Has blood in the stool (i.e. feces) and/or a fever been observed? IF YES, there may be an infection causing the diarrhea. A physician should be seen right away. Physicians will take a stool sample, test for the possible infections and recommend appropriate treatment. Some common infections include cryptosporidium, microsporidia, Mycobacterium Avium Complex (MAC), cytomegalovirus (CMV), giardia and salmonella. IF NO, consider seeing a doctor if symptomatic treatment (see step 3 below) does not stop the diarrhea within a few days. There may be an infection even without bloody stool or a fever.

Are any currently used medications known to cause diarrhea? Many anti-HIV drugs list diarrhea as a common side effect. A number of antibiotics like clarithromycin, azithromycin and ciprofloxacin can also cause diarrhea. Treating the symptoms may help in such cases (see step 3 below).

Is lactose intolerance a problem? A number of people with HIV cannot prop-

erly digest lactose, a sugar found in milk, cheese and other dairy products. Also, some medications come in capsules that contain lactose, such as the current formulation of saquinavir. If lactose intolerance is suspected, try eliminating dairy products to see if this improves the condition. It is often possible to correct the problem by using over-the-counter products designed to help digest lactose.

Is diet contributing to the problem?

High levels of fat in the diet are particularly difficult for the body to deal with during times of intestinal distress. In general, a low fat diet is easier to digest and puts less strain on the digestive system and liver. Many physicians make the mistake of encouraging people who have lost weight because of HIV to compensate by eating high fat diets. However, this can increase diarrhea.

Is the antiviral regimen working?

Sometimes, chronic diarrhea may be a direct result of HIV infection of the lymphatic tissues lining the intestinal tract. This is particularly difficult to combat since the best solution is potent antiviral therapy, yet diarrhea and poor absorption directly interfere with the uptake of these drugs. In this case, controlling the symptoms of diarrhea may help correct the underlying cause, by simply forcing the body to do a better job absorbing and retaining antiviral therapies.

Unfortunately, it is often difficult to determine the cause of diarrhea. Sometimes, repeated diagnostic tests must be run before a clear culprit is identified. When diarrhea is short-term and goes away on its own, it may not matter much. But when it is continuing and chronic, it is very important to keep searching for the cause, however unpleasant it may be.

Step 3: Treat the symptoms.

A number of over-the-counter medications and certain foods can temporarily help slow the diarrhea. However, these may just mask the problem without solving it. Identifying the cause(s) of diarrhea is critical to successful treatment, and symptom management should generally be considered a “bandaid” solution.

Anti-diarrhea medications: Imodium (loperamide), Kaopectate and Pepto-Bismol are over-the-counter drugs that can offer some relief for mild to moderate diarrhea. Lomotil (diphenoxylate) can help with moderate diarrhea, but must be prescribed by a physician. In the most severe cases, physicians may prescribe tincture of opium, a narcotic. Still another option is octreotide (Sandostatin), a synthetic hormone which slows the movement of food and liquid through the gut. However, if there is an infection causing the diarrhea, these drugs may prevent it from being cleared and may actually worsen the problem. Therefore they should be used with care. If the diarrhea does not go away in a few days despite using these medications, consult a doctor.

Bulking Agents (like Metamucil) and soluble fiber sources can help slow diarrhea by helping absorb liquids in the intestinal tract and causing bulking of stools. This approach is particularly useful with some drug-induced diarrhea. In general, soluble fiber is found in the “inside” or pulp parts of fruits and vegetables. Foods high in soluble fiber include oatmeal, white rice, grits, cream of wheat, bananas, soft breads (not whole grain), applesauce, etc.

Avoid insoluble fiber: Insoluble fiber is generally found in the outer skin of fruits and vegetables. This type of fiber doesn’t absorb water and prompts the intestines to move it along as quickly as possible, thus intensifying diarrhea. Diets which call for high fiber intake usually include large amounts of insoluble fiber, intended to speed clearance of the digestive tract. This is bad medicine for a person with diarrhea. It is also best to avoid typical “roughage” like lettuce, whole grain rice or wheat, and the skins of fruits or vegetables as these help clean out the intestines and can aggravate the bowels and intensify diarrhea.

Restoring the “friendly flora:” Certain “friendly” bacteria and yeast (meaning that they don’t cause infections) may help restore the environment of the gut. Such natural bacteria are often destroyed by commonly used antibiotics. As a general rule, people who regularly use antibiotics might consider routine use of products which help restore the natural flora. Acidophilus, various digestive enzymes and *S. boulardii* can be purchased in health food stores or buyer’s clubs.

Other treatments in development in-

clude Thalidomide, Bovine Colostrum and DEHOP (diethylhomospemene).

The bottom line is that it is important to diagnose the cause(s) of diarrhea as soon as possible and to treat appropriately while at the same time replenishing lost body fluids to prevent dehydration. Although anti-diarrhea medications are helpful, people should be cautious because these drugs may prevent infection-causing agents from leaving the body, thereby prolonging the problem if it is infectious in nature.

HIV Drug Side Effects

As more drugs are available to treat HIV and prevent and treat HIV-related opportunistic infections and malignancies, appropriately identifying the cause(s) of possible drug-related side effects becomes increasingly difficult. The following chart should only be used as a guide to help identify potential drug-related side effects.

Some of these side effects have been reported in medical literature, others are purely anecdotal. Obviously, not everyone taking a drug will experience that drug’s side effects. Most side effects show up in only a modest percentage of the people using a drug. Many people experience no obvious side effects, while others may experience several from the same drug. The manufacturer’s label, which is included with most prescriptions, typically lists how often different side effects have been seen in people participating in clinical trials. Drug side effects may be affected by interactions with other drugs (See the Drug Interactions Chart available through the hotline number below). A more extensive version of this chart, including laboratory abnormalities, is available by calling the Project Inform Treatment Hotline at 800 822 7422.

It’s important to recognize that no drug should be evaluated solely based on the number or type of side effects listed. Some drugs may have a high number of minor side effects, or side effects which impact on a large percentage of users, while others may have few or infrequent, but much more serious side effects. There is seldom any way

to predict what side effects will occur for an individual. In many cases, responses listed as drug side effects also occur as a consequence of HIV disease. It is often very difficult to tell whether the disease or the drug is responsible. Sometimes, even the anticipation of a particular side effect can influence how often it is reported in clinical trials. It is not uncommon, for example, for people receiving a placebo (harmless substances disguised to look and taste like a drug) to report the same side effects as those receiving the real drug.

This guide should primarily be used to help identify the possible causes of effects noted when using a drug. Often, the best way to determine whether a drug is the cause is to temporarily stop using the drug. However, this approach itself can have harmful consequences, such as encouraging faster development of drug resistance. In many instances, therefore, it may be useful to try to overcome a side effect rather than withdraw the use of a drug, especially when there are few good alternatives to the drug in question. Suspected side effects, and compensating strategies, should always be discussed with your physician.

Using the Chart

The left hand column (vertical) lists all the side effects reported for the combined list of drugs. The top row (horizontal) lists each of the drugs most commonly used in HIV disease. The columns underneath each drug heading lists the rough percentage of people reporting each side effect for each drug. (Legend: “3” means the side effect has been reported in greater than 15% of people in clinical trials; “2” = 5–15%; “1” = less than 5%; blank = not reported)

	AZT	ddl	ddC	d4T	3TC	SQV	RTV	IDV	NFV	NVP	DLV	AZI	CLA	RBT	TS	AP	GCV	FOS	CDV	FLU
Abdominal pain	3	2	2	3	2	1	2	2	1	1	1	1	2	1	3	1	3	2	3	2
Altered taste	2	3	1			1	3	1			1		2	1		3	1	1	1	1
Anorexia	3	1	1	2	2		2	1	1		1			1	1	3	3	2	3	
Athralgia (joint pain)	3	1	1	3	2	1	1	1	1		1			1	1	1			1	
Chills	3	2	1	3	2	1	1	1			1				1	3	2	2	3	
Constipation	1	1	1	2		1	1	1			1				3		1	1	1	
Depression	1	1	1	2	2	1	1	1	1		1					1	1	2	1	
Diarrhea	3	3	2	3	3	1	3	1	3	1	1	2	2	1	2	1	3	3	3	1
Dizziness	2	1	1	2	2	1	2	1	1		1	1			3	3	1	2	1	
Fatigue	2	2	3	2	3	2	3	2	1		2	1		1	2	3	1	2	3	
Fevers	3	2	3	2	2	1	1	1	1	2	1			1	3	3	3	3	3	
Headache	3	2	3	3	3	1	2	2	1	2	2	1	2	1	3	1	1	3	3	2
Insomnia	2	1	1	3	2	1	1	1	1		1			1	2	1	1	1	1	
Malaise	3	1	1	3	3		1	1	1		1				1	1	1	2	1	
Myalgia (muscle pain)	3	2	2	3	2	1	2	1	1	1	1			1	1	1	1	1	1	
Nausea	3	2	2	3	3	1	3	3	2	2	2	1	3	2	3	3	3	3	3	1
Nephrolithiasis (kidney stones)								1												
Neurological symptoms	1	1	2	3	1	1	2	1	1	1	1	1		1	1	1	2	2	1	1
Neuropathy	1	3	3	3	2	1	1	1			1				1		2	2	1	
Pancreatitis		2	1	1	2	1	1		1		1				1	1	1	1		
Paresthesia (numbness, prickling, tingling)	1					1	2	1	1	1	1						2	2	1	
Rash	3	2	2	3	2	1	1		1	3	2	1	2	2	3	1	2	2	3	1
Seizures		1	1						1							1	1	2		1
Vomiting	2	2	2	3	2	1	3	2	1		1	1	2	1	3	3	2	2	3	1

SQV=Saquinavir; RTV=Ritonavir; IDV=Indinavir; NFV=NELFINAVIR; NVP=Nevirapine; DLV=Delavirdine; AZI=Azithromycin; CLA=Clarithromycin; RBT=Rifabutin; TS=Bactrim; AP=Aero. Pentamidine; GCV=Ganciclovir; FOS=Foscarnet; CDV=Cidofovir; FLU=Flucytosine

Dealing with Neuropathy

Peripheral neuropathy (PN), or damage to the peripheral (or outermost) nerves, is a potential side effect of many anti-HIV therapies or HIV itself and can greatly affect quality of life. Early signs of PN can include a sensation of burning, tingling or numbness in the fingers or toes. Some people describe an electric shock sensation or a strange, plastic or scab-like sensation when something touches their fingers or toes. In severe cases, touching the affected area can feel like touching an open wound. In some cases, there may be a deep soreness or shooting pains in the muscles of the legs and lower arms that may be transient but always affect the same spots. In more serious cases, severe pain and altered feedback in the nervous system may even interfere with walking.

Currently, there are no effective treatments that can stop or reverse this nerve damage. The most effective management of PN includes identifying the cause and, if possible, eliminating it. In many cases, the best treatment is simply pain management, and the type of medication used is generally determined by the severity of the PN.

Neuropathy can be caused by certain drugs, most commonly ddC (Hivid), ddI (Videx), 3TC (Epivir), d4T (Zerit), isoniazid (INH), vincristine (Oncovin), dapson and vitamin B6. Alcohol use or deficiency of vitamins B12 and E can also cause PN. People with a history of diabetes or thyroid disease may have a greater likelihood of PN. Neuropathy can also be caused by HIV itself, and it's hard to know whether the disease or its treatment is causing the problem.

If a person is experiencing symptoms of PN, the following questions may help pinpoint the problem.

1. Are any medications in the treatment regimen known to cause PN?

These include ddI, ddC, 3TC, d4T and the other drugs listed above. Combination therapy with two or more of these drugs is believed to increase the risk of PN, though this is not well documented. PN will often go away if these drugs are dose-reduced or

discontinued. It can sometimes take several months for PN to fully heal after removing the problematic drug, though some relief is often felt within a few weeks. It is critical to consult a physician before changing a drug regimen, as dose reduction of certain drugs can invite drug resistance. Be aware also that sometimes the symptoms of PN increase temporarily after a drug is stopped, but diminish soon thereafter. In some cases, if drugs are continued despite worsening PN, the nerve damage may become irreversible.

2. Is diabetes, a thyroid problem or vitamin B12 deficiency suspected? These conditions may exacerbate or even cause neuropathy. In such cases, a physician can help design a treatment strategy for the condition. For vitamin B12 deficiency, vitamin B supplements may help, but too much vitamin B6 (over 200 mg per day) can worsen PN.

3. If the cause of PN can't be clearly identified

(i.e., it may be due to HIV itself), or if the problem does not correct itself after stopping the drugs that may have caused it, chronic pain management may be required. Choice of treatment depends on the severity of symptoms. In the case of HIV-induced PN, some of the same drugs which cause the

problem may in fact help relieve it.

Mild symptoms: (just a tingling sensation but no problems walking, etc.) In this case, some people consider using a conservative strategy of simply observing the symptoms. Others find that mild pain can be relieved by using non-narcotic pain relievers such as ibuprofen (Advil) at doses of 600 – 800mg 2–3 times daily.

Moderate symptoms: (pain and can't walk as far as desired) For moderate symptoms, people can take antidepressants such as amitriptyline (elavil) or nortriptyline. However, neither drug is approved for treating PN, nor are they believed to work best when combined with traditional pain medications.

Severe symptoms: (constant pain that results in inability to walk or sleep at night). When experiencing this level of pain, it is recommended that you see a pain specialist. Specialists will have far more experience treating severe, chronic pain than most HIV physicians. They are also more experienced in managing high level narcotics and the associated problems. In severe cases, physicians may prescribe narcotic pain relievers such as methadone, a fentanyl patch, vicodin, morphine or codeine. Of these, methadone is least likely to be accompanied by the typical dulled sensations and euphoria associated with narcotics. In theory, it is a good choice for PN, but many physicians are reluctant to prescribe it because use of methadone or other "high level" narcotics requires complex record keeping by the Drug Enforcement Agency (DEA). Most physicians prefer not to have the DEA overseeing their prescription practices. Consequently, as with many diseases that cause severe pain, people often receive inadequate treatment and suffer unnecessary levels of pain.

When using methadone or other high level narcotics, recognize that it may take several days to find the optimal dosage or balance between pain suppression and side effects. Strong narcotics can lead to painful constipation because they slow movement in the intestinal tract. This can be corrected

with the over-the-counter stool softeners, but harsh laxatives are not recommended.

When the pain from PN is so great as to be seemingly untreatable (rarely), a pain specialist may recommend a “nerve block.” In this procedure, a fluid, typically alcohol, is injected directly into a major nerve junction just above the sight of the worst pain. When they work, nerve blocks can be very effective and cause long-term reduction or elimination of pain. However, a major consideration is that they usually cause loss of sensation, and in worst-case scenarios, can be unpredictable. Clearly, nerve blocks should only be attempted by specialist, and even then only after getting a second or third opinion.

Other suggestions

None of the following suggestions have been formally studied, yet care providers and others offer them as suggestions for helping manage the symptoms of PN. For severe and prolonged pain, seeing a pain management specialist is key to developing a workable strategy.

Avoid tight-fitting shoes and socks.

People sometimes think that tight shoes can help with numbness and prevent rubbing, but they can actually exacerbate the pain and tingling. Many people find soft, loose cotton socks or things like loose, padded slippers to be helpful. Shoes should be neither tight nor excessively loose, and should offer good air circulation if possible.

Be sensitive to temperature concerns.

Most people report that neuropathy feels worse in hot weather or when feet are heavily covered and don't have much opportunity for air circulation.

Bed sheets resting on your toes can

also add to the problem. Some people use a semicircular hoop on which they rest their sheets to avoid contact. The important thing is to keep your feet uncovered at night. This helps keep the temperature down (which may help serious pains to “numb out”) and also prevents friction between the sheets and toes.

Get up and walk around! Although it may seem contradictory for people who are in pain and can't walk, getting blood to the feet by walking around can help relieve some of the pain. Too much walking, however, will only make the problem worse. A moderate amount of activity can distract a person from fixating on the pain, without adding to it.

Some people try acupuncture. While this can often bring quick relief, many people report that the relief does not last for long and requires very frequent treatment.

Deep tissue massage. Simply massaging sore feet helps improve circulation. Perhaps more importantly, it causes all the available neurons in that part of the nervous system to “fire.” Once they “fire” or give off the chemical signal by which pain is transmitted, they must rest awhile before they can do so again. The result is that the pain is temporarily dulled. This is the same phenomenon which occurs when we massage any sore spot on the body to make the pain go away.

Soaking feet in cool water. When pain is severe, perhaps too strong to allow a person to sleep, water treatment can help. Insert sore feet in a large dishpan (or special devices made for this purpose) and gradually fill it with room-temperature water. Once filled, let the water keep running gently while you lower the temperature. The

water will slowly become colder and eventually reach a point where most pain has stopped. Dry your feet off and go to bed, hopefully getting to sleep before the pain returns. This is also a good tactic to use while waiting for a pain medication to “kick-in.”

Biofeedback. Many people can be “trained” to deal with mild-to-moderate pain, largely by learning to divert their minds away from it. The pain from PN, after all, is not signaling any real harm to the body, as pain usually does. Some people ignore the pain and sensations of PN or live with them simply by learning to perceive them differently.

Treatments in Development

Nerve Growth Factor (NGF) NGF, currently only in clinical trials—may repair damaged nerves. Early reports suggest that it may be useful in eliminating the most severe, shooting pains associated with neuropathy, but results will not be released for another year.

Lamictal (lamotrigine) is an anti-epilepsy drug that may soon be entering clinical trials.

Commentary

Dealing with PN has become a way of life for many people with HIV. What was once a rare condition has, due to HIV disease, become common dinner-table conversation material. Hopefully, new and better drugs will reduce the likelihood of PN, either caused by drugs or by HIV itself. PN remains an important field for additional research, but one which sadly gets very little attention. It may be, as some say, just a matter of sore feet, but if those are YOUR feet, it can be a serious matter indeed.

Hopeful CMV Drug Stalled

CMV disease, and CMV disease in particular, is one of the most difficult opportunistic infections, typically requiring lifetime daily intravenous treatment with drugs such as ganciclovir. Although there is an oral form of ganciclovir, it is poorly retained by the body and is not an adequate substitute for intravenous therapy. This may change if a new oral form of the drug, proGan, proves to be effective. This new form appears to provide as much activity against CMV as the IV form. If this is confirmed in larger clinical trials, it will represent a major improvement in the quality of life for people with serious CMV infections.

ProGan is likely to be used both for CMV induction therapy (initial treatment) and for maintenance therapy (continuing treatment). It is also highly likely that proGan will be much more effective in preventing CMV disease than the current form of oral ganciclovir.

Unfortunately, Hoffman-La Roche, the developers of proGan/RS-79070, recently announced that it is putting two important studies of the drug on hold. The company believes there are very few new cases of

CMV disease due to the use of highly active antiretroviral therapy (HAART). They question whether there will be enough new cases of CMV to find people to participate in the clinical trials, or enough people to make the market for the new drug worthwhile. Only one other study with proGan is still enrolling participants with newly diagnosed CMV retinitis.

Even though the number of new cases of CMV disease may be down, this may only be a temporary effect. Many specialists re-

port that they are beginning to see more cases of CMV this year compared to last, probably due to people failing on HAART regimens. The number of drug failures will likely increase over time.

Efforts by Project Inform and other activist groups appear to be bearing fruit. In Project Inform's discussions with Hoffman-La Roche senior executives from Basel Switzerland, agreement was reached regarding the continued need of this drug. Renewed trials seem likely to go forward following presentation of a simplified drug development strategy to the U.S. Food and Drug Administration.

If the FDA agrees to simplified licensing requirements, and enough people with CMV can be found to fill the needed trials, the sponsor seems likely to make the necessary commitment of resources to keep the drug alive.

People who acquire CMV retinitis or already have it, need to know that there are alternatives to life-time intravenous therapy. Even today, many people can get this new oral drug through participation in clinical trials (call the Project Inform Hotline for more information).

Immune-based Therapy Briefs

Thymus CT Scan

A study conducted at the Gladstone Institute in San Francisco evaluating the state of thymus at varying stages of HIV disease and age ranges has reported preliminary information. The thymus is an important organ in supporting new T-cell development. This study shows that the thymus appears to be the appropriate size in people with CD4+ cell counts greater than 420, but there appears to be no detectable thymus in people with lower CD4+ cell counts. This means that strategies like thymus transplantation may be necessary in order to realize immune restoration in people with lower CD4+ cell counts. It is unclear at this time if suppressing HIV replication will control the unknown factors which lead to this loss

of thymic material, and allow for regeneration of the thymus.

Total Lymphoid Irradiation

A pilot study using radiation to treat HIV is enrolling at the Gladstone Institute in San Francisco. The study will administer a single, relatively low dose of radiation. During the process both the bone marrow and the thymus, important immune compartments, will be shielded. Volunteers will be required to be on aggressive anti-HIV therapy. It is hoped that radiation therapy will wipe out HIV in the lymph nodes and other tissues reservoirs, and allow the immune system to rebound with an edge of the virus. The study is not without risks, as radiation therapy is immune suppressive and has side effects.

Study of GM-CSF Enrolling

A study of GM-CSF (Leukine), a growth factor for certain immune cells, is in clinical trials around the country. The study is seeing if the use of GM-CSF, in addition to standard therapies, will delay HIV disease progression and death by enhancing immune function. In other human diseases, GM-CSF has been shown to reduce the incidence of various infections. In laboratory studies, GM-CSF appears to promote the function of macrophages, important target cells for HIV and which fight many AIDS-related fungal, mycobacterial and parasitic infections. It was initially feared that GM-CSF would stimulate HIV replication, but this has not been seen in human studies. The current trial is open to people with fewer than 100 CD4+ cells and allows volunteers to be on regimens. For more infor-

mation on trial sites in your area, call 1-800-Trials-A or see the internet site: <http://hivinsite.ucsf.edu>

Thalidomide study

Preliminary data from a study on the effectiveness of thalidomide (Synovir) for the treatment of HIV-related wasting syndrome suggest the drug may prove important to people with AIDS. It remains highly controversial because of its history and potential for causing birth defects if used by pregnant women.

The study enrolled 99 people who had lost greater than 10% of their body weight with no explanation other than HIV (i.e. no parasitic or other infections). Volunteers received either 100 mg/day or 200 mg/day of thalidomide or placebo for 8 weeks, then all were offered thalidomide.

Results were analyzed according to the originally assigned treatment groups. **Table 1** reflects the average weight gain at the end of 8 weeks.

Preliminary analysis suggests that at least half of the weight gained by participants was in the form of lean body mass, the most important kind of weight. Overall, 37 of the 99 people enrolled in the study (37%) dropped out for various reasons, including adverse events. Of those who withdrew, 11 were in the placebo group (34% of the placebo group), 9 were receiving the 100 mg/day dose of the thalidomide (25% of this group) and 17 were receiving the 200 mg/day dose (55% of this group). Side effects associated

with thalidomide use included drowsiness, rash, declines in neutrophil counts (neutropenia), pain or tingling in the hands and/or feet and dizziness.

Interestingly, at the end of 4 weeks, those receiving thalidomide also experienced a 0.3 log increase in viral levels (HIV RNA). This is consistent with the findings of another study that examined thalidomide for treating oral and esophageal aphthous ulcers (mouth sores). The overall implications or causes of this 0.3 log increase in HIV RNA are not known. Researchers have suspected that thalidomide would decrease levels of tumor necrosis factor (TNF-alpha), a chemical messenger associated with increased HIV replication and wasting syndrome. In neither of these studies did thalidomide treatment result in decreased TNF-alpha levels or decreased viral load. It should be noted that volunteers in both studies were not uniformly on highly active antiviral regimens. In both studies, however, the drug appears to be effective in treating the indication of concern, wasting and aphthous ulcers.

As more data becomes available, Project Inform will provide updates. Celgene, the company developing thalidomide for HIV-related weight loss, recently announced that their expanded access program has been streamlined and fully covers the cost of the drug for people seeking access who qualify for the program. For more information about the program, providers should call 1-800-801-8328. The company has applied

for FDA approval of thalidomide for the treatment of leprosy (ENL) and is expected to seek approval for use in HIV-related wasting syndrome later this year.

The company is also beginning to enroll a large multicenter study to confirm the benefits of thalidomide treatment for oral and esophageal aphthous ulcers. Data from the previous study for this purpose were discussed in *PI Perspective* #21. The first four weeks of the current study will compare three different doses of thalidomide for treating the ulcers. After four weeks, participants will be randomly assigned to receive either a maintenance dose of thalidomide or placebo, to see if continued therapy is needed to prevent relapse of the ulcers. An ongoing study is looking at thalidomide for treating diarrhea in people with HIV. This study includes people with diagnosable as well as un-diagnosable causes of diarrhea.

Thalidomide is known to cause serious birth defects when taken by pregnant women. For this reason, Celgene requires that women who access drug through the program either agree to refrain from reproductive intercourse or agree to use two methods of contraception, (i.e. one barrier and one hormonal) for the period beginning four weeks before, up to four weeks, after using thalidomide. The company also recommends that men using thalidomide use condoms because researchers do not know if the drug is present in semen. Thalidomide can cause serious birth defects if taken even once during first trimester pregnancy. If a woman taking thalidomide suspects for any reason that she may have become pregnant, she should stop taking the drug and consult with her health care provider immediately. It is very important that both women and men engaging in reproductive sex use precautions to prevent pregnancy if either partner is taking thalidomide.

Table 1: Thalidomide for Weight Loss

Treatment Group	Average weight gain at 8 weeks	Average weight gain at 12 weeks *
Thalidomide 100mg/day	3.3% (4.5 lbs)	4.2% (6 lbs)
Thalidomide 200mg/day	1.2% (2.2 lbs)	3.9% (5.7 lbs)

* reflects data from the phase of the trial where all participants received thalidomide

Ethnicity and Treatment

A number of people, particularly within communities of color and specifically within the African American community, remain skeptical about the effectiveness and side effects of anti-HIV drugs. Some of this can be traced to a small and inconclusive early Veterans Administration AZT study which appeared to show less benefit for people of color. Considerable distrust also dates back to the infamous Tuskegee experiments, in which African Americans were unethically used as research subjects without their knowledge.

Whatever the cause, this skepticism has caused people to decline antiviral therapy and the life-extending benefit it offers. Now, results from an important and much larger study appear to clarify this question and reduce some of the doubt and controversy in this matter. The study found no significant differences between Latino(a)s, African Americans and whites in their responses to antiviral therapies, as measured by drug tolerability, side effects, death rates and disease progression. The study seemed to indicate that, on some measures, Latino(a)s fared slightly better than either African Americans or whites, though this may be due to a lower number of Latino(a) participating in the study. Unfortunately, the study did not enroll enough Native Americans, Asians or

other ethnic groups to provide meaningful subgroup information relevant to these communities.

The CPCRA 007 (the NuCombo) study compared AZT + ddI, AZT + ddC and AZT alone in people older than 13 years with CD4+ cell counts less than 200 or a prior opportunistic infection. While none of these are considered optimal therapies today, they were the best available at the time the study began. About 45% of the 1091 participants were people of color, including 103 Latino/a and 367 African Americans, comparing them to 610 white non-Hispanic participants. Researchers saw no significant differences across the groups in terms of disease progression or death at the end of the study (Table 1 below).

The study also found no significant differences in terms of side effects. Latino(a)s tended to have fewer side effects than African Americans and whites. Results are shown in Table 2 below.

These findings strongly contradict the earlier 1991 Veterans Administration (VA) study, which was much smaller and included far fewer people of color. While the study seems conclusive in regards to the particular drugs studied, it will still be important to watch for differences in response to newer therapies in future studies. The best way to do this is by making sure that people from all communities affected by AIDS are routinely and fairly represented in the clinical trials used to approve new drugs.

Hopefully, this study will begin to allay fears among those in the African American and Latino communities who believe that antiviral medications are more harmful or less effective for them. Still lacking, however, are effective educational campaigns to spread this information, as well as all information in general about effective new treatments, to give people a chance to make informed decisions about their treatment. Without improved access to treatment information and medical care, many groups—African Americans in particular—will continue to lag behind in the current reductions in death and disease progression seen among white Americans. Socially, morally, and medically, we all share in the responsibility to make sure that no one is left behind as treatment advances extends the lives of HIV infected people.

Table 1: Disease Progression or Death by Treatment and by Ethnic Origin

	AZT + ddI	AZT + ddC	AZT alone
Latino/a	23.8%	32.1%	21.2%
African American	35%	32.3%	40.4%
White/non-Hispanic	36.4%	39.3%	42.2%

Table 2: Percentage Experiencing Adverse Events (Toxicity)

	AZT + ddI	AZT + ddC	AZT alone
Latino/a	23.8%	11.1%	14.5%
Black	33%	29.4%	26%
White/non-Hispanic	35.1%	38.8%	29.7%

National HIV/AIDS Treatment Information Hotline

Project Inform's toll-free hotline provides HIV/AIDS treatment information to people living with HIV, their healthcare and service providers and family members.

1-800-822-7422

Monday–Friday: 9am–5pm (PST)
Saturday: 10am–4pm (PST)

New Developments in Women and AIDS Research

Since that fateful day when the ACTG 076 study showed that AZT could reduce HIV transmission from mother to infant, women living with HIV disease and their advocates have been struggling to expand the realm of women-specific research beyond mother-to-child transmission and gynecologic (GYN) conditions. While both of these areas are extremely important, they do not encompass the entire spectrum of HIV disease in women. This article provides an overview of some recent advances made in our understanding of HIV disease as it affects women. Also in this issue is an article on recent information on gynecologic conditions associated with HIV.

Drug Blood Levels in Women

There has been some interesting women-specific information presented over the past year. One study revealed that women taking delavirdine and AZT experienced 1.8 times higher delavirdine levels in their blood at the trough, or lowest level between doses, compared to men. The level of delavirdine was also higher when measured at the peak or highest levels seen shortly after taking the drug. The clinical significance of the higher blood levels of the drug in women is unknown, though it hints of the potential for greater side effects in women than men who use the same dose. The effectiveness of the drug was equal in men and women, but this may not mean much since the clinical relevance and utility of delavirdine is still unknown. If a difference of this level were seen in more potent regimens, such as those including a highly active protease inhibitor, it could easily impact on both side effects and the effectiveness of therapy.

This information is interesting because 139 (or 19%) of the 718 patients enrolled in this study were women. This number far outweighs the usual 7–10% participation of women in other antiretroviral studies. It brings into question whether this difference is unusual or if it is hidden in other studies by the relatively small number of women typically enrolled. At the very least, it un-

derscores the likelihood that women and men might require different dosage levels of drug, simply due to weight and body mass differences. It is critical, when a drug is being developed, that sufficient numbers of women are enrolled in studies to be able to conduct these types of analysis. There is a shared, but generally unmet, responsibility between industry, government and the community in this regard. Industry and government need to address the barriers that exist for women to participate in research, and women also need to work to overcome both personal and systematic barriers to participating in clinical trials. It is only when large numbers of people in any specific subgroup participate in a study, that information specific to that group can be analyzed. Also, the FDA (Food and Drug Administration) needs to make this information a priority when considering the approval of new therapies.

Nelfinavir and Birth Control

A recent study shows that there is a drug interaction between the most recently approved protease inhibitor, nelfinavir (Viracept) and ethinyl estradiol E2 (oral contraceptives, birth control pills). Nelfinavir decreases the amount of oral contraceptives in the blood by 50%. This is a significant difference, not only because of the

risk of pregnancy, but also because women take oral contraceptives for menstrual regulation and prevention of a variety of GYN manifestations associated with HIV. It is critical that research on drug interactions with ethinyl estradiol E2, as well as other birth control therapies, be encouraged for all therapies to manage HIV. (For more information on drug interactions, call the Project Inform Hotline).

Opportunistic Infections

Wasting and body composition changes are an increasingly recognized AIDS-related condition which can and must be corrected. The definition of wasting continues to be a stumbling block for most women. Many clinicians continue to maintain that wasting is only a matter of concern when there is a loss of lean body mass (muscle). Women, who naturally have a much higher level of body fat, are ignoring substantial changes in their body composition because they are losing fat, not muscle. Part of the problem here is that wasting is not well characterized and is usually not addressed until an individual has lost significant body weight. At the recent National Conference on Women and HIV, a presentation on wasting discussed the loss of fat in women as the first step in the wasting process. Interestingly, this loss was at least partially attributed to the decrease in the female sex hormones, estrogen and progesterone. Unfortunately, it is still unclear what causes the decline in hormonal levels, but it may help to explain why many women report menstrual changes and irregularities as disease progresses.

There are quite a few ongoing studies trying to identify ways to counter the wasting process through the use of steroids, nutritional supplements, human growth hormone, exercise and even antiretroviral therapy. (For more information see the Nutrition and Wasting fact sheet available through the Project Inform Hotline.) Further research is needed to better understand the cause(s) of the wasting process. Several reports maintain that more women than

men experience wasting (30% or more). This may be due to a variety of medical reasons, as well as societal pressures. All people living with HIV should carefully monitor any body composition changes and address them immediately. Individuals should measure and record body statistics at least on a yearly basis, and weight should be monitored with the same watchful eyes as CD4+ cell counts and viral load measures. The most important thing to realize is that in order to fully recognize changes, establishing 'baseline' body composition information is important. All people living with HIV should begin recording torso and limb measurements, weight and body fat (if possible) with each yearly physical from time of diagnosis.

Another ongoing dilemma is when to stop and when to start using preventative therapy against HIV-related conditions in the era of triple drug therapy. As people see CD4+ cell counts rise and their viral load fall, the utopia of presumed good health takes over and no one wants to continue taking other medications. There have been several reports of PCP (pneumocystis carinii pneumonia), MAC (mycobacterium avium complex), and CMV (cytomegalovirus) cropping up in individuals with CD4+ cell counts well above the normal levels associated with risk of these diseases. The common factor in most of these cases is a significant increase in CD4+ cell counts and subsequent discontinuation of preventative regimens. For women, this story is frequently

different. Many women are not using preventative therapies at all and are choosing to take triple therapy in order to "take them out of the danger zone." In other words, in order to avoid taking preventative therapies, many women are choosing to start antiretroviral therapy for the first time at fairly low CD4+ cell counts. Many women, therefore, are not necessarily stopping preventative therapy, but rather never starting it when perhaps it should have been started.

In 1996, PCP (pneumocystis carinii pneumonia) still killed more women than any other AIDS defining illness. This occurred despite PCP being more than 99% preventable with one of the few cheap and easy to take drugs in AIDS (bactrim or septr). Bactrim is a sulfa drug that many people initially have an allergic reaction to (as many as 50%), but the good news is that about 85% of those people can tolerate it after a process called desensitization. Desensitization just means starting someone out with a very small dose to get their body used to the medication and then giving a little more with each dose (over a period of days) until the person is at the normal dose. It just gives the body a chance to adjust to the presence of the drug.

The question of when or whether to stop taking preventative therapies has yet to be answered. The current recommendation is to use preventative regimens based on the lowest CD4+ cell count measured, even if those numbers have increased dramatically.

For many women, this means using preventative treatments for the first time. Preventing secondary infections may be the most important tool we have for maintaining health and immune function. The more stress put on the immune system, the more likely it is to wear out. However, many physicians report anecdotally that they have been successful in taking people off preventative medications, while some others report that this approach has failed. The likely reality is that it works for some people but not others, and there is as yet no test or way of predicting who will succeed or fail. In this context, most physicians prefer the conservative approach of continuing the medications, since no one is likely to be hurt by this. Over time, however, we may learn how to better predict who can and cannot function without preventive medications.

For women living with HIV disease and AIDS, not unlike most other diseases, medical research is lagging behind. However, there is still much to be learned from the research that exists. Studies must be designed now to answer many of the burning questions about potential gender differences not only with respect to HIV, but also with respect to opportunistic infections and treatments. In addition, women and their advocates must be proactive and involved in the future development of the AIDS research agenda to ensure that women-specific issues are included and potential gender differences are fully explored.

National Conference on Women & HIV

The National Conference on Women & HIV was held May 4–7, 1997 in Pasadena, California. While the conference intended to unify various constituents of AIDS research—women living with HIV, their caregivers, providers, advocates and the research establishment—it failed to provide an environment to move forward a research agenda for women with HIV/AIDS. Fundamentally, the meeting failed to inspire and promote dialog, learning and progress. Conference presenters were not given adequate guidance and community participants, despite half-hearted attempts to develop a mentorship program, were not adequately supported. Unfortunately, conference attendees arrived with a variety of expectations and needs, most of which went unmet.

Despite the general disorganization of the conference, a few advances in research on women with HIV were presented that further our understanding of the disease. In addition, the conference did bring together a good mix of information on public policy, basic science, clinical care and behavioral science.

From the outset of the conference, it was clear that many common questions regarding women and HIV would remain unanswered. Very little women-specific treatment data were presented, primarily because the appropriate studies have never been conducted. How do women living with HIV disease develop treatment strategies and identify problems when there is little or no information on how or if drugs work differently in a woman's body?

This lack of women-specific information drove frustration to rage among the conference attendees. To harness that rage and make it productive, the research community must develop an agenda for advancing women's treatment issues. One suggestion from the meeting, driven primarily

by the community, is to take the Women's Interagency Health Study (WIHS) and fold it into the Multicenter AIDS Cohort Study (MACS). The MACS is a well funded and long running study which has been responsible for much of our current understanding of the natural history of HIV disease in gay and bisexual men. The WIHS is the natural history study for women, modeled after the MACS. However, most women's advocates have been largely disappointed in the program for reasons ranging from its administration to its scientific foundations. The MACS has access to excellent researchers and laboratories, whereas WIHS has but a small fraction of the funding available to the MACS, nor does it have the same level of basic science research expertise. Combining these studies would decrease the administrative cost of the two different mechanisms, increase the resources available to the WIHS and more fully round out the information gathered to be relevant to more people, especially women.

Some find the idea of merging the WIHS and the MACS fundamentally wrong, feel-

ing that women deserve their own natural history study that specifically addresses issues and concerns of women living with HIV disease. The feeling is that there should be increased funding specifically for women's research. They maintain that women do not want to be part of a study historically designed solely for men and would not participate in a combined study. In addition, they maintain that women-specific information will be lost in the MACS.

Women on all sides of this debate are hungry for information not only on the natural history of their disease, but also in the cutting edge immunology and virology that is propelling the science forward. It may be that the proverbial "all our eggs in one basket" approach is crippling us. First, the strengths and weaknesses of the WIHS should be reviewed and the focus narrowed to ensure that research is of high quality and provides useful information. Second, the MACS should be open to the enrollment of women. Third, a formal assessment of what would be lost and gained by devising a combined study, inclusive of men and women, should be conducted. Ultimately we don't have 5 plus years to wait for data to guide further research on women with HIV. Therefore, creative solutions, such as examining stored samples, need to be explored to help inform the research effort. In the face of dwindling AIDS research dollars, our ability to identify key questions now will drive our success in future research efforts.

Project Inform has recently announced the commencement of Project WISE, a program focusing specifically on treatment information and treatment advocacy for women living with HIV disease. Project Inform will continue the publication of WISE WORDS (formerly published by WISE in Atlanta), an informational newsletter geared toward women's issues. For more information, see the recent In Focus or call the Project Inform hotline at 1-800-822-7422.

Gynecological Conditions and HIV

Over the past year, data from studies have been presented at the International Conference on AIDS, the 4th Conference on Retroviruses and Opportunistic Infections and the recent National Conference on Women and HIV. These studies have reinforced the need for women to seek regular gynecologic (GYN) examinations, including pap smears and colposcopies as necessary so that GYN complications can be detected early and monitored regularly. A number of studies have consistently shown a significantly higher incidence of abnormal pap smears in HIV positive women compared to HIV-negative women due to the presence of Human Papillomavirus (HPV), Cervical Intraepithelial Neoplasia (CIN), Squamous Intraepithelial Lesions (SIL) and other GYN infections.

HPV is the virus that causes genital warts and can also lead to cervical cancer. In HIV-negative women, about one-third of genital HPV infections progress to cervical cancer. Women who are HIV positive with HPV are more likely to progress to cervical cancer than their HIV-negative counterparts. This may be due to the inability of an already weakened immune system to suppress HPV activity in addition to HIV. When HPV is present, but the infection has not yet progressed, the diagnosis is called dysplasia, a term used to describe a pre-cancerous condition. The extent or severity of the dysplasia is described as CIN 1, 2 or 3. The literal definition of the terms is as follows:

- Cervical: of the cervix,
- Intraepithelial – in or among the thin cellular layers
- Neoplasia: the process of growing or forming an abnormal tissue growth or tumor.

CIN specifically means abnormal growth or tumor in the tissue covering or surrounding the cervix. CIN 1 means that one-third of the sample shows dysplasia. CIN 2

means that one-third to two-thirds of the sample shows dysplasia and CIN 3 means that the whole sample shows cells with dysplasia. CIN does not necessarily describe what the abnormality is. Another term, SIL or Squamous Intraepithelial Lesions, describes the type of dysplasia by identifying lesions in the thin cellular layers of the vaginal tract. SIL is usually described as low-grade or high-grade SIL. These terms just refer to the amount and severity of the lesions.

In a study of 64 women receiving GYN evaluations every six months, 50% of the participants had abnormal pap smears upon initial examination. Similarly, a larger study reports that approximately 40% of the women with HIV, compared to 17% of HIV-negative volunteers, had abnormal pap smears and 30% of women with HIV presented with SIL, compared to 7% of HIV-negative women, at study entry. This difference is particularly interesting since pap smears have been shown in several studies to have anywhere from a 40–65% false negative rate for identifying CIN and about a 10–20% false negative rate for high grade SIL. In these studies, the reliability of pap

smears was compared to colposcopy. As expected, pap smears were shown to be less reliable than colposcopy. A pap smear simply involves a gentle scrapping of the cervix to loosen cells which are then picked up with a cotton swab or tiny brush, prepared on a slide and examined for infections or abnormalities. A colposcopy is a more invasive procedure involving the magnification of the surface of the cervix so the clinician can look for abnormalities to biopsy, if necessary. A biopsy involves the removal of a tiny sample of cervical tissue for further study. Although pap smears are not wholly reliable in detecting abnormalities, for many women they are preferable because colposcopies are more invasive, more uncomfortable and are not covered by all clinicians or health plans. For women living with HIV who have never had an abnormal pap smear indicating HPV or dysplasia, pap smears every six months are most likely sufficient. However, in women with a history of CIN or SIL, yearly colposcopies in addition to pap smears are probably a good idea. For women who continue to have irregular or abnormal pap smears, colposcopy is suggested followed by pap smears at least every three months until they become consistently normal.

Due to the potentially serious nature of many of these conditions, the development of less invasive, more reliable diagnostic procedures needs to be a high priority for the scientific community. It is a global issue affecting all women. However, until something else is available, colposcopies must be made available to women with a history of GYN abnormalities. Again, not all providers or insurers offer this test. Women living with HIV must sometimes pressure providers for colposcopies, when appropriate, as a diagnostic procedure to detect conditions early. This allows for early treatment that may prevent the development of life-threatening complications such as cervical cancer.

Viral Load, GYN Diseases, and Vaginal Secretions

Studies looking at viral load (HIV RNA) show that anti-HIV therapy can lower viral levels in vaginal secretions. One study compared viral levels (HIV RNA) in vaginal secretions among volunteers initiating antiviral therapy and those who did not. Decreases in HIV RNA in vaginal secretions were noted among 13 of the 14 women initiating therapy, whereas none of the 5 participants electing not to start anti-HIV regimens experienced similar reductions.

When three volunteers stopped antiretroviral therapy, HIV RNA levels in their vaginal secretions promptly increased. Other studies, conducted in men, show a similar correlation between HIV RNA levels in blood and semen. However, currently there is no evidence that lowering viral levels in vaginal secretions or semen make a person any less prone to GYN or other infections or less capable of transmitting HIV to others. However, it will be all but impossible to conduct trials to test this latter point and many researchers believe that the risk of transmission is inherently likely to be reduced when viral load is undetectable. Unfortunately, “reduced” doesn’t mean “eliminated,” so there is no basis here for changing sexual behavior or lowered concerns over safe sex.

Surprisingly, HIV RNA levels have also been shown to significantly increase in vaginal secretions in response to standard treatment for CIN. A study involving six women

looked at the effect of treating CIN using one of several standard surgical therapies, which includes cryosurgery, LEEP, cone biopsy or LEEP cone. Each method of treatment resulted in increases in HIV RNA. While treating CIN is desirable, there are unknown risks associated with increased viral levels in vaginal secretions. Increased risks may include other GYN complications as well as potential for increasing risks of transmission. HIV RNA levels returned to pre-treatment levels 8 to 14 weeks following CIN treatment. These data do not suggest that women should not treat CIN, rather it provides additional information to be aware of. It also suggests that topical anti-HIV therapies should be developed to suppress virus and alleviate the risks of unknown consequences of increasing HIV RNA levels in the vagina.

HIV levels in the vaginal tract may have implications regarding a woman’s suscepti-

bility to GYN infections and sexually transmittable diseases (STD) as well as implications regarding transmission. In several studies, HIV levels are shown to increase in the presence of STDs. Other studies have linked high rates of HIV infection with high rates of STDs in general. It is unclear if HIV levels increase only during active infections or if latent (non-active) infections also affect viral levels. It is also not known if high levels of HIV in the vagina increase the likelihood of outbreaks of existing infections, such as herpes and HPV, or increase susceptibility to new infections. Unfortunately, these questions have not been answered. However, it has been shown that when HIV RNA levels are reduced substantially in the blood, as a result of antiretroviral therapy, the likelihood of opportunistic infections decreases. This implies that there may be a lower susceptibility to GYN infections in individuals whose HIV RNA levels are suppressed. Further research must be done, but for the time being logic would suggest that suppressing HIV levels in the vaginal tract is desirable.

For women living with HIV, GYN manifestations can be an ongoing battle. The research is clear that the earlier an infection or condition is identified, the better the likelihood of successful treatment. In some cases, monitoring is the only treatment necessary. All women should take an aggressive, proactive approach to maintaining their health through regular GYN care.

Maintaining Adherence to HAART

Highly active antiretroviral therapy (HAART) has brought new hope and new challenges to people living with HIV. However, if these treatments are not used properly (i.e., doses are repeatedly skipped, taken at lower than prescribed dosages, or not taken at scheduled intervals), drug resistance will almost certainly develop more rapidly and the potential benefits of combination therapy can be lost. Moreover, resistance to one therapy may also result in decreased effectiveness of other therapies of the same class (cross-resistance).

This is particularly true in regard to protease inhibitors. The development of high level resistance to any one of these drugs almost certainly conveys some degree of resistance to all the other drugs of this type. Adhering to a treatment regimen is difficult under the best of circumstances. Studies have shown that even health care providers can find it difficult to take a simple course of antibiotics as directed. The new triple combinations used with HIV disease typically require that a person take a dozen or more antiviral pills per day with specific timing and dietary requirements. When a person must also use preventive or maintenance doses of drugs for opportunistic infections, the total daily pill count soars. Keeping track of one's medication alone becomes a major activity. It's little wonder that many people have trouble keeping up with the program.

Preliminary data from one clinical trial suggest that as many as 12% of the study population missed one dose in the preceding day, 11% the day before that. At least two other recent clinical trials reported that nearly all of the people who failed to achieve and sustain a viral load below the limit of detection had significantly deviated from their prescribed treatment regimen for a month or more. There are many possible explanations for failure to adhere to the treatment regimen. A recent study by the University of California Center for AIDS Prevention Studies (CAPS) showed that, of those people who admitted missing one or more doses:

- 40% said they simply forgot
- 37% slept through a dose
- 34% were away from home
- 27% had changed their therapy routine
- 22% were busy
- 13% were sick
- 10% were experiencing side effects
- 9% were depressed.

There appears to be little debate about the fact that it is difficult to maintain perfect adherence to today's complex treatment regimens. It is somewhat less clear what degree of non-adherence is tolerable and how quickly it contributes to drug failure. Most of all, it is not entirely clear what to do about it, though many useful strategies are evolving over time.

Initiating Therapy

Engaging in complicated courses of long-term treatment doesn't feel natural to most people. However, this challenge is not unique to people with HIV. Millions of people have learned to cope with diseases requiring complex, long-term management, such as diabetes. Whether or not you feel you are able to commit and adhere to a treatment regimen may be one factor to consider, along with lab results and clinical condition, in determining the appropriate time to begin highly active antiretroviral therapy (HAART). Giving careful thought to what benefits you hope to get from treatment, how you will evaluate the benefit and how you might manage side effects will be

helpful. Some people try a "dry run" before beginning therapy, taking empty gel caps on the prescribed schedule while sticking to the required dietary requirements.

Perhaps the first and most important aspect of adherence lies in choosing the right therapy in the first place. Drugs differ widely in:

Whether they can be taken with or without food

How many times per day they must be taken

What other drugs they can and cannot be successfully used with

Their side effects and how they make a person feel

Whether you have access to the facilities need for storage (for example, refrigeration for supplies of ritonavir [Norvir]).

Similarly, people differ widely in their personal habits and needs. A few examples:

- Some people are bound to rigid schedules defined by their employment, such as hourly workers.
- Some people have loose and constantly changing schedules or routinely move in and out of different time zones, such as many airline workers.
- Some people are unable to work and their schedules are dictated by a seemingly endless string of medical appointments.
- Some have children, elderly parents, or partners to care for as well.
- Some have people around them all the time to help remind of their medication schedules, while others are alone and must rely on timers, pill boxes and other devices.
- Some people suffer from wasting syndrome which makes eating difficult and critical; others have no dietary problems but don't eat on a regular schedule.
- Finally, some people have to deal with other challenging life issues such as substance abuse or homelessness.

To find a treatment regimen you can live with, it is necessary to reconcile the two sets of requirements: yours and the drug's. People who lead busy, but largely unstructured lives might prefer drugs that can be

taken easily with or without food and thus more easily fit in with their changing daily routines. Others whose time is tightly structured by job requirements might find it easier to accept more demanding drug schedules and therefore can select a regimen purely on the basis of its expected potency. People who have trouble eating or who are struggling with weight loss might wish to avoid drugs which can't be taken with foods. People who must take a large number of other drugs for treatment or prevention of opportunistic infections might avoid antivirals that have the highest number of drug interactions or require the greatest number of pills per day.

The goal is to select a regimen you believe you can live with, one that fits with who you are and how you live. There are, of course, no perfect choices in this regard. Some people may seek a regimen that most easily fits their lifestyle, while others may be willing to adapt their lifestyle in hopes of getting the most potent possible treatment. Also, the more HIV medications you have used previously, often the fewer choices you have about what to use next. Thus, often in more advanced disease, prior history with the drugs tends to dictate what can and can't be done.

Maintaining Therapy

Once a regimen has been selected, sticking to it requires planning, support and commitment.

Planning

Stable access to drugs is a critical requirement for effective use. People cannot adhere to a regimen if they do not have continuous access to the drugs. While it may sound obvious, many or even most people taking HIV medications sometimes find themselves running short of one or another treatment. This is almost always a consequence of poor planning. Skipping doses when you run out of a drug temporarily is still skipping doses, with all the consequences. Thus, it is best to try to plan to never have less than a week's supply of your entire medication needs on hand. Remember also that some drugs require much different storage than

others, so part of your planning must address the storage requirements. Once storage is addressed, it is often helpful to put aside an entire week's supply the first time the drugs are delivered, and then use only the remaining supply. This will also create an "emergency stash" should unforeseen circumstances cause your basic supply to run short. The "stash" should be rotated or replaced once a month to keep it fresh.

Keeping a steady supply of your prescriptions requires close coordination with your doctor and your pharmacist. When using sources like the AIDS Drug Assistance Programs or patient assistance programs sponsored by pharmaceutical companies, which are potential sources of drug access, more of the burden falls on you to make sure you order supplies as the program requires. But the main point is always to stay at least a week ahead of your needs. Your care provider should work closely with you to ensure access.

People with varying lifestyles may differ in their ability to adhere to a treatment regimen. People dealing with major life problems such as active drug use or homelessness face the most difficult challenges adhering to a treatment regimen. But that doesn't mean that adherence is impossible. Studies have shown that people with depression are also more likely to have difficulty taking their treatments consistently. If you suffer from depression and are considering treatment, consult a mental health professional as well as your regular provider. Outside of depression, there are very few reliable predictors of non-adherence. In reality, only you can make the decision as to whether you are ready and committed enough to maintain a steady course of treatment. If you are not ready or in a position to make a serious attempt at adherence, you might be better off to delay treatment. This option doesn't jeopardize your ability to use treatment effectively some time later in the future. In contrast, the misuse of treatment, through inconsistency or poor adherence, can indeed jeopardize future options by encouraging development of drug resistance that affects entire classes of anti-HIV therapy.

Support

Establishing a good working relationship with your provider is critical for maintaining adherence to a treatment regimen. A provider should be knowledgeable in the current standards of care for treating HIV and should be willing to spend time to thoroughly explain the benefits and challenges of treatment.

After the decision to start treatment has been made, it is important to clarify your treatment regimen with your physician. Knowing what medications you are taking and why will help to better understand the importance of adherence. One survey indicated that the vast majority of people were unclear of their treatment regimen only ten minutes after consulting with their physician. Some people understood the dosage but were confused about dietary restrictions. Others were unclear on the correct dosage or the timing of the doses. Since dietary adjustment can be a difficult at first, it is important to know what and when you can and cannot eat. Just as important, try to understand exactly what is meant by the dietary requirements. For example, many people interpret the requirements for indinavir (Crixivan) as saying that the drug should not be taken with food, which can be difficult for many people. The actual dietary requirement is that it shouldn't be taken with fatty foods. Light snacks and non-fat foods can be taken with the drug without concern. Similarly, the requirements for nelfinavir (Viracept) are often interpreted as meaning that it must be taken with food, when in fact the label says only that it should be taken with food. In some cases, there is a genuine medical need to take a drug with or without food, while in other cases, such as the use of ritonavir (Norvir), use with foods is recommended only to minimize side effects or unpleasant aftertaste.

A useful technique for understanding a treatment regimen is writing down instructions and repeating them back to the care provider, then checking them again with a pharmacist when you pick up or order the drugs. Use the team approach; your physician, nurse, pharmacist and other health

care providers can all be helpful with initiating and supporting effective therapy. Researchers CAPS have noted that people who actively foster a friendly and supportive relationship with medical office staff get better service from their providers. Bringing another person (family member or friend) to appointments ensures that there are two people to ask questions and get information.

Ask the doctor to be clear about potential side effects and how they may be managed. Being mentally prepared for possible side effects can make them easier to manage if they occur. Make an agreement with your care provider as to what the process will be if you experience a difficult side effect. Knowing that you will have timely contact with a provider may provide reassurance that side effects will be managed efficiently. It is also important to find out from your physician what to do if you miss a dose. If you do miss a dose, find out if you should make it up or simply take the next one. Also, note the missed dose and the reason for missing. There may be a strategy you can employ to avoid missing future doses. If you are not able to take all the drugs in your combination, don't take a partial dose. Contact your care provider immediately. If necessary, stop all of the drugs in your combination therapy until you are able to take a complete dose again.

Commitment

At the initiation of therapy, most people question what "adherence" means. It is important to keep an adequate level of drug in your blood stream 24 hours a day in order to prevent the development of resistance. Each time a dose is missed, the blood level of the antiviral drugs falls below the minimal necessary amount for several hours, creating a temporary opportunity for the selection and growth of drug-resistant strains of virus. There are no data telling us exactly when resistance to drugs begins but there is plenty of evidence that people who are adherent to their treatment regimens have a better and more sustained antiviral response. While no single episode of a skipped or late dose is likely, by itself, to trig-

ger resistance, the more often such episodes occur, the more likely resistance becomes.

Strategies for Adherence:

Some of the following strategies and tools have worked for many people taking triple combination therapy:

- Integrating your treatment regimen into your daily routines. Most people find it easier to fit their medications into their lives, rather than scheduling their lives around their medication. Use a daily activity, one that you do every day without fail, to prompt you to take medications. Take your medications before the activity; it's easier to remember.
- Counting out all your medications in daily doses for a week at a time. Use a pill box or a nail organizer from a hardware store to hold each dose. Setting up the weekly pillbox must become a routine weekend duty. Medications can also be divided daily by dose and put in separate canisters (some people use film canisters) marked with the dosage times. Some people put each canister near the place they will take a dose. For example, put the morning dose by the coffee pot, evening by the television set. This is more difficult with drugs that require refrigeration.
- Keeping a checklist for doses taken with a space to note how you are feeling.
- Using an electronic pill box or beeping alarm to remind you when to take medications. The downside of these mechanisms is that the currently available electronic pill boxes are too small and the alarms may be too obvious.
- Using a daily planner, especially at the start of a new treatment regimen. Inserting medication requirements in a planner, as if they were appointments, can be a useful reminder for many people. Still others use hand-held computers and inexpensive electronic organizers with scheduling functions to remind themselves of their daily medication needs. Electronic devices of this type can be purchased for less than \$50 dollars.
- Evaluating your treatment regimen about two weeks after you start. It may take a

few weeks of experimenting to figure out how to best schedule both your medications and other events in your life. For this reason it may be useful to start a 'dry run' of therapy, allowing time to adjust routines prior to actually taking the drugs.

- Planning ahead for weekends and vacations. People often miss doses when they are away from home. For most people, weekends are different from their normal weekday routine so it is important to plan ahead. Take into account the changed environment. Will you feel comfortable with your normal routine or will you need other strategies?
- Keeping all your medications with you when traveling. Baggage containing medication can be lost or delayed.
- Planning ahead for privacy if you need to hide the fact that you are taking medication. If you are not able to take your medication openly, try to find at least one person with a similar problem with whom you can discuss strategy. Some examples might be adjusting your lunch or break schedule to ensure privacy or keeping water in your bedroom at all times.
- Keeping a diary—include whatever is important to you: when you took treatment, reason for missed dose, how you feel, etc. Keeping a record like this serves as a reminder of how well, or poorly, you are doing with adherence.
- Using your support network to remind you of your medication requirements. Some people select a "treatment buddy" who can make daily reminder phone calls.
- Setting up a support network for your emotional needs as well. It's difficult to take treatment and also deal with daily stress, whether it be taking care of children, working or dealing with illness.

These strategies may not work for all individuals. Because of cultural, gender and socio-economic differences, some suggestions are more appropriate for some people than others. Different issues are more important in some settings than others. For example, in the Latino community, many individuals reported that people they knew

might not be able to reveal their HIV status or their use of medications. This places much greater emphasis on planning ahead for moments of privacy each day. For people struggling with lack of housing, active drug use or untreated mental health conditions, the strategies for successful treatment will often go beyond what we cover here. Still, even under the most challenging situations, people have daily routines which can be used as triggers for the use of medications.

Adherence strategies can and must vary from person to person and group to group. However the most effective method of ensuring success is motivation and commitment to a treatment regimen, along with the recognition that it is possible to accommodate the need for long-term treatment. It may take several attempts before you find the approach that works best for you, but people with other life-threatening chronic illnesses have long demonstrated that it can be done. As an elderly woman with diabetes said at a recent Project Inform Town Meeting, "if you want to live, you'll find a way to do it."

Commentary

Perhaps the greatest way in which adherence to HIV treatments differs from adherence in other chronic illnesses is the lack of immediate symptoms or consequences when adherence fails. In diabetes, for example, failure to adhere can quickly result in insulin shock or even death. In HIV disease, the effects of non-adherence are slow to appear, but nonetheless deadly. This lack of a rapid feedback or response places more of the burden for adherence on the intellect and a bit less on the immediate reaction of the body. A person with HIV infection must take a long-term view in order to have a long-term future.

Adherence is also a challenge to the many of the support systems for people with HIV. Managed care and other economic changes in the medical field have left providers with less time to spend educating patients. Moreover, most health care providers have little or no training in the self-adher-

ence tools that might help people who are undertaking a new treatment regimen. Training will be needed both in HIV treatments and tools of self-compliance. Some pharmaceutical companies already offer "adherence training" programs which have been developed for other illnesses. They are just now beginning to pilot test their use in HIV disease.

There are few effective structures in the HIV care and service industry to support people taking treatment effectively, such as treatment support groups and treatment-knowledgeable case managers. Many working in the HIV service field have been operating from a model of disability and death. The transition to supporting people who are living longer with complex treatments and social needs will require planning and shifts,

not only in programs, but in paradigms.

The best long-term solutions must ultimately go beyond helping the individual adhere to the schedules demanded by the drugs. Instead, they must begin to focus on making better therapies and longer-lasting formulations that are easier to use, more easily absorbed, have fewer side effects and drug interactions, and maintain more consistent drug levels in blood. This work is already well underway with studies beginning this month for treatments which may require only once per day dosing. The final solution, of course, is an outright cure to the disease, one which not only results in eradication of HIV and immune restoration, but no further need for medication. The prospects for this kind of solution are, unfortunately, less certain.

1592 Update

Though final details are still in debate, a modest-sized compassionate use program for the Glaxo Wellcome 1592 (2,500–5000 people worldwide) will be initiated for adults in July, followed by a much larger expanded access program (10,000–20,000 people) shortly after the turn of the year. Call the Hotline for details. Before everyone rushes out with high hopes to get this new drug, a few points should be considered:

- Simply adding 1592 to a failing treatment regimen is not likely to help much. For many, it will be wiser to wait until it is possible to start two new, previously unused drugs at the same time. Other new drugs are expected to go into some form of expanded access in late 1997 or early 1998.
- New clinical trial data suggests that 1592 is less likely to be effective in people who have previously used the AZT/3TC combination or ddI. There is clearly some level of cross-resistance between 3TC, ddI and 1592.
- Many people can afford to wait six months or so for the larger, second program, even if they are qualified for the early, smaller program. When people who

can afford to wait rush ahead because they WANT 1592 rather than truly NEED it, they may get it, but at the expense of someone else whose need may be far more desperate. Let the truly neediest people move to the head of the line.

- True side effects and efficacy of this drug are largely unknown. Even less is known about the best way to use it. One thing we've learned from protease inhibitors is that it's more important to use a drug wisely than it is to use it NOW.

In this era of long-term treatment strategies, the jump to 1592 warrants a cautious approach. Additional options, such as DMP-266 and Vertex W141, will follow shortly. For many, waiting will be the best strategy.

PI Perspective Survey Results

In 1996, Project Inform conducted a survey of PI Perspective readers. We received thousands of responses from our constituents, overwhelmingly telling us that the content of the PI Perspective was useful, the balance of topics was good and the reading level and presentation of information met their needs. As many readers may have noticed, Project Inform is instituting a ‘new look’ with this issue of the *PI Perspective*. While the look has changed, the information, based on our reader survey results, has maintained the same standards and characteristics as before. We have been able to add more treatment information to the PI Perspective with space gained by making the organizational newsletter, In Focus, a separate publication.

Survey Results

PI Perspective is read by a large number of women, and as we noted previously in our survey of the Project Inform Hotline, over 20% of Project Inform constituents are women. Project Inform is increasing its services to women living with HIV and has recently announced the initiation of Project WISE, a program focused on information and advocacy specifically for women.

The vast majority of people responding to our survey were age 30 or older (95%). Additionally, the majority of those responding were Caucasian (85%), with African Americans and Latinos being the largest minority ethnic groups reading the PI Perspective. The Outreach Department at Project Inform has implemented programs to specifically target and bring treatment information to youth and ethnic minorities to broaden the reach of Project Inform’s services.

Not surprisingly, the majority of Project Inform readers are people living with HIV or AIDS (67.2%), most of whom have known their HIV status for at least three years and a large majority of whom have known their HIV status for over 7 years. A small yet significant number of people (over 10%) have known their HIV status for 11 years or longer. People are primarily using the PI Perspective to help guide their personal treatment choices (62%), keep informed on new developments (77%) and share new infor-

mation with friends (49%), yet a significant number of health care (16%) and other service providers (19%) are reading Project Inform information to stay abreast of developments to better serve their clients.

On questions about readability and presentation of information, the majority of people, nearly 90%, noted that the materials are satisfactory the way they are. Slightly fewer (70%) noted an adequate use of graphics, although about 13% of readers said more would be helpful.

In addition to soliciting responses to specific items, readers were encouraged to provide us with written comments. Written themes echoed by more than twenty people included that the information was good, clear and highly useful. Additionally, over twenty written comments stated that the reading level was a little too complex. The overwhelming majority of written comments were very encouraging and positive. Those comments that were less supportive of the PI Perspective (less than 20) primarily encouraged more discussion of complementary therapies.

Based on these survey results, the staff at Project Inform is encouraged that the treatment information is meeting people’s needs and that Outreach and Advocacy programs are properly directed to identified areas of focus. The Information Department sends a word of thanks to everyone who participated in the reader survey!

The Basic Message

- Learn about HIV testing options and choose one that fits your needs! Be sure your privacy is protected!
- If you’re positive, don’t panic. If you make your health a priority, chances are you will be reasonably healthy for many years.
- Learn about your healthcare options and local support services.
- Get a complete physical and blood tests for CD4+ cell count and HIV level. Repeat quarterly and watch for trends. Women should get GYN exams and Pap tests every six months, more often if abnormal.
- Work with a doctor to develop a long-term strategy for managing HIV disease.
- If the CD4+ cell count is below 350 or falling rapidly, consider starting anti-HIV therapy. Test at least twice before taking action.
- If anti-HIV therapy fails to reduce your HIV level below the “limit of detection” or below 5,000 copies within 3–6 months, consider a different or more aggressive therapy.
- If the CD4+ count trend stays below 300, consider treatment for preventing PCP. If it stays below 200, start treatment for preventing PCP (if you haven’t already done so) and reconsider anti-HIV therapy if not on one. Learn about drug interactions and preventive treatments for opportunistic infections.
- If you started preventive therapies and your CD4+ cell count rises in response to anti-HIV therapy, ask your doctor whether it might be safe to stop certain preventive therapies.
- If your CD4+ cell count stays below 75, consider more frequent blood work—perhaps monthly. Consider therapies for preventing MAC/MAI and CMV.
- Regularly seek support for your personal, spiritual and emotional needs. It takes more than medicines to keep you well.