

PI *Perspective*

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Closing the Gap ... Next Steps in Optimizing Therapy

Media stories about the success of new therapies have left the public with the impression that the AIDS epidemic is all but over. News outlets seem to feature weekly stories about people struggling to restart careers and get on with life now that their illness is in remission. The first six months of widescale use of protease inhibitors and triple combination therapy have indeed brought many people to new plateaus in their fight against HIV infection. But it is uncertain how long these advances will be sustained and it is clear that the miracle simply isn't happening for everyone. Patients and physicians are left to celebrate victory or ponder failure whichever happens. Rather than dwell too much on either, a better approach is to try to understand the reasons for drug failure and to overcome them.

PI Perspective #19 outlined the first step for optimizing treatment through long-term strategic thinking about the use of therapies. This issue explores three more approaches - (1) a call for the next step in diagnostic technology - access to viral resistance testing; (2) a call for creation of alternative forms of existing drugs to help combat the problems faced by people with advanced disease; and (3) a renewed emphasis on immune restoration therapy. Without attention to these areas, the advances in AIDS research will be short-lived for some and nonexistent for others.

The Next Step in Diagnostics

Viral load monitoring is rapidly becoming a routine aspect of HIV care. While some questions remain, scientific debate about the general utility of the test largely ended with the XI International AIDS Conference in Vancouver. Most physicians would agree that wise use of antiviral therapies requires the guidance offered by viral load tests. Most would also agree that these tests don't provide all the information needed to make truly informed decisions about treatment, particularly for people with a long history

of prior treatment use. A viral load number, on its own, says little about which drugs to use alone or combine. The best results in studies have come when people used a three drug combination which included first time use of one of the better protease inhibitors or nevirapine plus two of the older nucleoside analogues. For best and most consistent results, one - ideally both - of the nucleoside analogues

What's needed is a tool that can tell which drugs are still active in each person and which have been affected by viral resistance. On a limited scale, such technologies already exist.

used should be new to the patient, or at least known to be active for the person (i.e. the virus has not yet developed resistance). Here lies the challenge. For those who have already used most therapies it is almost impossible to know which

drugs are still active and which will fail due to resistance. When a person using a combination begins to experience drug failure, it is equally impossible to know with certainty which of the drugs in the combination are no longer active. The simple choice may be to replace all the drugs, but few people have enough untried alternatives available to make this possible. Moreover, tossing out the entire regimen may discard one or more drugs which are active and does little to optimize or preserve options for the future.

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1965 Market St., Suite 220
San Francisco, CA 94103

Administration
415-558-8669

Fax
415-558-0684

Local Hotline
415-558-9051

National Hotline
800-822-7422

<http://www.projinf.org>



active for a person and which have been affected by viral resistance. On a limited scale, such technologies already exist. Now, they must quickly be refined and made routinely available. Ideally, every time a person gets a viral load test done, a drug sensitivity/resistance test should also be done. This poses a substantial challenge as it is difficult for many to get the basic viral load test, let alone a resistance test. But clearly, until true curative therapy is developed, management of HIV disease will require such testing.

Methods for testing drug resistance and sensitivity are described in detail in the article on HIV Resistance on page 6. There are two basic approaches, called *phenotypic* testing and *genotypic* testing. Phenotypic testing measures the ability of the virus, taken from each person, to grow in the presence of each drug. It provides a direct confrontation, in a lab culture, between a person's virus and each of the drugs used to treat it. If the virus is resistant to a specific drug, it will grow aggressively in the presence of that drug. If the virus is still sensitive to the drug, there will be little, if any, growth. Different degrees of resistance can be determined by measuring how well, or how poorly, the virus grows. The process is repeated for each therapy. The advantage of this approach is that it provides a direct and quantifiable measure of the ability of the available drugs to suppress the person's virus. The disadvantage is that it is cumbersome, time consuming and costly.

The other approach, *genotypic* testing, is more indirect as it doesn't test drugs against the virus. Instead, it gives a detailed analysis of the genetic changes (mutations) which have occurred in the virus. Mutations at given locations (codons) in the genetic material are known to cause, or are associated with, resistance to specific drugs. The simplest version of this test merges microcomputer chip technology and human biology. A drop of fluid from a viral load test will be used to generate a list of all known mutations. This will

provide information about the likely usefulness of any protease inhibitor, the new non-nucleoside reverse transcriptase (NNRTI) drugs and the older nucleoside analogue drugs, in an individual. The advantage of this type of test is that it provides a full picture of resistance, across all known drugs, in one quick procedure. The limitations are that it only works for

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mutations which scientists know how to identify, and it cannot quantify the degree of resistance.

Commercial development of both approaches is underway. The challenge is to make the tests quick, easy and relatively inexpensive. Beyond that, these approaches must be evaluated in studies to prove that the information they provide predicts drug failure and clinical effects. This part of the work is only beginning and getting it done should become a major part of the activist agenda in the coming year. Studies must be initiated as soon as

possible to collect the data necessary for FDA approval, which is required to guarantee third party reimbursement for the tests.

One approach is to make the tests available, free of charge, to people who are willing to have their data collected in a large database. This, coupled with data from one or more clinical trials, should be sufficient to warrant FDA approval. People participating in the database or the clinical trials, of course, should be given immediate access to the information provided since it is so crucial to their health care management. No one should have to wait two to three years before they can access their test results.

A large database would meet the goals of collecting data for FDA approval while at the same time providing critical information for making treatment decisions.

New Formulations: Filling the Gaps

It would be naive to expect that even the best of the new triple combination therapies could prove successful for every person. In the past, failure to benefit from a new therapy has been written off as an expected limitation of any drug. This expectation, long accepted in AIDS, effectively writes off the lives of thousands of people. This is particularly hard on people who see themselves being left behind as their friends benefit from new therapies. While it would be misleading to suggest that problems of drug failure can be solved in every case, much can be done. It is very likely that many of the causes of drug failure can be identified and overcome.

The most obvious but overlooked cause of drug failure can be found in the other symptoms of HIV disease. The advent of protease inhibitors has made patients and physicians very aware of the problems due to inconsistent dosing and inadequate blood levels of these drugs. Both these conditions contribute to drug failure by hastening viral resistance. Much attention has been given to educating

PI Perspective...

- Distributes information on the best proven treatment options;
- Advises on access to treatment;
- Encourages personal empowerment through active participation in treatment strategies;
- Increases awareness of the obstacles that impede progress in research.

PI Perspective -

*not a newsletter...
but a unique tool for change on
behalf of people with HIV.*

patients about the need for compliance and discipline: taking the right dose of a drug on a regular schedule without interruptions. However, little recognition has been given to the fact that the nature of HIV disease makes such rigorous adherence impossible for many people, no matter how committed and disciplined they are.

Many people in later stages of HIV disease experience degrees of wasting syndrome due to poor absorption through the intestinal tract. This problem may be due to HIV infection in the gut. While the cause of wasting cannot always be determined, it is a common problem. When food is poorly absorbed, oral drugs are likely to face a similar problem. The result is that only small and inconsistent doses of a drug reach the blood stream, hastening viral resistance and failure. Thus, those with greatest need for therapy become least likely to benefit from it. They are caught in a difficult cycle — malabsorption prevents intake of the drugs which might help correct the damage to the gut. No absorption, no healing of the intestinal tract. Once caught up in the cycle, it seems almost impossible to break free.

A related problem is loss of drug activity due to rapid expulsion of stomach contents. This can be due to vomiting and nausea at one end, or through the colon and out at the other - in other words, diarrhea. If a drug moves through the body too quickly in either direction, very little is absorbed into the blood. Nausea, vomiting, and diarrhea can be caused by HIV, by other drugs the person takes, or other opportunistic infections.

Oral intake of drugs can be difficult for many people with HIV infection. These problems might be solved to some degree by the use of alternative methods of drug administration. Such methods include:

- ♦ oral reformulations, including liquids, designed for better absorption;
- ♦ combination with antiemetic agents (drugs or herbs which suppress nausea and vomiting);
- ♦ intravenous formulations, which can readily be used by many people with advanced disease who have IV

ports for other purposes, such as CMV treatment;

- ♦ patches and other skin-based delivery mechanisms;
- ♦ suppositories (already widely used for some drugs);
- ♦ self-administered injection formulations;
- ♦ time-release or liposomal formulations.

Companies commonly favor the development of oral formulations that facilitate use of drugs (and widen their market potential). The very nature of HIV disease, however, creates ethical and market demands for alternative formulations. Even if only 10% of people with HIV disease need such formulations, ethics demand the formulations be developed. A few such alternatives are available now, showing the feasibility of this recommendation:

- ♦ AZT exists in an IV formulation, primarily used in treatment of HIV-infected mothers during delivery of babies; AZT also exists in a liquid for pediatric use.
- ♦ Nevirapine (Viramune) exists in an IV formulation for research studies in HIV-infected mothers.
- ♦ 3TC (Epivir) exists in a liquid formulation, available for pediatric use but readily used by adults.
- ♦ Testosterone supplements and pain management drugs, such as morphine, exist as skin-patches.

Regardless of the intended function of these formulations, they can be used off-label for any purpose. It is not clear, however, that simple liquid formulations will be any better absorbed than oral pills, but it is quite certain the IV formulations would have a distinct advantage.

Virtually none of the pharmaceutical companies selling products for AIDS have researched how their products are absorbed by people with advanced disease. Most studies testing the absorption, blood levels and half-lives of AIDS drugs have been conducted in healthy volunteers, not in people with advanced disease. Simply taking more drug doesn't always help if malabsorption is the problem; more drug tends



to cause more stomach distress. The stomach simply seems to be the wrong entry point for drugs in some people with advanced disease. Also, those with wasting syndrome may have different acidic levels in their stomach which can affect drug absorption.

A few small companies specialize in creating alternative delivery mechanisms for drugs. An immediate goal of AIDS activism should be to speed development of better formulations, including time-release versions to maintain constant blood levels of drug and hopefully, therefore, slow viral resistance. Only in this way can we ensure that an entire group of people living with AIDS is not left behind to

watch while others benefit from the new therapies.

A few points for AIDS activism around this issue include:

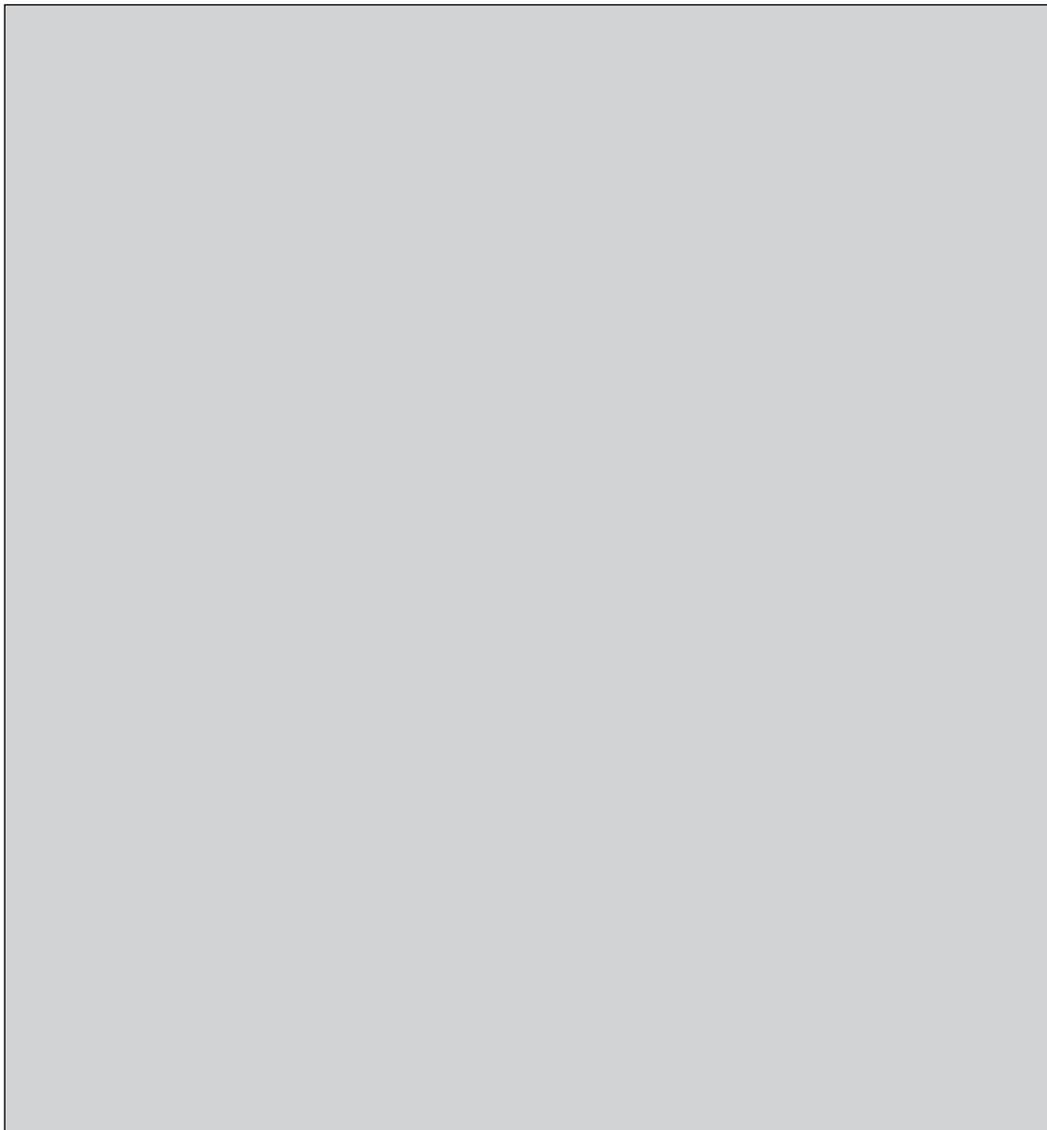
- ♦ *insisting that pharmaceutical firms conduct more studies* to determine how their products are metabolized by people with malabsorption and wasting syndrome;
- ♦ *polling pharmaceutical firms* to determine which products exist in alternative formulations, which might be reformulated, and what they intend to do about it (This initiative is already underway at Project Inform. Pediatric AIDS activists have long fought similar battles to force

industry to develop formulations suitable for use by young children and for combating perinatal transmission.);

- ♦ *discussions with the various clinical trials groups* to make a point of testing drugs, their bioavailability and alternative formulations in people with advanced disease;
- ♦ *discussions with the Food and Drug Administration* to see what can be done to ease moving new formulations through the approval system so that patients in need are not denied access merely due to bureaucratic delays.

Pursuit of these issues should help bring the advances of new therapies to a broader spectrum of the HIV-infected population. Today, the most seriously ill people, as well as those too young to fight for their own needs, often have the fewest and least effective options for therapy. This need not be the case. But, without strong public pressure and patient demand, little is likely to be done because it affects only a small, and not very profitable, portion of the "HIV marketplace."

Project Inform is committed to advancing the two causes identified in this issue of *PI Perspective* - diagnostic testing for viral resistance and development of alternative drug formulations. We urge others, both individuals and patient advocacy groups, to join us in this effort. Without progress on both of these fronts, exciting new therapies will not benefit all those who need them, and their long-term utility will ultimately be challenged by viral resistance. Researchers already have the scientific tools needed to confront and overcome both sets of obstacles.



Why Drugs Fail

With all the good news about how well some drugs are working for some people, it's very frustrating for others to find they're not getting the kind of results they had hoped for. There are many possible causes for drug failure, even when using drugs which have been proven to be effective in clinical studies. Remember that a study reports on average responses. No matter how successful a drug appears in a study, it is not proof that the drug will work in any particular individual. ALL drugs produce varying results in different people, just as they produce varying side effects.

Why do drugs fail? The first answer is simply because they do. Medical science cannot explain everything and no drug or treatment in medical history has been universally successful. But some potential causes of drug failure are known, and this knowledge sometimes leads to suggestions for overcoming the problem. The most common causes of drug failure include:

Cause	Explanation	Solution
Resistance to a drug	When a drug suppresses replication, the organism fights back by trying to create variations of itself (mutations) which can continue replicating despite the drug. When it succeeds, the drug may no longer work. Improper use of a drug hastens this process. Sometimes mutations occur naturally, even before a person has ever taken a drug. Sometimes a person was infected by someone who already had the resistant mutation.	Try other therapies, changing at least two elements of the combination therapy at the same time; if possible, first get tested for resistance so you will know which drugs are still active for you.
Improper use of a drug	Failure to take a drug as prescribed is probably the most common cause of drug failure. Improper use speeds the development of resistance.	Use the therapies as prescribed. If this fails, try new therapies and use them exactly as directed.
Inadequate absorption or metabolism of a drug	This may be common in people with wasting syndrome and malabsorption problems. If the gastrointestinal system can't process foods properly, it probably won't do a very good job with drugs either.	Sometimes increased doses of the drugs will help, though this risks greater toxicity. When possible, use alternate formulations, such as IV and IM delivery, skin patches, suppositories, and altered oral forms. Try to address the gastrointestinal problem.
Concurrent infections	When a person is fighting other serious infections, the rate of HIV replication may be greatly accelerated; also, metabolic imbalances associated with active infections may cause a drug to absorb or metabolize differently than in a healthier person.	Seek aggressive diagnosis of all signs of an underlying infection, and then treat the infection.
Drug interactions	Many drugs affect the absorption of others, causing blood levels of drugs to increase or decrease. When this occurs, it is equivalent to improper dosing of either or both drugs.	Check the interactions of the drugs you're taking in Project Inform's <i>HIV Drug Book</i> , or the Drug Interaction fact sheet. Adjust dosing or change to drugs that do not interact.
Diarrhea	If a drug is going out as fast as it's coming in, there is little chance that it will be properly absorbed.	Find and correct the cause of the diarrhea, or at least seek symptomatic relief.
Impatience	Sometimes we expect too much too soon. Generally, those with advanced disease or ongoing infections are slower to respond to therapies.	Discuss the situation with your doctor, monitor carefully, and have patience.

HIV Resistance: A Primer

HIV resistance has recently become a major concern for people with HIV infection. Resistance usually occurs when the drugs being used are not potent enough to completely stop HIV replication. If HIV can reproduce at all in the presence of drugs, it has the opportunity to make changes in its structure (mutations) until it finds one that allows it to reproduce in spite of the drugs. Once such a mutation occurs, it then grows unchecked and soon is the dominant strain of HIV in the individual. The drug becomes progressively weaker against the 'new' strain of HIV (though it may still have some value).

Most of the research on HIV resistance has been done in laboratory studies. It is unclear how much information from these studies is relevant to humans. However, increasing research on HIV drug resistance is being incorporated into clinical studies. Such studies will give us better understanding of whether the changes in HIV structure seen in test tubes have a predictable effect in the body. On the surface, it certainly seems so since the presence of resistant strains is readily correlated with declining drug benefits.

Resistance appears to develop more rapidly in people with lower CD4+ cell counts compared to those with a more intact immune system. This is probably because people with low CD4+ counts generally have higher levels of viral activity (viral load) and require better drugs to suppress the virus.

There are two general ways in which researchers attempt to determine whether resistance is occurring. One approach, called *genotypic* testing,

seeks to determine any changes to a part of HIV's genetic structure, which change the way the virus makes key proteins (like the protease or reverse transcriptase enzyme). Such changes are referred to as mutations. It is known that certain mutations result in the loss of a given drug's effectiveness, so researchers primarily look for these known mutations. The other approach, called *phenotypic* testing, is a more direct measure of resistance. It examines the amount of drug needed to inhibit the growth of HIV in a laboratory setting. In its natural state, when

...there are some drugs, such as 3TC (Epivir), which require only a single mutation to induce high level phenotypic resistance.

HIV is not resistant to a particular drug, known levels of the drug completely suppress viral replication. Resistant HIV requires higher levels of the same drug to get an equal level of suppression. However, it is not feasible to increase the dose of a drug indefinitely as this leads to increased toxicities. Most drugs are already given at near their maximum tolerated dose. Thus, if a person's resistant virus requires 10 times more drug before it will stop replicating, the person can not simply take a larger dose of the drug to overcome resistance. Generally, any time viral mutations make it necessary to use a dose 4 times higher than standard to suppress replication, the virus is considered to have high-level resistance. The only choice is to use a different drug.

Not all genotypic changes lead to phenotypic changes, and a lot of work is being done to better understand these findings. Generally, it takes a few genotypic changes before you see a phenotypic change. However, there are some drugs, such as 3TC (Epivir), which require only a single mutation to induce high level phenotypic resistance. Both genotypic and phenotypic resistance testing have their drawbacks. While phenotypic resistance is probably more relevant, it does not necessarily provide information about which drugs a person might still benefit from. Genotypic resistance gives specific information about changes

UPDATE!

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The Basic Message

- ✍ **Get tested, anonymously.**
- ✍ **Learn your options** and line up your support.
- ✍ If positive: **maximize your health, get a complete physical, a full immune health workup and get informed!** (See the PI document "Day One.")
- ✍ **Get baseline CD4+ and HIV RNA tests, repeat quarterly.** Chart the trends. Women should get "gyn" exams and "pap" tests every six months.
- ✍ If the CD4+ trend is downward or already below 500, and HIV RNA above 5,000, **or** if HIV RNA is above 30,000-50,000, regardless of other factors, **optimize nutrition and consider combination antiviral treatment.**
- ✍ If viral measures do not decline below the limit of detection or at least below 5000, **consider a more aggressive antiviral regimen.**
- ✍ If the CD4+ trend stays below 300, **consider preventive treatment against PCP** (oral drugs if possible). If the count continues to fall below 200, **reconsider an antiviral regimen** if not already on one and **learn about preventive treatments** against other opportunistic infections. **Learn about drug interactions.**
- ✍ If CD4+ count stays below 75, **intensify monitoring**, consider prevention against MAC/MAI and CMV infections. **Learn about preventive therapies.**

in the enzyme and scientists know, to some degree, which changes affect which drugs. But those changes do not always mean that the drug has completely lost effectiveness. Ideally, both genotypic and phenotypic information would be obtained to make the best treatment decisions. Unfortunately, measuring genotypic or phenotypic drug resistance is difficult, laborious and expensive. Only a few university laboratories can perform these tests. Work is proceeding on increasing availability of these technologies.

Cross-Resistance

There is increasing concern about cross-resistance. Cross-resistance occurs when changes which cause resistance to one drug also cause resistance to another. This is important with the protease inhibitors because results show that resistance to one protease inhibitor may lead to cross-resistance with other protease inhibitors. This will almost certainly be the case between indinavir (Crixivan) and ritonavir (Norvir). Resistance to these drugs results in a very similar genotypic profile. Therefore someone who has developed resistance to one of these drugs will probably get no benefit from the other. A lot of debate surrounds cross-resistance between indinavir, ritonavir and saquinavir (Invirase). Results are only available from a small number of people but they suggest that about 50% of the those who develop resistance to either indinavir or ritonavir will be cross-resistant to saquinavir. And at least 20-25% of those who develop resistance to saquinavir will have cross-resistance to indinavir and ritonavir. Some people argue that these data support using saquinavir as a first protease inhibitor, since the risk of cross-resistance seems lower. Most virologists strongly disagree. Because saquinavir offers so little potency compared to the other protease inhibitors, its use does not warrant incurring any risk of cross-resistance. People who are resistant to saquinavir but not cross-resistant to indinavir or ritonavir will likely have reduced and shorter antiviral response with either drug, because saquinavir resistance requires at least one mutation which

contributes to resistance to indinavir and ritonavir. Effectively, saquinavir resistance provides the first step toward resistance to the other protease inhibitors.

Very little information about cross-resistance is available on nelfinavir (Viracept) and the Glaxo Wellcome/Vertex protease inhibitor 141W94 (also known as VX-478). Both drugs are currently in clinical studies. Laboratory studies suggest that there is a slight chance that nelfinavir will be cross-resistant to indinavir and ritonavir and a likely chance it will be

Several studies have proven that combining two drugs delays the development of resistance to one or both drugs compared to when either drug is used alone. Other studies suggest that three-drug combinations extend this benefit even further.

cross resistant to saquinavir. However, only human studies will determine the true resistance and cross-resistance profile. Laboratory studies suggest that there is no cross-resistance between 141W94 and other protease inhibitors. Phenotypic testing of a few people known to be cross-resistant to the three approved protease inhibitors has shown them to still be sensitive to 141W94. Other laboratory studies indicate that resistance to 141W94 may cause HIV to become more sensitive to the other protease inhibitors. Again, only human studies will determine whether this will actually occur.

Several studies have proven that combining two drugs delays the development of resistance to one or both drugs compared to when either drug is used alone. Other studies suggest that three-drug combinations extend this benefit even further. As a result, many people believe that the best way of preventing, or at least delaying, resistance is to use multi-drug combination therapies. This does not mean simply adding a protease inhibitor to a combination that someone has been on for many months as resistance may have already developed or started to

develop. Rather, this involves using the protease inhibitor in addition to one or two other drugs that have not been previously used. Although it is likely, it has not been proven that three drugs provide more protection against resistance than two, or four drugs more protection than three. As the number of drugs increases, so does the risk of drug interactions and toxicity.

Resistance Testing Technology

Several companies are working on new technologies to detect resistance rapidly and these technologies are currently in clinical studies. One test which is being offered by Specialty Labs in Santa Monica, California detects genotypic changes affecting the nucleoside analogue drugs but not changes which affect non-nucleoside reverse transcriptase inhibitors or the protease inhibitors. This test costs about \$300 and currently some insurance companies are covering these costs. Due to start-up problems, there have been some delays in getting results from this test.

A group in Belgium is developing a process called the RT-antivirogram which provides phenotypic resistance testing of the nucleoside analogue drugs and the non-nucleoside reverse transcriptase inhibitors. Work is being done to extend this to include phenotypic testing of protease inhibitors.

Affymetrix of Santa Clara California has developed a high technology GeneChip system which detects genotypic changes in both the protease and reverse transcriptase enzymes. This system should be able to determine the presence of resistant mutations for all of the currently approved antiretroviral drugs. Conducting this test can be fairly simple because it can use the same blood sample used to test viral load by PCR (polymerase chain reaction). Interpretation of the test results is somewhat more difficult. Unfortunately, this test is not yet available commercially although we expect that there will be limited access to this technology soon. Project Inform has made further development and availability of this test a high level advocacy goal for the coming year.



Antiviral Update

Optimal use of protease inhibitors combines them with at least one other drug that has not been used previously. The non-nucleoside reverse transcriptase inhibitors (NNRTIs), like nevirapine (Viramune) or delavirdine (Rescriptor), may provide a new option for those who have used the nucleoside analogues. As options for combining drugs grow, data on how these drugs interact will become more necessary and more complex.

Non-Nukes plus Protease Inhibitors

Early results from interaction studies of nevirapine and saquinavir show that nevirapine decreases saquinavir levels by about 27%. Since the levels seen with the current formulation of saquinavir are already too low, adding nevirapine may not be a good idea as it will reduce the potency of saquinavir more and may hasten saquinavir resistance. But the benefits of nevirapine must also be considered. Until the combination is fully studied, there will be no clear answer.

More is known about interactions between delavirdine and protease inhibitors. Delavirdine (400 mg three times daily) raised saquinavir (600 mg three times a day) levels 5 fold and slightly lowered delavirdine levels. In this study, higher saquinavir levels raised liver enzyme levels. This might be a useful combination, but effectiveness studies are needed. People trying this combination need to monitor their ALT levels for the first few weeks. A study of delavirdine (400 mg twice daily) and ritonavir (300 mg twice daily) showed slightly lower delavirdine levels and no change in ritonavir. No information is available on how this affects HIV. It is unknown if the two drugs will interact at the standard doses (400 mg three times a day of delavirdine and 600 mg twice a day of ritonavir); much higher doses than those used in this study. Finally, delavirdine with one dose of indinavir raised indinavir levels about 50%, without changing

delavirdine levels. The recommended dose of indinavir (800 mg thrice daily) is already optimal, and interaction with delavirdine (without dose adjustment) may increase the risk of toxicity from indinavir. There is no data on this combination and its viral suppression.

Early results from a study of DMP 266 (a non-nucleoside reverse transcriptase inhibitor) show good activity. The study enrolled 16 people with CD4+ cells between 100 and 500. They were assigned to receive either DMP 266 (200 mg once a day) or placebo for two weeks; indinavir (800 mg three times a day) was then added for at least 12 weeks (see **Table 1**).

Table 1: DMP 266 and Indinavir

Regimen	Viral Load drop @ 2 weeks	Viral Load drop @ 12 weeks
Placebo	0.0 logs	NA
DMP 266	1.67 logs	NA
IND alone	NA	2.0 logs
DMP 266 + IND	NA	3.2 logs

IND = Indinavir

After 2 weeks, those on DMP 266 had a 1.67 log drop in viral load and after 12 weeks of DMP 266 and indinavir there was a 3.2 log drop with a 150 CD4+ cell rise. People on placebo for the first 2 weeks had no drop in viral load, but after 12 weeks of indinavir alone they had a 2 log drop and a 120 CD4+ cell increase. Side effects included headaches, diarrhea and sinusitis. Also, DMP 266 lowered indinavir levels by 37%. Despite this reduction, the antiviral effect of combining the drugs was positive. DMP 266 may be useful to combine with protease inhibitors for people who have taken all the nucleoside analogues. However, more information is needed before it can be optimally used.

Non-Nukes and Nukes

A study of ddI with or without delavirdine was stopped when it was seen that it would not show a difference between the two treatments. The study enrolled about 1200 people with fewer than 300 CD4+ cells, who had had

prior AZT therapy. Another study compared AZT to AZT + delavirdine (200, 300 and 400 mg three times daily). About 1100 people with 200 to 500 CD4+ cells took part (**Table 2**).

Table 2: AZT and Delavirdine at Week 60

Regimen	CD4+ Cell Change	Viral Load Drop
AZT	-40	0.4 logs
AZT + DLV (200 mg)	-20	0.3 logs
AZT + DLV (300 mg)	+15	0.6 logs
AZT + DLV (400 mg)	0	0.4 logs

DLV = Delavirdine

Delavirdine absorption varies among individuals; someone taking 200 mg may have higher blood levels than someone taking 400 mg. These results tell us more about the study designs than about the potential of the drug. Nearly all studies tested it in two-drug combinations but three-drug therapies are more effective.

More data from the CAESAR study of 3TC (see *PI Perspective #19*) are in. Almost 1900 people with 25 to 250 CD4+ cells began the study already using AZT, AZT + ddI or AZT + ddC. They added 3TC (150 mg twice daily), 3TC + loviride (a non-nucleoside reverse transcriptase inhibitor) at 100 mg three times daily, or placebo. Those on 3TC had a 54% lower risk of progression and/or death, and a 53% lower risk of death. There was no difference in progression and/or death between those who just added 3TC and those who added 3TC + loviride (see **Table 3**).

Table 3: Existing Therapy with...

Therapy plus	#	Progression or Death	Deaths
Placebo	482	81(16.8%)	22(4.6%)
3TC	935	80(8.6%)	22(2.4%)
3TC+ Loviride	475	38(8%)	13(2.7%)

Table 4: Ritonavir and Saquinavir

Regimen	CD4+ Change	Viral Load Drop
400mg RIT + 400mg SAQ (2x day)	+ 91 [^]	2.7 logs [^]
600mg RIT + 400mg SAQ (2x day)	+113 [^]	-3 logs [^]
400mg RIT + 400mg SAQ (3x day)	+74 [*]	2.1 logs [*]
600mg RIT + 600mg SAQ (2x day)	+88 [*]	2.2 logs [*]

[^] = 12 weeks * = 6 weeks
RIT =ritonavir SAQ =saquinavir

Protease Inhibitors

More data are in from a study of ritonavir with saquinavir (see *PI Perspective #19*), in which 132 people with 100 to 500 CD4+ cells are participating. All had been on nucleoside analogues (see **Table 4** for updated results). People on the 600 mg dose of ritonavir and saquinavir were more likely to experience elevated liver enzymes and triglyceride levels. Those on the three times a day dose were more likely to stop therapy due to such toxicities as diarrhea, tingling around the mouth, fatigue and nausea.

Early results from the Glaxo/Vertex protease inhibitor 141W94 (also VX-478) show promise. Forty-two people with 150 to 400 CD4+ cells partici-

pated in this 4 week study. About half had been on prior nucleoside analogue therapy and none had previously taken protease inhibitors (see **Table 5**).

Table 5: 141W94 Results at 4 Weeks

Regimen (Vertex)	Median CD4+ Cell Change	Median Viral Load Drop
300mg 2x day	+ 64	- 0.6 logs
300mg 3x day	+ 85	- 1.0 log
900 mg 2x day	+ 35	- 1.7 logs
1200 mg 2x day	+ 110	- 2.0 logs

New Concerns for Some Combinations

Combining d4T with AZT: For several years, researchers have noted a theoretical risk in combining d4T (Zerit) with AZT. While they have different side effects and no known harmful interactions, the two drugs compete chemically for the same elements when they are metabolized. This suggested that when the two drugs are used together, they might diminish each other's effects. Until now, there have been no clinical data to prove or disprove this concern. In late October, researchers participating in ACTG (AIDS Clinical Trials Group) study 290 were notified of the first evidence that this problem may be real. Preliminary analysis of data from 129 people in the trial showed that people receiving the d4T + AZT combination fared worse than those receiving ddI + AZT, or ddI or d4T alone. The main difference was a pronounced decline in CD4+ cells over 36 weeks for those on the d4T + AZT combination. Viral load and clinical outcome data are not yet available.

ACTG 290 recruited people with at least 6 months prior AZT use. They were randomized to one of four groups: (1) d4T plus AZT; (2) ddI plus AZT; (3) d4T plus placebo; (4) ddI plus placebo. The doses for each drug were 40 mg twice daily of d4T, 200 mg three times daily of AZT, 200 mg twice daily of ddI.

The only significant outcome seen was a decline in mean CD4+ cells in the d4T + AZT group. In this group, the CD4+ decline set in immediately and worsened through week 36. The decrease was 20 CD4+ cells/mm³ at week 4, 82 cells at week 24 and 57 cells at week 36. The difference at week 48 was not significant, but only a few volunteers had reached this point so the data are inconclusive. While these data cannot be considered conclusive because of the small study size, they are nonetheless quite significant and should serve as a fairly important warning to avoid combining these drugs, at least in people with prior use of antivirals. No differences were seen in clinical outcomes, and viral load data are not available.

A second study, ACTG 298, is testing similar combinations in people without prior history of antiviral use. A preliminary analysis was made to see if it confirms the results of ACTG 290. Surprisingly, it did not. People in the group combining AZT with D4T did not suffer any unusual loss of CD4+ cells. This suggests that the problem combining the two drugs may be unique to people who have had long prior experience with AZT. The reason for any of this remains unclear.

Combining Nevirapine with Indinavir: New data are available on interactions between nevirapine (Viramune) and indinavir (Crixivan). A study found that indinavir had no significant effects on nevirapine drug levels. However, in an 8 hour period, nevirapine decreases the average indinavir level in blood by 27%. Of more concern, when the amount of indinavir was lowest (at the end of the 8 hours), blood levels fell by 38% – possibly low enough to allow the virus to become resistant to the drug.

It is too early to make recommendations based on these data. Two alternative interpretations could be:

- ♦ Maintain the standard dose of indinavir. With synergy between the two drugs (i.e. 1+1= more than 2), together they may be potent enough to offset the lower indinavir levels.
- ♦ Increase the dose of indinavir to 1000 mg three times daily, to offset the reduced levels. This may result in higher overall levels of indinavir, with possible additional side effects and higher prescription costs.

More information and recommendations will become available for *PI Perspective #21*.



Update on Immune-Based Therapies

Immune-based therapies address the interaction between HIV and related infections and the immune system. They can be directed at all aspects of HIV disease. They may aim to enhance the immune system's ability to suppress HIV infection itself, reduce the risk of damage of infections, or suppress harmful immune responses associated with disease progression.

New information on triple-drug therapies shows that suppressing virus replication can slow the destruction of the immune system and sometimes results in improved immune status. Even with potent new antivirals, restoring parts of the immune system destroyed by HIV infection may be needed if we are ever to see a cure. Modulating the immune system productively is an extremely daunting task. The challenge in developing immune-based approaches is that we lack many of the tools for studying and understanding how the immune system works.

One complexity of these approaches is that many of the functions of the immune system in AIDS lead in contrary directions. Many of these therapies stimulate the immune system and may promote HIV replication as well as harmful inflammatory responses. This highlights the need for a strategy to control HIV replication. Some parts of the immune system may need to be suppressed rather than stimulated, while other parts may require the opposite. Though attractive as theories, most immune-based therapies are experimental and are not proven to extend life or improve quality of life. Some of these therapies are quite toxic, which is not surprising as often it is our own immune responses to infections which cause the flu-like symptoms, fevers and aches associated with illness.

Immune-Based Therapies: the

Immune Environment

To achieve immune restoration, it is important to know if the compartments where immune cells are derived and mature are intact. Dr. McCune of the Gladstone Institute in San Francisco is conducting two studies to examine the state of these compartments. One involves bone marrow biopsies and the other involves CT scans of the thymus. The thymus

Even with potent new antivirals, restoring parts of the immune system destroyed by HIV infection may be needed if we are ever to see a cure.

is the major organ where new thymic lymphocytes (T-cells) mature (both CD4+ and CD8+ cells). It decreases in size with age. Scientists are uncertain if it functions at all in adults, but suspect that it may be damaged early in HIV disease. Dr. McCune is examining people with a wide range of CD4+ cells counts and ages. Preliminary observations suggest that the thymus shrinks more than expected in adults when CD4+ cell counts fall below 200. While thymus size does not necessarily indicate its function or state of infection, it does provide some information. The purpose of the bone marrow study is to see if bone marrow in HIV-infected people retains the key cells and functions needed for a healthy immune system. While neither study offers therapeutic benefit, each will advance knowledge about the immune system. Both studies offer compensation. The thymus scan study particularly needs HIV-infected people under the age of 30. To participate in either study, call Pamela Carrol at 415-695-3815.

Another study, conducted by Dr. Schooley at the University of Colorado, is collecting bone marrow cells from people with HIV and freezing the cells for later use, perhaps to help restore the immune system later in the disease. The study, called AIDS Clinical Trials Group (ACTG) study 285, administers filgrastim (Neupogen or GCSF) to people across the spectrum of CD4+ cell counts. They are given filgrastim by injection daily for up to

a week to promote growth of key cells in the bone marrow. At different time points, blood is examined to determine the amount of bone marrow stem cells which can be captured. Also, the status of HIV infection and the function of the cells will be examined. The stem cells will be frozen and thawed at different times to see if this alters the cells. Researchers will also see if these stem cells can be modified to resist HIV infection. While this study will not offer therapeutic benefit, it is a critical study for increasing knowledge which will speed research on many cell-based approaches. To participate, contact Virginia at 1-303-372-5539.

Efforts have also begun with thymus transplantation. A study by Dr. Richard Hong at the University of Vermont has enrolled 4 of 6 volunteers. It involves transplanting thymic tissue into the material between the stomach muscles. Healing after the surgery can be painful for a few weeks, and side effects can include gas and stomach pains. Participants are given ATG, a drug which helps clear remaining thymic cells from the transplanted material. The side effects of ATG can include spiking fevers, rigors and hives. Immune suppressive agents, such as prednisone, may be administered to control the hives. To protect the new thymic tissue from HIV, the transplants were done with combination antiviral therapy. Researchers are looking for changes in the type of CD4+ cells, particularly those cells which are newly developed through the thymus, rather than those cells which have simply divided in the blood. Hopefully, the new cells will have better function.

Other thymus transplant studies are being done at the Prince of Wales Hospital in Australia by Dr. Dwyer and Dr. Markert of Duke University. Dr. Markert urges realism about when to expect results from thymus transplantation. In the bone marrow transplant setting, immune reconstitution can take 6 to 12 months, as it takes time for bone marrow cells to mobilize and mature through the thymus. In children born without a thymus, development of

a full set of T-cells can take several years following a thymic transplant. These observations have implications for anti-HIV therapy as well. If it takes this long for a full complement of new cells to develop through the thymus, people experiencing rapid increases in cell counts with anti-HIV therapy should be cautious about going off preventative therapy for opportunistic infections. Any initial rise in CD4+ cell counts is likely to represent a rapid expansion of existing cells and may not be a dramatic improvement in immune function. If key types of cells have been lost, they will not be quickly replaced. New cells maturing through the thymus will take much longer to contribute to the numerical cell increases.

**Immune-Based Therapies:
Increasing Cell Numbers**

Several groups are researching ways to increase the number of cells. For now, one reliable way to build and sustain increases in cell populations seems to be triple combination antiviral therapy, which also reduces viral load. Thus, nearly all studies using immune therapy to increase cell numbers build upon triple-drug antiviral therapy. The most researched cell expansion therapy is interleukin-2 (IL-2) and efforts are only beginning to move other CD4+ cell expansion techniques into clinical studies.

IL-2 stimulates CD4+ T-cells to divide, increasing their total numbers. If cells responsible for specific functions are already destroyed, there is no reason to expect IL-2 therapy to restore those functions as it can only expand the existing cell population. Dr. Lane has described this situation as being like a box of scrabble tiles. In a box, the tiles all look the same, but as you turn them over each has a different letter. Similarly, cells have unique functions. If all of the P's in the box are destroyed due to HIV infection, increasing the number of existing tiles will not bring the P's back. Regardless of what one does, spelling PCP won't be possible. However, with even a few P's left, expanding their number may increase the time the immune system

will be able to spell PCP. This is one of the difficulties in assessing the benefit of cell expansion. It may be possible to increase the number of cells, but functional immune status may not dramatically improve. Similar limitations may affect the cell increases achieved by antiviral therapy. When people's CD4+ cell counts fall below 200, it is well established that the risk of PCP increases and preventative therapy is required. It's far from clear that the risk for PCP disappears as CD4+ cell counts climb, especially in people who have already experienced opportunistic infections.

Early IL-2 studies showed that people with CD4+ counts greater than 200, who were on antiviral therapy could achieve dramatically increased CD4+ cell numbers. Some of the best responders saw CD4+ cell rises from 400 to over a thousand, which were sustained for 6 months or longer, without the continued use of IL-2. But such responses were rarely seen in people with lower baseline CD4+ cell counts.

People with less intact immune sys-

tem were more likely to experience increases in HIV replication, and the antivirals originally available (AZT, ddI, ddC and d4T) were incapable of controlling this increase in virus. New, more potent antivirals have become available, renewing interest in evaluating IL-2 in people with more advanced disease. In one recent study, 36 people with CD4+ counts less than 300 received IL-2 + zidovudine (ZDV), IL-2 with co-administration of zalcitabine (ddC) *only* during the IL-2 infusions, or zidovudine alone.

IL-2 was given by infusion, starting at 12 million international units daily for 5 days, every 8 weeks. The IL-2 dose was lowered, as needed, to manage reactions, which include flu-like symptoms, rashes and fevers. Indinavir was given at doses of 600 mg, 4 times daily. Participants had either previously been on IL-2 therapy with no improvement in CD4+ cell counts, or they had been in a control group whose CD4+ counts had declined over time. All had been on previous antiviral therapy.

Preliminary data, reported in *PI Perspective #17*, showed that those receiving the combination of IL-2 + indinavir had a increase of 185 CD4+ cells by week 14, which continued to rise. By week 25, increases were 200 over pre-study levels. Those receiving indinavir alone saw a CD4+ cell rise of 83 by the 14th week of study, which continued to rise to 175 by week 25. After 14 weeks, volunteers could add other antivirals to their regimen. Those receiving IL-2 with intermittent indinavir therapy had the least desirable responses after the first 14 weeks of study, and were allowed to go on continuous indinavir therapy. Those receiving indinavir alone were permitted to add IL-2. At week 50, 8 people in each of the groups were receiving IL-2. Those receiving IL-2 saw substantial increases in CD4+ cell counts, and viral load (HIV RNA) remained below pre-study levels. Data in **Table 1** categorize *all* those who received IL-2 according to the therapy they *originally* received, realizing that at week 14 everyone was allowed to add other antivirals or IL-2 therapy.

Among the those receiving IL-2, no deaths or new opportunistic infections occurred. One person who opted not to receive IL-2 died after developing AIDS-related dementia.

A study involving 60 people with CD4+ counts greater than 200 receiving either IL-2 with antiviral therapy or antiviral therapy alone was recently reported in the *New England Journal of Medicine*. Among those receiving IL-2 the mean CD4+ count rose from

Table 1

Initial Study Group*	Mean Baseline CD4+	Mean CD4+ @ Week 50	CD4+ Rise Over Baseline
IL-2 + IND	205	464	259
Intermittent IL-2 + IND	191	415	224
IND Alone	144	376	232

IND = indinavir IL-2 = interleukin-2
*participants who *added* IL-2 after 14 weeks.

tems using IL-2 were more likely to experience increases in HIV replication, and the antivirals originally available (AZT, ddI, ddC and d4T) were incapable of controlling this increase in virus. New, more potent antivirals have become available, renewing interest in evaluating IL-2 in people with more advanced disease. In one recent study, 36 people with CD4+ counts less than 300 received IL-2 + zidovudine (ZDV), IL-2 with co-administration of zalcitabine (ddC) *only* during the IL-2 infusions, or zidovudine alone.



428 to 916 over 12 months, while those on placebo experienced CD4+ decreases from a mean of 406 to 349. There were no differences in viral load response between the two groups. IL-2 is perhaps the most widely available immune-based therapy. Large trials are ongoing. IL-2 is approved for treating kidney cancer and thus many people are using it “off label” for HIV disease. For information on clinical trials, call 1-800-TRIALS-A.

Another way to increase CD4+ cell counts involves growing CD4+ cells outside the body, then reinfusing them. Experiments have drawn CD4+ cells from people at various stages of HIV-disease and grown the cells in the presence of concentrated antivirals. Under these conditions, HIV can be eliminated from the cells. But, the resultant cells are still highly infectable by HIV. Dr. June has used particular factors to induce cell growth, notably anti-CD3 and CD28 antibodies, and the resultant cells appear to be highly resistant to HIV infection. Dr. June has recently moved this technology back into the clinic and is now reinfusing cells into volunteers to assess the safety of this approach.

Interestingly, the cells which Dr. June grows appear to have no CKR5 (also called CCKR5) on their surfaces (see *PI Perspective # 19, Opening the Door On HIV*). CKR5, a protein on the surface of various immune cells, is a critical piece in the puzzle of how HIV infects cells. In order to gain entry into CD4+ cells, the virus latches on to both CD4 protein and CKR5. Without CKR5 on the cell, the most common form of HIV, called non-syncytia-inducing (NSI) HIV, is not able to infect a cell. The cells which Dr. June grows do not have the CKR5 receptor and are thus believed to be uninfected by the most common NSI form of HIV. However, the cells that Dr. June grows *do* have a surface protein called CXCR4 (fusin). This protein is critical for a different, less common, syncytia-inducing (SI) form of HIV to infect immune cells. There are naturally occurring immune chemicals,

called beta-chemokines, which may bind up CKR5 and CXCR4 and help block HIV from infecting cells. This is depicted in **Figure 1**. Since the recent discovery of CKR5's role in HIV infection, it has been suggested that some people who are exposed to HIV, but seem resistant to infection, have defective CKR5 genes. Moreover, additional information suggests that a number of people with HIV who are long-term non-progressors also have partially defective CKR5 genes, perhaps explaining why HIV is so slow to ravage their immune systems.

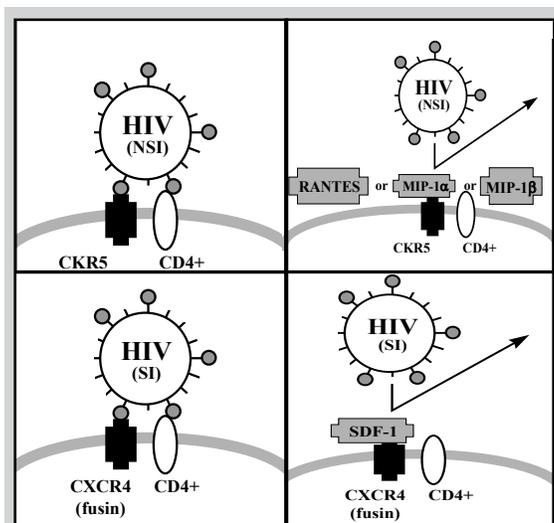


Figure 1: Beta-Chemokines block entry of HIV into cells

Immune-Based Therapy: Enhancing Cell Function

Expanding the number of cells does not necessarily improve immune function. Studies involving cell therapy, passive immune therapy and cytokine therapy all seek to enhance immune function.

Allogeneic cell therapy involves taking cells from a healthy HIV-negative person and transferring them to a person living with HIV. The functional immune responses from the healthy donor may help the recipient fight infections, even HIV. Studies conducted or underway have transferred cells from close family members. Two studies of allogeneic cell transfer, one at St. Francis Hospital in San Francisco and the other at Case Western Reserve in Ohio, are currently enrolling vol-

unteers. These studies were designed to confirm encouraging preliminary results reported from an unpublished effort conducted in the mid-1980s.

A number of cell transfers have already taken place at St. Francis with minimal side effects. Investigators report no significant changes in CD4+ cell counts, but maintain that it is still too early to draw conclusions and that increased counts are not necessarily expected. They do see positive trends, however. The studies are open to people with less than 200 CD4+ cell counts, who have family members with suitable cell types. To participate, contact Jacqueline Mayer at Case Western Reserve in Ohio (216-844-8175) or Sher Viera at St. Francis in San Francisco (415-353-6215).

Another approach involves expanding HIV-specific CD8+ cells. Some CD8+ cells can seek out and destroy infected cells. This is called a cellular immune response and is thought to be important in controlling HIV. Dr. Lieberman engineers CD8+ cells to recognize and destroy the dominant strains of HIV in a person's body. After infusing the HIV-specific CD8+ cells, CD4+ counts rise for a few weeks then return to baseline. Overall, CD8+ cell counts remain stable, yet people have trends toward greater HIV-specific cell activity.

There have been no side effects associated with therapy.

In Washington State, a CD8+ cell therapy approach is ongoing at the Fred Hutchinson Cancer Research Center under Dr. Greenberg. He has noted that in bone marrow transplants, where CMV disease is a danger, when CMV-specific CD8+ cells are expanded and infused, it is possible to wholly prevent CMV disease. Dr. Greenberg is expanding HIV-specific CD8+ cells, and also CMV-specific CD8+ cells, and has reinfused these cells into people living with HIV. He plans to modify these cells to produce IL-2, hopefully extending their lifespan.

In addition to enhancing immune function through cell therapy, researchers are looking at augmenting another arm of the immune system, antibody

responses. Cellular responses control infections inside cells, while antibodies control infectious agents outside. HIV exists in both places. Many opportunistic infections, especially bacterial infections, are found outside cells. Antibody replacement is called passive immune therapy because antibodies are administered intravenously. Passive immunization has been around for over 100 years. In the context of HIV, antibodies can destroy infected cells, slow cell-to-cell transmission of the virus and kill cell-free HIV. Passive immune therapy includes transfer of antibody preparations and monoclonal antibodies (antibodies engineered in a laboratory), have been studied in people with HIV.

One form of passive immune therapy takes plasma, rich in antibodies, from people who are HIV+ and healthy, and infusing it into others in more advanced-stage disease. Studies of this approach have had mixed results. In people with advanced disease, some data suggest that this approach may be useful in preventing opportunistic infections. The following is a summary of results from a number of studies:

- ♦ A California study saw a rise in CD4+ cells, but only in those with CD4+ counts greater than 50.
- ♦ A French study showed no effects on CD4+ cell counts, cytokine production or viral load.
- ♦ A Swedish study which infused 11 volunteers twice monthly over 3 months, saw no changes in CD4+ cell counts, but cellular responses appeared to be enhanced.
- ♦ A Swiss study suggested that there may be some clinical benefit from this approach, even though it had no impact on CD4+ cell counts.

Why these studies yielded such differing results should be examined. Some suggest benefit, while others suggest the therapy has no impact on the disease process at all. A well designed study is the only way to answer this question.

Clinical work has begun in the United States and abroad. An AIDS Clinical

Trials Group (ACTG) trial of a monoclonal antibody, F105, is ongoing. Early data show that F105 is safe, but may not have an impact on immune or viral measures. In a second phase of the study, participants will be pre-screened to make sure their virus is sensitive to the antibody. Other research includes an ACTG study comparing various doses of two monoclonal antibodies, 2F5 and 2G12, to combination of both.

Monoclonal antibodies to HIV, CMV and hepatitis are all being explored in trials. While MSL 109, a CMV mono-

Not all vaccinations cause increased viral replication and replication due to the flu itself would be much higher and more prolonged than that caused by vaccination.

clonal antibody, seems well tolerated (see *PI Perspective #17*), a large study compared standard CMV therapy to standard therapy in combination with MSL 109 and showed that people receiving MSL 109 had *less* favorable outcomes. Research into a hepatitis B monoclonal is still in early human testing and reports suggest that at higher doses it may reduce levels of hepatitis virus. More study is needed to see if this approach is useful in fighting infections common to people with HIV.

Immune-Based Therapy: Exploring New Ideas

A variety of approaches capitalize on increasing information about immune dysfunction associated with HIV disease. Immune suppressive therapy, for example, is being tested to evaluate the role of inhibiting immune activation in HIV disease. Another approach, using radiation, targets the immune compartments which harbor the virus, such as the lymph nodes and quiet, non-dividing, infected cells.

Studies of people infected with both tuberculosis (TB) and HIV show that in such a state of chronic immune stimulation, people progress to AIDS and die more quickly than those infected only with HIV. People co-infected with TB

and HIV also have higher viral levels than those with HIV but not TB. When people co-infected with HIV and TB treat their TB, HIV levels fall dramatically. Nearly all physicians have noted similar effects when patients are fighting other opportunistic infections, such as PCP, MAC or CMV. Studies looking at the impact of vaccination, which can stimulate the immune system, on viral replication show that influenza vaccination increased viral load over 100 fold in some people. In less than 2 months, viral load returned to pre-vaccination levels. This study shows the harm of immune activation, not vaccination. HIV replication due to the flu itself would be much higher and more prolonged than that caused by vaccination. These data show activation of the immune system can increase viral replication and accelerate disease progression, suggesting that immune suppression may have a place in treating HIV disease.

An Israeli researcher, Dr. Bentwich, and others note that in HIV, activated CD4+ cells generally are not reproducing and thus loss of CD4+ cells is due to destruction *and* reduced production of new cells. Dr. Bentwich argues that chronic immune stimulation, and not the direct killing effect of HIV, causes immune deficiency in AIDS. The truth is probably between the two theories. Certainly HIV is destroying immune cells, leading to immune deficiency, but the effects of chronic stimulation contribute to this deficiency. There are several studies examining the effect of triple-drug therapy including protease inhibitors on immune activation. The findings of Dr. Bentwich and others do not call into question the usefulness of anti-HIV therapy. It is HIV, after all, which stimulates the immune system; decreasing the amount of HIV should decrease immune activation.

Certain cytokines are known to increase HIV replication; these include tumor necrosis factor-alpha (TNF-alpha), IL-6 and IL-1. While these cytokines increase HIV replication, others may block it. Interleukin-10 (IL-10) may be one. In test tube studies, Dr. Fauci's group at the National



Institutes of Health (NIH) has shown that IL-10 inhibits HIV replication in macrophages, and inhibits IL-6 and tuberculosis-induced HIV replication. It may do this by inhibiting cell activation.

IL-10 is known to be immune suppressive and the group proceeded slowly into human studies, first examining IL-10 in healthy HIV-negative people. A single injection of 1, 10 or 25 micrograms/kg was given to volunteers. Their cells were drawn at various times, and exposed to HIV in cultures. IL-10 appeared to decrease the cell's production of cytokines which stimulate HIV replication, such as TNF-alpha, and the cells appeared to be resistant to HIV infection. Within 24 hours the cells regained their ability to make TNF-alpha, and to be infected by HIV. Based on these findings, Fauci's group moved into a small study of IL-10 in people with HIV. Early results show that one dose of IL-10 decreases HIV replication for 12 to 24 hours. With increased doses, viral suppression seems to remain stable, but the duration of suppression is increased. Expanding this trial to include a second infusion is warranted. IL-10 is thought to block HIV entry into cells, as well as inhibit the production of cytokines which stimulate HIV-replication, because of its ability to inhibit cell activation. Because IL-10 is immune suppressive, it is important to proceed with caution.

Trails of immune suppressive agents, such as cyclosporine, have been initiated both inside and outside the NIH. Studies thus far have yielded mixed results. Some suggest this approach may actually accelerate the disease process, others suggest there may be beneficial impacts on clinical outcomes. The ACTG's Immunology Committee is evaluating the impact of corticosteroids, also immune suppressive in some regards, on immune function through a study of prednisone for the treatment of HIV-related kidney toxicity. A study of methotrexate, another such agent, has also begun.

Since the baboon-to-human bone marrow transplant, there has been increasing interest in radiation for

treating HIV. The patient thrived, yet the baboon cells may not have survived for long in the recipient's body and may not have contributed to his improved health. Researchers wonder if the radiation therapy which preceded the infusion of baboon cells may have destroyed reservoirs of virus, allowing recovery of immune status. One major reservoir for HIV

it would be expected that a volunteer's immune system would 'bottom out' approximately 10 days after the therapy, leaving a person at risk for infections until immune recovery begins. Radiation therapy may also destroy the 'friendly flora' in the gut, and cause nausea and stomach cramping. These side effects might be minimized with the use of anti-nausea drugs, as well as natural remedies, such as acidophilus. While this approach, especially at high doses, may be quite toxic, it may be that lower, less toxic levels of radiation therapy will produce a desired set-back in the virus' entrenchment. To participate in this study, call 415-695-3820 and ask for Diane Schmidt.

In Memory

We dedicate this issue of the
PI Perspective to:

Michael Freiberg

Howard Mark

Connie Norman

Rex Palmer

Peter Rosenfeld

Mike Winstead

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

*Their memory lives on in the work
that remains.*

is the lymph nodes. Also, possible obstacles to eradicating HIV from the body are infected, quiet, non-dividing cells. These cells rest quietly for up to 3 years and once activated may produce virus, thus rekindling infection (see *Eradication of HIV, PI Perspective #19*). Radiation therapy may not only target the lymph nodes, but may also destroy these quietly infected cells. This would prove likely if HIV-infected cells are more susceptible to radiation damage than healthy cells.

A small study of total lymph node irradiation (TLI) is being proposed at the Gladstone Institute and San Francisco General Hospital. This study will compare triple-drug antiviral therapy to triple-drug therapy with varying doses of TLI. The bone marrow and thymus will be shielded from the radiation to preserve the immune compartments where new cells are derived and mature (see page 11). This study is proceeding slowly and cautiously, first with extremely low levels of radiation, and increasing doses only after safety has been established. Radiation therapy is not without side effects. Especially at higher dosages,

Summary

Immune reconstitution has progressed dramatically. This is partly due to Project Inform's Project Immune Restoration (PIR), one of the few efforts focusing research attention on immune-based therapies and specifically therapies for people with advanced-stage HIV disease. Project Inform recently presented PIR to scientists at the first meeting of the Laboratory of Human Virology, which may be the most prestigious basic science forum on HIV. The project represents a model for community interaction with research, and has helped move ideas into the clinic at breakneck speed. The 6th meeting of the Immune Restoration Think Tank, a component of PIR, has just taken place in Atlanta, Georgia. The next *PI Perspective* will discuss this meeting. Accolades and thanks go to the treatment activists of Atlanta who helped support the recent meeting of the Think Tank, and to activists from ACT UP/Golden Gate, whose ongoing help with the project has been essential. For more on Project Immune Restoration, call the Project Inform National HIV Treatment Hotline at 800-822-7422 and ask for the *Project Immune Restoration Fact Sheet*.

Opportunistic Infections Update

Recent developments in preventing and treating opportunistic infections have involved two new therapeutic approaches. The first is the development of liposomal formulations of established drugs, which improve the delivery of drug throughout the body by packing microscopic quantities of the drug in a shell of fat (liposomes). The second is development of a new class of drug nucleotide analogues. Both increase the options available for treating a growing range of infections.

Fungal Infections

A recent study showed that itraconazole may be effective in preventing some fungal infections. The study followed 295 people with CD4+ cell counts of less than 150 who live in areas where histoplasmosis is common. One group received 200 mg itraconazole 4 times daily, while the other was given a placebo. Prevention failure was defined as a fungal infection throughout the body (systemic) or mucosal candidiasis requiring multiple or prolonged systemic therapies. Failure occurred in 29 of 149 (19%) people receiving itraconazole and 42 of 146 (29%) of those on placebo. In those with fewer than 100 CD4+ cells, it significantly delayed the onset of histoplasmosis, cryptococcosis and all systemic fungal infections. However, it did not delay recurrent infection. Toxicities associated with itraconazole were usually mild and temporary, but two cases of nonfatal Stevens-Johnson syndrome (a potentially life threatening form of rash) did occur among people receiving itraconazole.

A 30 person study compared intravenous (IV) amphotericin B with IV liposomal amphotericin B for treat-

Guidelines on Cidofovir

Gilead Sciences has issued a warning about the proper use of the intravenous (IV) formulation of cidofovir. The warning follows reports of a few cases of one or two doses of IV cidofovir leading to kidney damage and possibly contributing to death. The company reports that these reactions were seen in people who had a mild level of kidney problems already, or who had just finished some other therapy with kidney-associated toxicities. These guidelines are recommended for IV cidofovir therapy:

- Cidofovir should not be used in people with serum creatinine levels of more than 1.5 mg/dL (milligram per deciliter), creatinine clearance of 55 mL/min (milliliter per minute) or less, or a urine protein level of 100 mg/dL or more. Physicians should use the Cockcroft-Gault formula to estimate creatinine clearance
 - ♦ **men**, $(140 - \text{age}) \times \text{kilograms of weight} / 72 \times \text{serum creatinine in mg/dL}$
 - ♦ **women**, $(140 - \text{age}) \times \text{kilograms of weight} \times 0.85 / 72 \times \text{serum creatinine in mg/dL}$
- Cidofovir should not be used with other treatments that have nephrotoxic (kidney damaging) potential such as foscarnet, amphotericin B, aminoglycoside antibiotics, intravenous pentamidine, and certain anti-inflammatories. People planning to use cidofovir should allow at least 7 days to "wash out" other such agents before beginning on cidofovir. Data from some trials suggest that previous use of foscarnet, in particular, may increase the likelihood of kidney toxicity when using cidofovir.
- To minimize the possibility of kidney damage, an intravenous infusion of normal saline solution (0.9 liters over 1 to 2 hours plus, if possible, an added liter during or immediately after the treatment) and oral probenecid (2 grams 3 hours before treatment, 1 gram 2 hours after, and 1 gram 8 hours after, for a total of 4 grams) must be used for each infusion of cidofovir.
- Do not exceed the recommended dosage (5mg/kg), frequency or infusion rate (one hour infusion weekly for two consecutive weeks).
- Monitor renal function (serum creatinine and urine protein) within 48 hours before each infusion.

ing cryptococcal meningitis. Fifteen people received 4 mg/kg of the liposomal formulation and 13 received 0.7 mg/kg (the usual dosing) of the standard formulation for the 3 week study. Two people on standard amphotericin B withdrew due to toxicity. All participants were given follow-up maintenance therapy of 400 mg per day of fluconazole for 7 weeks. Participants' cerebrospinal fluid (CSF) was tested for cryptococcal cultures weekly for the first 3 to 4 weeks. A positive response was defined as 2 consecutive samples which were free of cryptococcal cultures. After 21 days, 10 of 14 people using the liposomal formula responded, compared to 3 of the 8 remaining people using the non-liposomal therapy. The median time to sterilization of the CSF for those on

liposomal amphotericin B was 14 days compared to 21 for the non-liposomal version.

Hepatitis B

Many people with HIV are at risk for, or are co-infected with, hepatitis B (HBV), which can cause cirrhosis of the liver. A small study looked at the safety and effectiveness of adefovir dipivoxil (GS 840) in treating HBV infection. Fifteen people with HBV took 1 daily tablet of 125 mg of adefovir and 5 people took a placebo tablet, for 28 days. An HBV viral load test measured antiviral activity. Thirteen participants were also HIV-infected and 5 had previously been treated with interferon-alpha, a common treatment for hepatitis B.

Adefovir produced a significant decrease in HBV viral load levels while



the participants receiving the placebo had a slight increase. However, viral loads returned to baseline within 6 weeks of stopping treatment. People from earlier trials have taken 120 mg daily of adefovir for as many as 14 months without signs of cumulative toxicities.

Side effects associated with treatment were two cases of moderate nausea and changes to liver function. During therapy 3 people experienced elevated liver enzymes, four saw similar liver reactions following the therapy. Interestingly, none of these enzyme changes were seen in the HIV-infected participants, leading the researchers to speculate that the higher enzyme levels were part of an immune response.

CMV Retinitis

Cidofovir (Vistide), an anti-CMV drug administered by direct injection into the eye or infused intravenously, had shown promise against CMV. However, new reports have raised issues about both administration of the intravenous treatment (see insert on previous) and the effectiveness of the intraocular treatment.

A previous study indicated that cidofovir injected into the eye once every 6 weeks (with probenecid, which is used to reduce kidney toxicity) was very effective and well tolerated for treating CMV retinitis. New data may indicate that it is less well tolerated than previously indicated. Thirty-one of the planned 90 people received either 5, 10 or 15 micrograms of cidofovir without probenecid. CMV progression was assessed by retinal photographs. Median times to CMV progression was 30, 29 and 41 days for the three doses respectively. Significant toxicities were seen in this study, 87% of the participants had iritis (inflammation of the iris) and 16% of people had hypotony (decreased pressure in the eye). While this data is disappointing, another ongoing study, this time including probenecid, may shed light on this question.

MAC Management

Results from recent studies shed light on preventing and treating Mycobacterium Avium Complex (MAC) disease. MAC is a leading cause of death for people with AIDS. People with fewer than 75 CD4+ cells are most at risk, and about a quarter of people with AIDS have MAC disease. MAC can infect the intestinal tract, the bone marrow, the lungs or several other body organs. Some of the symptoms of MAC disease include fevers, night sweats, weight loss and abdominal pains. Because these symptoms are similar to those of other infections, it can be difficult to diagnose MAC in its early stages. It is usually diagnosed by culturing blood to detect the organism. It can take weeks for a definitive diagnosis, so people are often started on anti-MAC therapy if they have symptoms of MAC, with the presumption that they have MAC disease.

Since treating MAC requires a combination of at least two powerful drugs, the potential for serious drug interactions makes it essential to weigh the risks and benefits of all the different treatment options. Even prevention of MAC is best done with a two drug combination. Some anti-MAC approaches may prolong survival more than others. But it is difficult to do large studies enrolling people with advanced HIV disease and the relative survival benefits of the anti-MAC regimens may never be clearly defined. Thus, each individual faces the prospect of choosing a therapy based on somewhat unpredictable factors such as quality of life, risk of side effects and more or less frequent need for additional therapy. Though not clearly documented, it is possible that new, more effective treatments for HIV disease may themselves improve the effect of MAC treatment, perhaps through the contributions of an improved immune system.

Available Preventative Therapies

Three drugs are approved by the Food and Drug Administration (FDA) to prevent MAC disease - rifabutin (Mycobutin), clarithromycin (Biaxin) and azithromycin (Zithromax). Rifabutin was the first drug approved for MAC prevention based on two studies showing that people receiving the drug had a 30-50% reduction in the risk of developing MAC compared to people receiving a placebo. Two studies using clarithromycin for MAC prevention also show promising results. In one study, people receiving clarithromycin were about 70% less likely to develop MAC compared to people receiving a placebo. Additionally, people receiving clarithromycin lived longer than those receiving placebo. The second study compared clarithromycin to rifabutin to the combination of the two drugs. This study found that both clarithromycin alone and the combination were significantly superior to rifabutin alone in preventing MAC disease, though there were no differences in survival between the three groups. Although clarithromycin appears to be superior to rifabutin, one disturbing aspect of these data is the high incidence of clarithromycin-resistant MAC. In one study, 60% of people who developed MAC despite preventative clarithromycin therapy became resistant to the drug. Thus clarithromycin could not be used as part of the treatment regimen. In the second study, 30% of people using clarithromycin developed resistance and the combination of rifabutin and clarithromycin did not decrease the risk of clarithromycin resistance. Additionally, people receiving the combination had significantly more side effects compared to people receiving either drug alone.

A study comparing azithromycin to rifabutin to the combination showed azithromycin to be comparable to rifabutin, and the combination was significantly better than either drug alone. Only about 10% of people receiving azithromycin alone, who developed MAC, were resistant to the drug. Interestingly, the study found that the combination prevented the emergence of both azithromycin- and

clarithromycin-resistant MAC. No studies have yet reported on a direct comparison of clarithromycin and azithromycin. Because the two drugs are very similar, developing resistance to one is likely to result in resistance to the other (cross-resistance). However, because rifabutin belongs to a different class of drugs, there has been no evidence of cross-resistance between rifabutin and either azithromycin or clarithromycin.

Prevention Commentary

People should test for tuberculosis (TB), a closely related organism, before starting therapy to prevent MAC. If someone has active TB, treating with a single drug is likely lead to multi-drug resistant TB.

Care is needed when combining protease inhibitors with drugs used to prevent opportunistic infections, to avoid potential drug interactions. Both rifabutin and clarithromycin have drug interactions with some, if not all, of the available protease inhibitors. Azithromycin has no known drug interactions with the protease inhibitors and may be attractive for those taking a protease inhibitor. Also, in prevention studies, azithromycin was taken only once a week (1200 mg) compared to once daily (300 mg) for rifabutin and (500 mg) twice a day for clarithromycin. Some physicians think a 600 mg twice a week dose of azithromycin may be more beneficial as this may reduce some side effects. A twice a week dose may also give a more constant level of drug in the body and thus further reduce the risk of resistance.

The use of clarithromycin in MAC prevention was associated with a survival advantage compared to placebo, however no survival advantage was seen when compared to rifabutin. This does not necessarily mean there is no difference, but only that the limited available studies were not capable of showing one. The problem with clarithromycin resistance is troubling. It is generally regarded as the treatment of choice for MAC, so some physicians are reluctant to use the drug as pro-

phylaxis (prevention), but rather save it as option for treating the disease if needed. It is still unknown why the addition of rifabutin to azithromycin was able to delay or prevent the emergence of azithromycin/clarithromycin resistance, but the addition of rifabutin to clarithromycin failed to do so.

Interaction between rifabutin and clarithromycin increases risk of uveitis, a painful eye inflammation. There are many drug interactions with rifabutin

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so it must be used cautiously.

Available Treatments

The current Public Health Service (PHS) recommendations for treating MAC disease include using either clarithromycin or azithromycin and ethambutol (Myambutol) and one or more of the following if needed: clofazimine (Lamprene), rifabutin, rifampin (Rifadin, Rifamate, Rifater or Rimactane), ciprofloxacin (Cipro), or, in some situations amikacin (Amikin) as a third or fourth drug. However, the Division of AIDS of the National Institute of Allergy and Infectious Diseases recently recommended that clofazimine not be used since the addition of the drug did not result in any added benefit and may result in increased risk of death.

Several studies to determine the optimal drug regimen for treating MAC disease have been completed. All of these studies have included clarithromycin and ethambutol in addition to other anti-MAC drugs. These studies suggest that the optimal treatment regimen for MAC disease is clarithromycin and ethambutol and that the addition of clofazimine does not result in any additional benefit. Furthermore, several studies have shown that there were significantly more deaths among people receiving a higher dose of clarithromycin

(1000 mg twice a day) compared to those receiving the approved dose of clarithromycin (500 mg twice a day). It remains to be seen whether adding another anti-MAC drug to the clarithromycin + ethambutol combination will result in additional benefit. Studies are ongoing to find an optimal treatment regimen with azithromycin.

Treatment for MAC requires lifelong maintenance therapy. Currently, there is still no consensus about any one "best" maintenance regimen, or if full 'treatment' doses are needed for the maintenance phase or if lower doses can be used. As a goal, an optimal maintenance regimen should not increase the risk of developing a drug resistant strain of MAC and should be generally well tolerated.

Treatment Commentary

Physicians have had less experience with the use of azithromycin for the treatment of MAC compared to clarithromycin. There is also less data available about the use of azithromycin for this indication. Although the MAC treatment recommendations are to use either azithromycin or clarithromycin with ethambutol, azithromycin is not approved by the FDA for this indication. However, many physicians believe that azithromycin is as effective as clarithromycin for treat MAC.

A growing number of physicians and researchers believe that people should continue to take aggressive antiretroviral therapy even when they are being treated for an opportunistic infection. This approach requires an effective antiretroviral therapy regimen which will not interact with the MAC treatment regimen. This is critical because potential drug interactions may result in serious side effects as a result of increased drug levels in blood or may increase the risk of resistance to either MAC and/or HIV because of decreased



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Weight Loss Update

Unwanted weight loss in people with HIV can be caused by one or more factors simultaneously. For one person it may be due to mouth sores and depression; for another, it may be due to infections and metabolic imbalances. Because these factors are so diverse, one treatment strategy alone will not work for everyone.

The hallmarks of successfully dealing with weight loss include careful monitoring, and treating early and aggressively. Even if someone is overweight, when pounds are coming off and no dieting is going on, something is wrong and needs to be addressed.

People living with HIV note that unwanted weight loss can go undiagnosed. This is especially true for women who can be affected by HIV and weight loss differently than men. This observation underscores two aspects of managing weight loss:

- ♦ Everyone must drive their own treatment and proactively develop intervention strategies.
- ♦ Aggressive monitoring of weight, with the same watchful eye given to CD4+ cell counts and HIV RNA viral load levels, is critical.

If a problem is identified, a two-pronged approach is crucial. Both addressing the factors causing weight loss and malnutrition, and maintaining or gaining weight are critical.

Opportunistic infections including parasitic, viral, bacterial and/or fungal infections in the gut and elsewhere may contribute to weight loss. Many of infections cause diarrhea, change the balance of the gastrointestinal (GI) tract or compete with the beneficial organisms in the gut. Often, symptoms of one infection can conceal other problems. Treating the obvious infection can make it possible to see hidden problems. However, drugs used for treatment may have their own impact. For example, strong antibiotics can kill

the beneficial bacteria in the gut. The use of acidophilus may help to replenish these populations.

Both drugs and infections have been associated with diarrhea, depression, mouth sores, changes to the sense of taste, nausea, vomiting and loss of appetite. All of these can contribute to weight loss.

People living with HIV note that unwanted weight loss can go undiagnosed. This is especially true for women who can be affected by HIV and weight loss differently than men.

Medications can help with diarrhea, but may not address the real problem. A commonly overlooked cause of diarrhea in people living with HIV is lactose intolerance (difficulty processing lactose). Cutting back on products which include milk or lactose may reduce diarrhea. Some of the drugs used to treat HIV and opportunistic infections are packaged with lactose. Because these drugs may be unavoidable, it may be helpful to use products which replace the enzymes needed to break down lactose. Even in cases when an infection or drug effect cannot be identified as causing diarrhea, other approaches may be worthwhile. For more information on dealing with diarrhea, call the Project Inform National HIV/AIDS Treatment Hotline at 1-800-822-7422.

Appetite loss may also contribute to wasting. Appetite stimulants are an option to help increase the desire to eat. Marinol (pharmaceutical THC, see *Medical Marijuana* on page 20) is one approved approach, and megace is another. Megace (megasterol acetate) is an estrogenic hormone. It can alter sex characteristics in men, leading to enlarged breasts, impotence, etc. Weight gain associated with both marinol and megace is due primarily to fat rather than lean body mass. Many experts consider lean body mass to be more important than fat for weight gain. Additionally, some studies suggest that both marinol and megace

decrease testosterone levels.

Lack of nutrients can tax the body and further aggravate the problem. Vitamin supplements or weight gain products which promote the building of protein are an easy way to simply increase the amount of nutrients available for absorption. An appropriate product should be high in protein and low in fat to help increase lean body mass. It should also be lactose free to reduce the chance of diarrhea, and should be low in sugar (which can promote the growth of candida, an oral yeast infection that can contribute to absorption problems). A word of caution: some products advertised for people living with HIV are very high in sugar and have no, or little, protein.

An option for those with hormone imbalances is to supplement or replace those hormones. Anabolic (protein-building) steroids, like testosterone, are hormones which promote the building of lean body mass. They should not be confused with corticosteroids, which are immune suppressive and used to treat inflammation and autoimmune conditions. It is unknown what effect anabolic steroids have on HIV replication and disease progression in the long-term.

Testosterone- Some men living with HIV have low testosterone levels (hypogonadism). This deficiency can lead to fatigue, depression, lack of sexual drive and difficulty maintaining muscle mass. Testosterone replacement therapy is recommended for these problems.

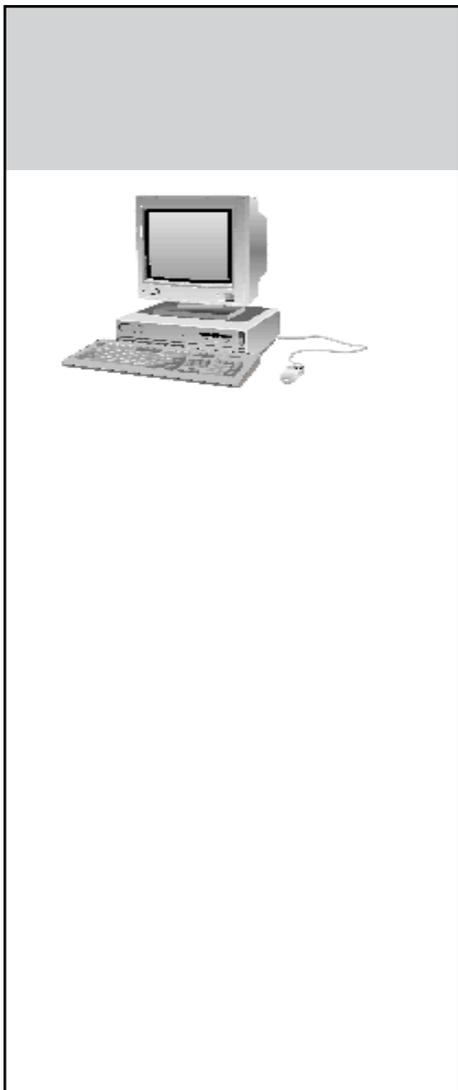
Testosterone can be injected or administered using a patch on the skin. The injections are taken once every two weeks and result in an initial flood of the hormone, which can temporarily shut down the body's ability to produce its own testosterone. A high level of the hormone is also associated with side effects such as irritability and aggressive behavior. In addition, injected testosterone is processed through the liver and can cause liver damage.

Two companies, SmithKline and Alza Pharmaceuticals, have developed

timed-release transdermal patches similar to the nicotine patches used to help quit smoking. The side effects seen with injected testosterone are not generally associated with these patches, which deliver the hormone at a steady rate, more closely mimicking the body's own cycle of production.

The SmithKline patch (Androderm) can be put anywhere, but can cause skin irritation and must be moved daily. The placement area must be shaved, and the same spot cannot be used more than once every two weeks. The Alza patch (Testaderm) does not cause skin irritation and does not have to be moved around, but it must be worn on the (shaved) scrotum.

Oxandrolone- Oxandrolone is an ana-



bolic steroid in pill form. It is less potent in many ways than testosterone therapy, and is non-virilizing; women can use it without developing secondary male sex characteristics (increased body hair, deepening of the voice, etc.). A large amount of data has been collected, outside the context of HIV, that support the use of oxandrolone in women. It is approved for treating unwanted weight loss of 'unknown etiology' (cause is unknown), and people with HIV-associated wasting can get oxandrolone through prescription. Several ongoing studies are using doses which are much higher than those approved by the Food and Drug Administration (FDA), to determine if people living with HIV can use higher doses of oxandrolone safely. These higher doses are thought to be preferable for people with HIV-disease, but they are very costly, making clinical trials of oxandrolone a way for some people to access the drug. Clinical trials of oxandrolone are currently enrolling.

rHGH- Recombinant Human Growth Hormone (rHGH) is another possible intervention for those with wasting. In August, the FDA granted Serono Laboratories accelerated approval for recombinant human growth hormone (rHGH) for treating HIV-related wasting syndrome. Data suggest that 30% to 40% of people who used rHGH (also called Serostim) benefited from the therapy. Interestingly, rHGH therapy was associated with *decreases* in body fat and *increases* in lean body mass, suggesting that it may adjust the body's ability to process protein.

Common side effects associated with rHGH therapy include bone and joint pain, as well as swelling of hands and feet. These effects can usually be managed by dose reductions or discontinuing therapy. The approval of rHGH for the treatment of HIV-related wasting syndrome marks an important addition to options for dealing with unwanted weight loss in HIV-disease. However, there are rumors that safety concerns regarding the use of rHGH have been under-reported. These concerns are not supported by the data Serono submitted to the FDA, but they highlight the need for

increased monitoring. For physicians seeking full prescription information on rHGH (Serostim), the company has established an 'Access Line', 1-800-714-2437 (Weekdays, 8:30 am to 5 pm, EST).

Other Therapeutic Approaches: A third possible approach is to adjust certain immune signaling chemicals. HIV-related weight loss is sometimes associated with elevated levels of an immune system chemical called tumor necrosis factor (TNF).

Thalidomide- Thalidomide appears to decrease TNF levels and may be useful in treating HIV-associated wasting. A study of thalidomide is ongoing to determine the drug's effect on HIV-associated weight loss. Women using thalidomide during first trimester pregnancy have a nearly 100% risk of causing serious birth defects in their unborn child. The impact of thalidomide use by the father during conception is unknown. Because thalidomide may also change the metabolism of oral contraceptives, women with HIV who have sex with men should consider using multiple forms of birth control, including a barrier protection, to avoid pregnancy while she is taking thalidomide. Other side effects associated with thalidomide use include fatigue and peripheral neuropathy.

Comments

Treatment for the cause of unwanted weight loss can be complicated and can involve several interventions. Similarly, how an individual treats the symptoms of weight loss will depend on a complex interaction of variables. These variables include the causes of the weight loss, available treatments, and side effects and food interactions related to the individual's current therapies. Even personal life-style factors (e.g. willingness to eat more, take vitamins, exercise, etc.) must be taken into account when treating HIV-related weight loss.



Medical Marijuana and Dronabinol

Recent debates and events in California regarding the medical use of marijuana have raised the discussion of the issue to the status of a ballot initiative. By the time readers receive this issue, California voters will have decided whether or not to legalize the use of marijuana for medical treatment. Marijuana has been used for years to manage side effects of treatments and symptoms associated with such conditions as glaucoma, migraine headaches, cancer and AIDS. Many people living with HIV use marijuana to manage agitation, spasms, chronic pain, depression, nausea arising from chemotherapy and loss of appetite.

Concerns have been raised about marijuana's impact on the immune system, lungs, hormonal levels and mental processes. Little research has been conclusive with respect to the potential toxicity of marijuana use. The same can be said for most research attributing positive results to using marijuana. Further, its sale and use remains illegal, hampering research into its use in treating HIV-related conditions.

In one sense, marijuana has been available for medical purposes for several years. Dronabinol (Marinol), a pharmaceutical version of THC – the most psychoactive component of marijuana – received FDA approval in 1991 for appetite stimulation in people with AIDS. It is available with a prescription. Studies in people with HIV-related wasting syndrome show that dronabinol can increase appetite for as long as five months, the duration of the longest clinical trial conducted. While some people find dronabinol helpful in managing weight loss, others feel that marijuana is more effective. Dronabinol can be absorbed erratically, making manag-

ing its psychological side effects, like euphoria and disorientation, difficult for some people.

There are several areas of concern for those considering marijuana or dronabinol for their conditions:

Contaminants

There is often little information available about the source and growing conditions of marijuana. If pesticides or other chemicals are used in growing the marijuana, they can have adverse affects on health.

By the time readers receive this issue, California voters will have decided whether or not to legalize the use of marijuana for medical treatment.

Marijuana can contain mold and fungi that may lead to infections. Microwave the marijuana on high for 1 minute, or baking it for at least 15 minutes at 275 degrees, may reduce the risk of infections by mold and fungi contaminants.

Impact on the body

Smoking marijuana can cause irritation to the esophagus and lungs, and possibly increase the likelihood of lung infections. Using a water pipe or ingesting the drug in some other way (e.g. as a tea, in food, etc.) can reduce this irritation. Caution must be exercised as the cooling effect of a water pipe can also greatly increase the amount of marijuana smoke taken into the lungs, possibly intensifying other side effects.

Some studies report that THC is an immune-suppressive agent that reduces T-cell reproduction and other immune functions. Therefore, people who use marijuana or its derivatives may be more susceptible to common infections.

Use of THC is associated with reduced levels of testosterone, a hormone which helps build muscle and weight. Testosterone levels are often suppressed already in HIV-infected men, and low levels are associated with weight loss, depression, decreased

sexual drive and lower energy. THC may have similar effects on other hormones in women. Anyone using marijuana or dronabinol should monitor their hormone levels.

Side Effects and Drug Interactions

The use of THC can cause euphoria, drowsiness, agitation, difficulty concentrating and short-term memory loss. These changes are temporary but can be disruptive.

THC can interact with other mood altering medications such as Valium (diazepam), Librium (chlordiazepoxide hydrochloride), Xanax (alprazolam), Seconal, Nembutol (pentobarbital) or phenobarbital, by exaggerating their effect. It can also cause longer retention of these drugs, increasing the potential for toxicity and overdose.

Using dronabinol and marijuana at the same time may lead to THC overdose which can be severe enough to cause fainting.

THC combined with amphetamines or cocaine can increase blood pressure and heart rate.

Commentary

Many people with HIV use THC in either form as an appetite stimulant. Others report that smoking marijuana eases symptoms of HIV and drug side effects. These benefits, when real, may come at a price, as is the case with any drug. People using marijuana or dronabinol for symptomatic relief need to make sure their use of the drug does not divert them from addressing the causes of their distress. For example, loss of appetite is seldom the only cause of HIV-related wasting. HIV-related weight loss can be caused by many factors, including life-threatening infections. Often these causes confound one another. Treating symptoms of unwanted weight loss without addressing the underlying causes may be risky strategy. For more information on wasting and related issues call the Project Inform National HIV/AIDS Treatment hotline at 1-800-822-7422 and ask for the *Nutrition and Weight Loss Fact Sheet*.