PROJECT inform PERSPECTIVE
Information, Inspiration and Advocacy for People Living with HIV/AIDS

On the Road Between Euphoria and Failure

Nearing the end of the second year of the "protease inhibitor era" patients, physicians and treatment activists are anxiously looking for clearer answers about the use of these new drugs. Thanks largely to the media, public expectations have been driven so high that no therapy could live up to the promises made for these drugs.

On the one hand, such optimism has brought a welcome renewal of hope. Carried to an extreme, however, it also contributes to a disturbing new carelessness about prevention, safer sex and the all too real risks still posed by HIV. It is disappointing indeed to realize that the improvements in AIDS therapy could so quickly lead to increased risk behavior and purportedly serious philosophical debates about such topics as "bare-backing." In contrast to the optimism, however, are reports of high levels of treatment failure, leading pessimistic voices to renew their belief that all people with HIV remain doomed to an early death. From this perspective, it's only a matter of time before all drugs fail everyone. Neither point of view serves as a useful basis for constructing effective long-term strategies against AIDS.

Those with the most optimistic views must come to recognize that even the best currently available therapies offer no cure and that they are not the ultimate solution to this disease. HIV-infected people should not assume that the current generation of drugs will work for the rest of their normal lifetimes, nor that these drugs can be used for decades without serious side effects, some of which we may not discover for years to come. The original hope of a few scientists that the drugs would result in eradication of HIV now seems unlikely, leaving only the option of life-time maintenance therapy – and no currently available drug or combination is good enough for that. In a broad sense, the present drugs will almost certainly fail over time. But this doesn't mean that therapy, overall, is doomed to failure. Cheaper, less toxic and easier-to-use therapies must be developed before we can talk realistically about life-time management of HIV disease. Fortunately, such therapies will continue to be developed, at least as long as the pharmaceutical industry sees AIDS as a profitable market.

Whatever their limitations, the current generation of drugs represents a major advance over anything we've had before, and the full extent of their benefits has not yet been measured. In the optimal circumstances of controlled clinical studies and with careful adherence, the success of these drugs is surprisingly strong at two years out. Once people achieve truly "undetectable" levels of virus on the newer ultra-sensitive viral load assays, the development of drug resistance is dramatically delayed. We don't know how long this can be sustained, but the duration is already being measured in years rather than months. Another unknown is the accumulation of long-term side effects. Recent findings about diabetes and other metabolic changes, such as redistribution of body fat, must be watched very carefully. However, despite widespread belief that these recently reported effects are associated with protease inhibitors, careful data collection is beginning to question this assumption. Preliminary analysis of several case studies suggests that the phenomena are not associated with any particular protease inhibitor, nor even with the class of drugs itself. Rather, it appears that these conditions may exist across the entire population of HIV-infected people.

Part of the dilemma for patients and physicians is that both sets of facts – the optimistic and the pessimistic – are true to varying degrees with different groups of people. But there is no way to predict how the matter is going to play out for any single individual.

Analyzing "Failure" Rate Reports

A few recent studies have reported "failure" rates on the new therapies as high as 53%, but such figures may be misleading if taken out of context. In the most widely quoted study, this percentage includes people who never responded in the first place and those who could not tolerate the associated side effects, as well as those who responded initially but later saw a return of detectable virus. It also includes a high proportion of people who reported difficulty adhering to the strict dosing regimens required by the drugs.

We've known all along that the drugs work much better in people who are just beginning treatment, compared to those who have been using therapy for years. We've known that it is difficult for many people to use the drugs precisely as prescribed and that any significant or repeated deviation from the prescribed program would contribute to hastened drug resistance. And it's been clear from the beginning that side effects could interfere with peoples' ability to use these drugs properly.

Considering all these things, it's actually surprising that the drugs have worked as well as they have in so many people. Almost any AIDS hospital or practice in the country can confirm that the drugs have reduced death and disease rates dramatically.

When people report high "failure" rates in the context of such overwhelming evidence of success, it suggests that we need to take a very careful look at what is meant by "failure." Typically, "failure" in recent studies simply means that a person using the drug either was unable to achieve "undetectable" levels of virus, or saw a return to "detectable" levels after initial success in making it "undetectable." This is a very narrow

and technical definition of "failure," especially when it is accompanied by record low rates of new opportunistic infections and deaths. Failure is being defined solely as some degree of change in a laboratory marker, making no distinction between someone whose viral load reached 500 copies HIV RNA and someone whose viral load has soared to 5 million. It also doesn't tell us if a person who failed one therapy was able to go on to some other therapy that brought viral replication back under control. It also doesn't tell how many of the people in the studies had their best chances for successful long-term therapy wasted by early use of the original version of saquinavir. Use of this drug has now been clearly implicated as a cause of early failure on the drug itself and on subsequent, more potent protease inhibitors. In one study, prior use of the original version of saquinavir was identified as a primary predictor of failure for people using indinavir.

More importantly, it's not clear what the clinical consequence is of seeing a return to measurable viral load. Evidence suggests that a rise in the HIV RNA level is not accompanied by an immediate return of symptoms or a loss of the improvement experienced in measures of immunity. It just means that the viral load has moved above a certain arbitrary threshold. Even though keeping viral levels "undetectable" is associated with the largest and longest lasting benefits from treatment, drugs and combinations which caused significant reductions in viral load (without achieving the goal of "undetectable") were still associated with improved clinical condition and longer survival time.

We also don't know how much of the reported "failure" is due to relentless, natural progression toward resistance, versus how much it is being hastened by non-adherence to the prescribed regimens. Without such data, it's impossible to determine how applicable the reported "failure" rates are to people who are highly adherent. Clinical data suggest that people who can carefully adhere to "the program" have a much higher (though still not perfect) success rate.

Despite these uncertainties, we do know the answer to some questions about treatment failure and resistance. Most relevant are data from presentations at the Resistance meeting in the summer of 1997, in St. Petersburg, Florida. A key study there showed that when people achieved "undetectable" levels of virus on the new ultra-sensitive assays (measuring down to 50 or 20 copies of virus), they are very likely to have a long and successful run on their treatment regimen, probably measured in years. In contrast, those who never reached "undetectable" or, surprisingly, those who only reached "undetectable" on the older, standard viral load tests (measuring only down to 500 copies of virus), were likely to experience "drug failure" (rising viral load) within 6 to 12 months. The ability to reach "undetectable" status on either version of the test was greatly affected by the individual's viral load prior to initiating therapy. If it was low to begin with, it was easy to keep it undetectable for long periods. The higher it was at the start, the tougher it was to reach "undetectable."

What to Do?

What does this mean to people struggling to make wise decisions about the use of these new drugs? Here are a few questions people find themselves facing, and a few possible answers:

I'm doing OK for now, but am I doomed to see my drugs fail? How soon?

No currently available HIV treatment regimen is likely to last for a full normal lifetime and none has been shown to "eradicate" the virus. Until we can completely suppress viral replication, drug resistance is likely to contribute to treatment failure over time. How long it can be fully suppressed is uncertain. When people achieve undetectable levels on the new ultra-sensitive viral load tests, the durability of response is greatly enhanced and seems to produce a result beyond the initial expectations of most scientists. When the new therapies work and reach their goal, they seem to work remarkably well. If this is your experience, the message is clear: as long as you're following the general "rules" about 3-drug combination therapy, just keep doing what you're doing. If you're one of the lucky few who at least temporarily achieve "undetectable" viral load on a 2-drug regimen, you might want to consider adding a third potent drug before your viral load starts to rise again. Since the new ultra-sensitive tests seem to be important for predicting durability of treatment effect, their availability must be hastened. Until that test becomes widely available, people can take some comfort in recent research that suggests that when people persist a year or longer at the "undetectable" level on the standard test, it's quite likely they are also "undetectable" on the ultra-sensitive test. Your own adherence to your regimen will likely remain the most critical variable affecting the durability of your treatment.

What's going to happen when the drugs fail?

We don't know clinically when viral load returns to measurable levels, how quickly the immune system might be compromised again. We do know that it does not signal immediate decline to clinical illness or death. The rates of return to clinical illness and new opportunistic infections are nowhere near as high as the reported rates of "treatment failure." There is plenty of evidence that even temporary success in suppressing viral load can lead to significant levels of immune restoration. The longer suppression of virus is maintained, the larger the improvement seems to be. It may be that clinical and immunologic decline simply lags behind the return of viral load by several months, but even if this is the case, it gives a cushion of time while awaiting new and better therapies.

Some virologists also believe that the highly mutated form of virus that evolves to resist the drugs is in many ways not as "fit" or destructive as the original "wild type" virus that most people started with. The virus has to pay a price, perhaps a high price, for accumulating all those mutations it needs to become resistant to the drugs. Collectively, those mutations may make fundamental changes in the virus and its capabilities. It may still be capable of replicating, but it may be diminished in other ways, such as its ability to damage the immune system. At worst, things would only be back to where they were before the advent of the protease inhibitors, with new drugs on the way.

When these drugs fail, will anything help?

Yes, there is hope that other things may help, but we need to be especially realistic on this point. Few people will have a good response on a second protease inhibitor after the first one succumbs to resistance. There is significant cross-resistance between all the protease inhibitors released thus far, no matter what drug company representatives claim. But when there is only a modest return of measurable virus, we needn't think of resistance as a simple, on-off thing. It comes in degrees from high level resistance, which will cripple a drug, to low level resistance, which might be overcome by increased doses of the drug or changes in the companion drugs. Some level of resistance might be low enough to be overcome by a quick change to more aggressive therapy. Sometimes it can be overcome simply by finding two or more new, highly potent drugs that aren't cross-resistant. And sometimes, viral load only reappears temporarily, likely in response to a secondary infection, and soon becomes undetectable after the infection has been cleared.

Beyond these points, there are a number of new drugs in the pipeline, some of which might be useful despite current resistance. For example, two new protease inhibitors in early clinical trials (GW141 in Phase II/III from Vertex/Glaxo Wellcome and PNU-140690 in Phase I from Pharmacia and Upjohn) are different from all current protease inhibitors and might offer the potential of being active despite resistance to the earlier drugs. Also, efavirenz (Sustiva®, previously known as DMP-266), a powerful new non-nucleoside reverse transcriptase inhibitor which seems to work particularly well with protease inhibitors, is already available in small expanded access programs and should become generally available next year. There are also sev-

The PI Perspective is a publication of:
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eral new classes of drugs now in clinical trials. These include: T-20 (a fusion inhibitor which has already shown activity against protease inhibitor resistant virus), integrase inhibitors and zinc finger inhibitors. Some new research is also re-emphasizing the potential of combinations which employ hydroxyurea. Of course, there's also the whole field of immune restoration which should not be forgotten in our battle against this disease.

Is There a Bottom Line?

For those just contemplating therapy or currently using it successfully, the bottom line is to resist any tendency to swing back in the direction of hopelessness. Instead, this is a time to re-emphasize the importance of adherence and using therapy aggressively enough to fully suppress viral replication. Maintaining a positive attitude and taking decisive, informed and effective action are the only proven ways to get the greatest possible benefit from the available therapies.

For those already facing the prospect of "treatment failure," however one chooses to define it, the bottom line begins with a staunch commitment to hope. It must include an aggressive pursuit of new options and inventive uses of old ones (see the article "*Strategies for Protease Inhibitor Failure*" page 4). It means never succumbing to the defeatist notion that "there's nothing I can do." *There is always something you can do* – new therapies, new combinations, new trials and new outlooks. We may or may not ever find a true "cure" for HIV disease, but with each passing year, it is increasingly reasonable to expect to see successful lifetime management of the disease achieved within the current generation.

For the general public, HIV-infected or not, the bottom line here must be to take realistic stock of the imperfect but still advancing state of AIDS research. Everyone must understand that AIDS is not cured, not one person has seen his or her virus "eradicated," and the fight is bound to go on for many more years. Excessive optimism and overselling the current state of therapy can harm people just as surely as HIV disease itself. It can diminish public support for research and funding for care. It can invite reckless behavior by people who falsely perceive the threat of HIV to be reduced. It can diminish the willingness of the pharmaceutical industry to invest in new and better solutions. And it can drive people to despair when all they hear is how well everyone else is doing, while their personal experience isn't so rosy. Even when the new therapies work well, they add great challenges to the lives of those who must use them. Dealing with AIDS is far from simply taking pills.

Finally, until lasting and universal solutions are found, we must all recommit to prevention, which has at times been left on the sidelines in the wake of talk about "undetectable virus" and "morning after medications." Those who today have come to think HIV disease "isn't so bad" have an awful shock coming should they ever let such a misguided belief cause them to cross over the line to HIV sero-positivity.

Perhaps this new awareness of the limitations of treatment will be a good thing. It may ultimately help us get on with the business of making sure that better, safer and easier to use therapies become available as quickly as possible, and that everything that can be done to prevent new infections is being done.

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Strategies for Protease Inhibitor Failure

Project Inform's "Antiviral Strategies" discussion paper previously addressed the question of treatment strategy for people who have already used and "failed" most existing combination therapies.

Perhaps the most important rule in such a situation is to seek highly potent, optimal uses of available therapies. This means it is often more important to wait to start two or more new drugs simultaneously than it is to take immediate action. In short, using HIV antiviral drugs correctly is more important than using them at any particular moment. Simply adding a single new or different drug is unlikely to help. The most recent information suggests that even adding two new drugs is seldom sufficient for people failing on previous regimens. Instead, the best chance of success may come from starting a completely new regimen. The earlier strategies also stressed the opportunity for people in this category to seek out clinical trials of truly new agents. Unfortunately, there often aren't many clinical trials, or new drugs, to choose from.

Since the initial discussions of antiviral treatment strategies in *PI Perspective #19* and *#21*, additional options have been identified; but there is only minimal data from clinical trials to support these approaches. In some cases, there are little or no data at all, but the following suggestions represent the weight of some degree of "expert" opinion or the case experience of primary care physicians. Since every case of "treatment failure" represents a unique medication history and different contributing factors, it is unlikely that any one approach will be universally successful.

In all of the following suggestions, emphasis is given to the choice of protease inhibitors and other highly potent agents, such as the non-nucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine (Viramune®), delavirdine (Rescriptor®) and efavirenz (Sustiva®). These are likely to play the most important role because of their potency. Even though powerful new nucleoside analogue reverse transcriptase inhibitors (NARTIs), such as abacavir (1592), are becoming more available, existing evidence suggest they will offer little potency in people who have been heavily pretreated with other drugs of this type. Nonetheless, they may play some modest role in overall therapy when other drugs have failed. Preference should be given to those NARTIs which have been least used previously by the individual patient. If all NARTIs have had similar periods of use, a good strategy might be to give preference to the ones known to be slowest to develop resistance. At the top of this list are ddI (didanosine/Videx®) and d4T (stavudine/Zerit®).

Possible Approaches

Changing protease inhibitors *(not very likely to be effective after drug failure).* Assuming a person has developed true resistance to an existing protease inhibitor therapy, the likely effects of switching to any other protease inhibitor can be summed up in a few words. Such a switch is unlikely to result in significant or long-lasting additional suppression of virus. Switching protease inhibitors because of side effects or issues with taking the regimen is not the same as a switch due to resistance. Switching for reasons other than true resistance has a reasonable chance of success.

Studies have shown that neither indinavir (Crixivan®) nor the newly enhanced saquinavir (Fortovase®) is particularly effective in people previously treated with the original saquinavir (Invirase®). The same is likely to be true to switching to ritonavir (Norvir®) or nelfinavir (Viracept®). Similarly, only a very small percentage of people who switched from an existing protease inhibitor to nelfinavir in that company's expanded access program experienced significant success. A more recent study showed that, contrary to the manufacturers claims, when nelfinavir fails after being used as a first protease inhibitor, people do not respond well to indinavir or ritonavir. Switching between ritonavir and indinavir is also unlikely to work in most cases. Project Inform has argued all along, people should assume that there will be significant cross-resistance between any of the currently available protease inhibitors, and there is little reason to choose one or another as the first therapy in hopes of avoiding cross-resistance. Clinical data now confirm this view across all possible sequences of the known protease inhibitors. There may be individual, but unpredictable, exceptions to this. As a general rule, people have only one good opportunity to use a protease inhibitor.

Combining protease inhibitors *(not as easy as originally thought).* The hope of combining two protease inhibitors for people who have developed resistance to an initial protease regimen is to overcome partial resistance by increased drug potency. However, little if any of the clinical experience has actually tested dual protease inhibitor combinations in this fashion. Most research has tested such combinations in people using protease inhibitors for the first time. Also, protease inhibitors have typically been combined at lower-than-standard doses in hopes of reducing toxicity, rather than at standard doses in hopes of increasing overall potency. Some specifics:

- *ritonavir + saquinavir (Invirase® or Fortovase®) combination;* While this is commonly used as a "salvage" strategy after failure of a first protease inhibitor, almost all the data supporting this combination comes from people who are just beginning their first use of a protease inhibitor. In the one known study tracking its use after initial protease failure, the combination was found to be effective only about 25% of the time, and even then, the results were not sustained for long. The potency of this combination should be the same whether using the old version of saquinavir (Invirase®) or the new version, because both result in the same levels of drug in the blood when used along with ritonavir.
- *nelfinavir + saquinavir (Fortovase®) combination;* Again, this is only supported by data in people using protease inhibitors for the first time. Its success in treating protease-resistant virus is unknown (and unlikely).
- *ritonavir + indinavir combination;* This is a very new avenue of clinical study, initially focusing on first-time users of protease therapy. The hope that might make this useful after initial protease failure is the sheer potency expected from combining two of the most powerful protease inhibitors, along with the fact that ritonavir should also dramatically increase the levels of indinavir. The proper or safe doses for this combination are not known and the risk is that when full doses of each drug are used, there may be significant side effects, similar to the effects of taking higher-than-standard doses.

Combining therapies for synergy *(some anecdotal claims of success).* This approach mixes drugs whose chemical properties or absorption into the body are enhanced when used together. The hope for this approach is to overpower partial resistance.

- *delavirdine + indinavir combination;* Although delavirdine has not been proven very effective in any clinical trial to date, it can effect the absorption of other drugs and increase their potency, much like ritonavir. It does a good job of increasing the levels of indinavir. A number of physicians report anecdotal success with this combination in people who have failed initial protease combination therapy. The two drugs are typically taken at their standard doses, though it is unclear what affect this has on toxicity. Particular care should be taken to watch for an increase in potential liver toxicity and kidney toxicity. Proponents of this approach report a fair degree of success in returning patients to undetectable viral load and sustaining this for 6 months or longer, even after initial failure on indinavir.

- *efavirenz + indinavir combination;* Studies in people first initiating protease inhibitor therapy have found this combination to be highly effective in suppressing HIV RNA levels. Although it hasn't yet been tested in people with protease resistant HIV, the high potency offers the hope that it might be capable of overcoming partial resistance. It is likely that efavirenz will combine usefully with almost any other protease inhibitor as well.
- *nevirapine + a previously unused protease inhibitor or dual protease combination;* When employed along with one or two additional nucleoside analogue drugs, this approach seeks to overpower partially resistant virus.
- *ddI + hydroxyurea + single or dual protease inhibitor combination, with or without a NNRTI (nevirapine, delavirdine, or efavirenz);* Small studies have continued to confirm that the ddI/hydroxyurea combination offers unique properties and might work even in people with highly drug resistant virus. Of the NARTI drugs, ddI is perhaps the slowest to develop resistance and there is no known pattern of resistance affecting hydroxyurea. Some researchers also believe that d4T is slow to develop resistance and combines particularly well with ddI and hydroxyurea.

Experimental Approaches

- *GW141 (a new Glaxo Wellcome/ Vertex protease inhibitor) plus abacavir (1592, a new Glaxo Wellcome NARTI) plus efavirenz (a new Dupont Merck NNRTI).* A small nationwide clinical trial of this combination will begin before year's end, targeting people who have failed all existing therapies. In laboratory studies, GW141 does not demonstrate cross-resistance with other protease inhibitors, and abacavir shows only partial cross-resistance to 3TC and ddI. Thus, this combination theoretically offers hints of good potential, even in a protease inhibitor resistant population. However, an early pilot arm of this study combining just the GW141 and abacavir did not appear to work well. Only time will tell if adding the third new drug, efavirenz, will change the outcome.
- *AR177 (Zintevir®, an integrase inhibitor from Aronex) plus adefovir (Preveon®, a new type of RT inhibitor from Gilead Sciences) plus efavirenz.* While this approach sounds intriguing because it combines two new classes of drugs (an integrase inhibitor and a nucleotide analogue), neither AR177 nor adefovir has shown much potency as individual therapy. Nonetheless, the overall combination still warrants careful study.

A Final Word

Virologic failure doesn't necessarily mean clinical failure. Were this the case, we should already be seeing a great reduction in the clinical benefits of treatment, but this is not the case. Rates of new opportunistic infections and death remain at an all-time low, despite the growing incidence of virologic treatment failure. Many people assume that when they run out of options capable of completely suppressing viral load, they might as well go off their current antiviral therapies. Some even believe this will be helpful, based on the theory that this will permit their virus to regain sensitivity to the drugs. Most researchers dispute this view, pointing out that once resistance occurs, some quantity of virus with the resistant properties will always be retained and will quickly reassert itself. Many researchers also believe it is a mistake to discontinue therapy even when all possible combinations no longer seem able to suppress viral load below pre-treatment levels. They argue that even when all available therapy options have failed to suppress virus, it may still have an important effect. In this situation, therapy continues to shape or control the pool of virus, permitting only the growth of the mutated, resistant strains while blocking growth of more potent "wild-type" virus. The "wild type" is the natural state of HIV, the condition it prefers and in which it is most potent. Virologists believe that for each mutation a virus accumulates in the body, it pays a "price," forcing it to deviate from its preferred, natural state. While highly mutated virus may still be able to replicate to some degree, it is not clear that it is still as capable of harming the immune system.

However, other virologists worry that continuing on therapy when it appears to be "failing" virologically, may encourage the accumulation of even more mutations. This could make it more difficult for future drugs of the same classes to work, should such drugs come along. These arguments make sense only if new drugs of the same classes come along which aren't cross-resistant to existing drugs. So far, in protease inhibitors, this has never been the case. In situations like this, people are forced to make a gamble, choosing between effects of the known, available drugs and the unknown effects of future drugs. Just which choice results in the longest survival is unknown.

There is considerable initial evidence that people retain immunologic benefits from therapy long after losing the battle for complete viral suppression. Also, some virologists suspect that when patients see only a modest and stable return of measurable virus, without returning to the pre-treatment levels, the PCR test may be measuring defective, mutated copies of virus rather than productive virus capable of reproducing itself. For any of these reasons, it may be important to continue to use therapy to keep virus in its "unhappy" state. True loss of virologic control still does not imply complete return to the devastation of AIDS. In short, even when all options "fail" (by today's definitions), hope is not lost.

The Science and Marketing of Simpler Dosing

Adherence to difficult drug regimens is a critical issue for people using combination therapies. As data have accumulated about the need for reasonably strict adherence to drug dosing regimens, so too has the demand for simpler, easier-to-use drugs.

Pharmaceutical companies have gotten the message that people want less frequent dosing and fewer pills to simplify their complex daily routines. But rather than see new drugs designed with this in mind, we are instead beginning to see old "TID" (three times per day) drugs simply redefined or relabeled as "BID" (two times per day) drugs. Changes in AZT dosing led this trend. This in turn made it possible for Glaxo Wellcome to begin marketing a new single pill combining both AZT and 3TC (called Combivir®) in a convenient, twice-daily dosing package. Very soon, we will see similar efforts to redefine some of the protease inhibitors. Studies are underway seeking to redefine both indinavir (Crixivan®) and nelfinavir (Viracept®) as drugs that can be taken only twice daily. Abacavir (formerly GW1592), the new Glaxo Wellcome nucleoside analogue, will be marketed from the start in twice daily doses and efavirenz (Sustiva®), a new non-nucleoside from Dupont Merck will be the first AIDS drug prescribed for once daily use.

People generally welcome changes that make drugs easier to use. But few people so far seem to acknowledge that the stakes here are considerably higher than just a matter of personal convenience and that this issue warrants great caution. At stake is the long-term success or failure of therapy, which may or may not be jeopardized by reduced dosing frequencies of some drugs. Were convenience the only issue, having the flexibility to dose twice daily would always be superior to three times daily. But first and foremost, the goal of any dosing strategy must be to keep a steady and adequate level of the drug in the bloodstream from one dose to the next. If that goal is not met, at least two serious problems may be created:

1. Because of the longer times between doses, the blood level of a drug used only twice daily may fall below the minimum needed to sustain full suppression of HIV. When this occurs, it creates repeated daily periods of inadequate dosing, a condition which actively favors the development of drug resistant virus.

2. The switch to fewer daily doses makes it even more critical that people strictly adhere to the schedule. If skipping one dose out of a day's three doses is a problem, as everyone agrees, skipping one of a day's two daily recommended doses is likely to be even more so as one dose represents half a day's entire requirement.

The hope is that easier dosing will result in higher levels of adherence, that many people who are incapable or unwilling to adhere to a thrice daily regimen will be able and willing to adhere to twice daily dosing. This may or may not be so, but it is certain that the consequence of non-adherence will be more severe when fewer daily doses are used. There will be even less room for occasional error.

Scientific Concerns

If changes to simplify dosing are supported by sound scientific evidence that adequate drug levels are being maintained throughout the day, the duration of treatment effectiveness will not be shortened. If such evidence is lacking, changing to a more convenient dosing regimen runs the risk of doing more harm than good. At the moment, the companies seem anxious to rush these changes through the FDA approval process based on as little data as possible.

In the hotly competitive market for AIDS drugs, pharmaceutical companies face an inherent conflict of interest over this issue. Simpler dosing is not just a scientific matter, nor just an issue of patient convenience. It is, from the manufacturer's point a view, a very important marketing consideration. Companies that can offer simpler, BID (twice daily) dosing establish an important marketing advantage compared to competitors who might still be selling a TID (three times per day) drug. This inherent conflict pits the interests of the Marketing Department against the beliefs of the research personnel, and ultimately against the interests of the patients.

In order to change their product labels to recommend twice-daily dosing, they must first convince the Food and Drug Administration (FDA) that the dosing change produces results equivalent to their previously approved dosing schedule. While this sounds reassuring, it is not convincing on a scientific level. In short-term testing, there is likely to be little difference between the dosing schedules. Both should work well, for a while. The real question is the long-term duration of effectiveness. Over time, if the new dosing schedules result in daily periods of inadequate dosing, it will almost certainly add up to quicker development of resistant strains of virus. The real test is how well people are doing after a year, or perhaps two years of treatment on the two different regimens. Unless the FDA demands clinical testing which is capable of showing this kind of information, patients and physicians can only be misled by the outcome. All of this has become even more critical in the last year as awareness has grown of the widespread cross-resistance between drugs in the same families. For practical purposes, people have only one good shot at using a protease inhibitor. It could easily be ruined by an inadequate dosing schedule, and the patient is left with little or nothing to pick up the pieces when the failure comes.

Once they get FDA approval, manufacturers will rush to make bold new advertising claims touting the new "advantage" of their drugs. One possible outcome might be that the simpler dosing will improve adherence among people who are inclined to miss a dose now and then. This group might achieve a net benefit, since they aren't likely to be getting the best long-term benefits anyway. However, if marketing and advertising suggests that the new dose is "best" for everyone, it could cause those who currently are not having trouble with adherence to switch to what is for them a less effective regimen, resulting in more rapid failure. Nothing in currently planned studies will be capable of sorting out these questions. Simpler dosing might provide a net benefit for some and a net loss for others.

For now, the FDA is gambling, with very little evidence, that the differences between two dosing schedules will show up with a year-long study. Perhaps so, perhaps not. There simply is no way to know. It may be impractical to demand that the FDA require true, long-term studies to fully test these new, easier regimens. However, it may be possible to demand that the companies perform continuous, long-term follow-up of the people who participate in the dosing regimen trials. Records should be kept for two years or longer to determine the real long-term outcome, and they should attempt to distinguish between the effects in patients with varying degrees of adherence.

A Recommendation

For now, it is wise to assume that there was a good reason for the dosing schedule recommended when a drug was first approved. People should stick to that schedule until someone proves that a different schedule is truly equivalent over the long term. Once sufficient data exist that a simpler regimen may be useful, it should be cautiously offered as an alternative by the sponsors – not aggressively marketed – to people having trouble adhering to the proven, initial regimen. Then perhaps if long-term follow-up proves true long-term clinical equivalence, a time may come when the new dosing may be

recommended for standard use.

The desire for easier dosing regimens is not a bad thing. But the goal should be achieved the right way – by designing new and better formulations, not just by changing the labels on older drugs after rushed, short-term studies. Simply changing the label on an existing drug is a very tempting short cut, but it is not necessarily in the real interests of people whose lives depend upon long-term success of drug regimens.

Finally, patients and physicians should note that switching one or another drug to twice daily dosing doesn't necessarily simplify a person's daily routine. It can just as easily complicate it. For example, if the other drugs a person takes require a thrice-daily regimen, changing to a twice daily antiviral might result in a person now having 5 distinct "drug taking" periods in the day.

Project Inform urges anyone who is asked to participate in marketing surveys or focus groups on this subject to consider the more complex issues involved above and beyond the simple desire for easier dosing. Simpler dosing is a reasonable objective, but should not come at the cost of the long-term durability of therapy.

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Project Inform Drug Delivery Conference

Over the last two years, Project Inform has become acutely aware of the difficulties many people face in using the treatments available for HIV. Almost no one is satisfied with the number of pills and pill-taking intervals required each day.

The demands for careful adherence to dosing schedules are somewhat driven by the weaknesses of the drugs themselves – levels of the drugs in the blood rise and fall throughout the day between doses, leading to opportunities for the development of resistant virus. To compensate, drugs are delivered at excessively high doses. While this may help maintain adequate levels throughout the day, it also contributes to toxicity. For many people, taking a large quantity of pills is simply not possible because of nausea, wasting, or damage to the intestinal tract. Still others fight a daily battle with diarrhea, which interferes with uptake of the drugs into the blood.

At least some of these problems can be solved with new drug delivery technologies under development by the highly specialized drug delivery industry. To facilitate change and new opportunities in this area, Project Inform sponsored a meeting on October 16, 1997 to explore the possibilities of using alternative drug delivery methods for HIV therapies. Entitled "Exploring New Technologies to Overcome the Challenges of HIV/AIDS Treatments," sixty participants were invited, representing drug delivery companies, pharmaceutical companies, government and AIDS treatment advocates. The goal of the meeting was to see if there might be opportunities to improve the utility of HIV-related therapies with the help of the new drug delivery technologies. In a sense, the meeting was also an opportunity for "match-making" between companies which make drugs and companies which make better ways to deliver them. Working together, they may benefit people with HIV by improving the distribution of drugs over time in the body or finding ways to bypass some of the obstacles which interfere with proper uptake of drugs. Some of the drug delivery systems discussed may be able to help people better adhere to their treatment regimens by reducing the number of times people will have to take their medications or by giving them ways to use the drugs in a less toxic and more tolerable fashion. Other techniques may allow drugs to specifically target certain cells, such as those in the lymph nodes or in the brain.

This type of work represents part of our efforts to influence the long-term development of therapies for HIV disease. There may be no instant or immediate payoff in the form of a new mechanism for drug delivery, but over time we believe that meetings of this type will make as much of an impact as new drugs themselves. Project Inform will continue to organize these kinds of meetings which foster collaboration to help prolong and improve the lives of people with HIV.

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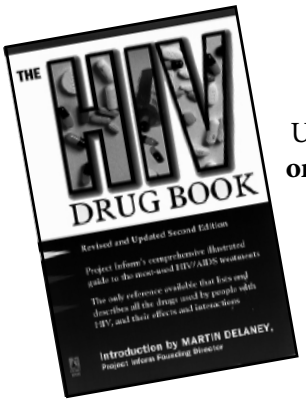

The HIV Drug Book

Second edition!

Updated by the staff and volunteers of Project Inform and published by Pocket Books, the **second edition** will be available in bookstores January 1998 with a new cover, a new look and a lot of new information at the old price of $18 US and $24 Candian.

Over 30 new individual drug profiles...
Updated information and new articles...
A summary of the new guidelines on using anti-HIV drugs...
A discussion of Adherence to HAART...
And more.

Update on Antivirals

Research into anti-HIV therapy is producing hopeful results almost weekly. Yet some issues remain stubbornly difficult to address. Studies have shown that many people, by starting at least two new potent drugs (generally from classes of drugs that they haven't used before) in their combination therapy, can achieve sustained suppression of HIV. Yet it is also likely that starting only one drug that is potent by current standards will lead to only short-term benefit.

Overall it is very important to develop a long-term strategy that is well tolerated, has a reasonable dosing schedule, includes two highly potent therapies and leaves other treatment options open if a change of therapy is necessary. While these sound like simple rules, they are often difficult to implement because of the limited number of new drugs available and because of cross-resistance between those already available. One possible improvement is that new drugs now being developed generally have a more favorable dosing schedule (either taken once or twice daily) which makes them a more desirable choice for people starting therapy for the first time. However, there is still very little information available to guide the choice of a second or third treatment regimen after an initial combination loses its ability to suppress viral replication. Real and lasting progress in this area will require not only more new drugs but new classes of drugs that work no matter what treatments a person has used previously.

Efavirenz (DMP 266, Sustiva®)

A recent study indicates that the combination of the non-nucleoside reverse transcriptase inhibitor efavirenz and the protease inhibitor indinavir (Crixivan®) continues to show potency after 48 weeks. One hundred and one people with CD4+ cell counts ranging from 100 to 500 and HIV RNA of greater than 20,000 copies participated in this study. The majority of the volunteers had previously been on nucleoside analogue reverse transcriptase inhibitors (NARTIs), such as AZT or 3TC. They received either indinavir alone (42 people) or indinavir + efavirenz (59 people). During the study, the doses of both drugs were adjusted to improve potency. The dose of efavirenz was initially 200 mg once a day, but after 36 weeks this was raised to 600 mg daily because the higher dose may have better antiviral activity. The dose of indinavir was increased from 800 mg to 1000 mg every 8 hours after data indicated that efavirenz decreases indinavir levels by about 30%. After 12 weeks of the study, people receiving indinavir alone, were switched to receive indinavir + efavirenz + d4T to reduce the possibility of resistance developing to indinavir. The results after 48 weeks are shown in **Table 1**.

Table 1: Indinavir and Efavirenz

Therapy Regimen	Viral load drop	% below 400 copies HIV RNA	CD4+ cell increase
IDV + EFV	2.38 logs	88%	240
IDV (12 wks, then) IDV + EFV + d4T	1.89 logs	68%	150

IDV = Indinavir EFV = Evivirenz

Table 2: Merck 035 at Two Years

Therapy Regimen	% viral load below 500 copies	Average in reduction viral load	Average increase in CD4+ cells
Started IDV + AZT + 3TC	81%	- 2 logs	+ 230
Started IDV, at 24 wks added AZT + 3TC	36%	- 1.2 logs	+ 110
Started AZT + 3TC, at 24 wks added IDV	40%	- 1 log	+ 100

IDV = Indinavir

These are clearly some of the most impressive two-drug combination results observed to date and challenge the current idea that people have to be on at least a 3-drug combination. The dose of efavirenz used in other studies has been increased to 600 mg once daily. Efavirenz was generally well tolerated. Reported side effects included rash, headache, diarrhea, dizziness and nausea.

Indinavir (Crixivan®)

Important new information from the long-running Merck 035 study has been reported. This study, which we have previously reported, included 97 people with average CD4+ cell counts of 144 and HIV RNA levels of about 43,000 copies. They received indinavir alone, AZT + 3TC or AZT + 3TC + indinavir. After 24 weeks everybody was switched to the 3-drug regimen. Everybody had used AZT extensively before entry (about 85% had developed resistance to AZT) and about 80% had also been on prior ddI, ddC or d4T. However, all were using 3TC and a protease inhibitor for the first time. After following the group for two years, 81% of those who started with the 3-drug combination continue to have fewer than 500 copies of HIV RNA. However, of those who originally received indinavir alone or AZT + 3TC only 36% and 40% respectively now have fewer than 500 copies of HIV RNA, even though after 24 weeks they were switched to the 3-drug combination. Similarly, after 2 years of the study, there was an average 2 log reduction in HIV RNA for people originally receiving the 3-drug combination, 1 log reduction for those receiving AZT + 3TC and a 1.2 log drop for people starting on indinavir alone. Additionally, after 2 years of the study there was a median 230 CD4+ cell increase among people originally receiving 3-drug therapy, versus a 100 CD4+ cell increase for people on AZT + 3TC and a 110 CD4+ cell increase for people on indinavir alone. The results are shown in **Table 2**.

Preliminary results from a small study comparing indinavir at the approved dose (800 mg every 8 hours) to two different doses taken twice daily (every 12 hours) show that, in the short-term, the every 12 hour dosing seems as effective initially as taking indinavir every 8 hours. This study enrolled 87 people who had not used 3TC or protease inhibitors before. Their median viral load was about 38,000 copies of HIV RNA and their median CD4+ cell count was 279. They received indinavir at 800 mg every 8 hours, 1000 mg every 12 hours or 1200 mg every 12 hours. In addition, all participants took AZT + 3TC. All three doses were generally well tolerated,

Table 3: Indinavir (IDV) with AZT + 3TC

IDV Dose	VL drop at 24 weeks	% <500 HIV RNA	% <50 HIV RNA	CD4+ cell increases
800mg / 8 hrs	1.6 logs	45	45	140
1000 mg / 12 hrs	2.1 logs	75	70	80
1200 mg / 12 hrs	2.2 logs	75	60	90

Table 4: Hard vs. Soft Gel Saquinavir

NARTIs +	Viral load drop	% below 500 copies HIV RNA	CD4+ cell increases
HGC SQV	1.6 logs	43%	120
SGC SQV	2.0 logs	80%	90

HGC = Hard Gel Caplets SGC = Soft Gel Caplets

although there appeared to be slightly more side effects among people receiving the 1200 mg every 12 hours dose. The results are shown in **Table 3**.

It would be a mistake, however, to conclude from these data that taking indinavir twice daily is as effective or more effective than the standard thrice daily dosing. The real test of equivalency in dosing will be measured in the durability of the treatment response – how well it holds up over time. Data after 1 year will be more convincing, and 2-year data the most convincing of all. (See "*The Science and Marketing of Simpler Dosing*" on page 6.)

It is important to stress that these are *very* preliminary results with only a few people reaching the 24-week point of the study. The long-term effect of indinavir taken every 12 hours is still not known.

Indinavir + Ritonavir (Norvir®)

Interesting results have been reported on the combination of indinavir + ritonavir. A very short-term study was conducted in people who were *not* HIV-infected, to avoid the risk of causing protease inhibitor resistance in HIV-infected people. People received either indinavir alone (800 mg every 8 hours), or one of the following twice daily regimens: 600 mg indinavir + 200 mg ritonavir; 400 mg indinavir + 300 mg ritonavir; 600 mg indinavir + 300 mg ritonavir; or 400 mg indinavir + 400 mg ritonavir. Results indicate that these two therapies can be taken together twice a day and that 400 mg of indinavir + 400 mg of ritonavir may be the optimal dose. On this schedule, the peak level of indinavir was about the same as that seen on the approved 800 mg every 8 hours dose. The trough level of 400 mg of indinavir with 400 mg ritonavir was about 4-5 times higher than that seen when the 800 mg dose is taken *without* ritonavir. ("Peak level" refers to the highest level of the drug seen in the blood for a given dose and it usually represents the greatest risk for side effects. The "trough level" is the lowest level and is associated with a greater risk of developing resistance to the drug.) Furthermore, this higher trough level was seen in spite of taking the combined drugs within 30 minutes of eating a light meal. In effect, ritonavir slows the 'breakdown' of indinavir and as a result prolongs and increases the presence of indinavir in blood - just as it does with saquinavir. The higher trough levels of indinavir suggest that a combination of this sort may help prevent the development of drug resistance.

Although these data provide encouraging news about a possible combination of the two most powerful protease inhibitors, it is too early to suggest that people try this combination. There is thus far no data at all about the results of combining the two drugs in HIV-infected people or any way to compare this combination to other available treatment regimens.

Hard vs. Soft Gel Saquinavir

Preliminary results from a study comparing the currently approved hard gel (HGC) formulation of saquinavir (Invirase®) to Fortovase®, the new soft gel formulation (SGC), shows that the new formulation has much better activity than the current version in people who have not been on prior antiretroviral therapy. The study enrolled 171 people with a median viral load of 63,000 copies of HIV RNA and a CD4+ cell count of about 400. They received either HGC saquinavir (600 mg three times a day) or SGC saquinavir (1200 mg three times a day) in addition to two nucleoside analogue reverse transcriptase inhibitors (most of the participants chose AZT + 3TC or d4T + 3TC). The results after 16 weeks are shown in **Table 4**.

These results clearly show that SGC saquinavir is more potent than the currently approved version. While the dose of SGC saquinavir is twice that of HGC saquinavir, the amount of drug that is actually found in blood is about 10 times higher.

Somewhat surprising results were observed in a study of SGC saquinavir and nelfinavir (Viracept®). One hundred and fifty-seven people with an average of about 300 CD4+ cells and HIV RNA of about 63,000 copies received one of the following combinations:

- SGC saquinavir (1200 mg three times daily) + 2 NARTIs,
- nelfinavir (750 mg three times daily) + 2 NARTIs,
- nelfinavir + SGC saquinavir (750 and 800 mg respectively three times daily), or
- nelfinavir + SGC saquinavir (750 and 800 mg respectively three times daily) + 2 NARTIs.

About half the participants had not been on any prior antiretroviral therapy. The results after 16 weeks of therapy are shown in **Table 5** on the following page.

Not surprisingly, analysis of this study showed that people who had not been on prior antiretroviral therapy experienced better results than those who had been on previous therapy. Somewhat unexpectedly, the combination of nelfinavir plus two nucleosides and the combination of SGC saquinavir + nelfinavir showed only average and relatively disappointing activity. Furthermore, people who received the dual protease inhibitor combination experienced more diarrhea than those using only one of the two. However, no conclusions should be drawn about the study as it is small and the amount of data reported thus far is only minimal.

Nelfinavir (Viracept®) Cross-Resistance

Two different studies of cross-resistance between nelfinavir and the approved protease inhibitors have produced mixed results. Cross-resistance is when you have developed resistance to one drug which results in resistance to another drug. One of the studies evaluated 19 people who had increasing viral loads while on regimens containing nelfinavir, and were switched to receive ritonavir (400 mg twice daily) + HGC saquinavir (400 mg twice daily) + d4T + 3TC. People with less advanced disease responded

Table 5: Soft Gel Saquinavir and Nelfinavir

Therapy Regimen	Viral load drop	% below 400 HIV RNA	% below 50 HIV RNA	CD4+ cell increases
SGC SQV + 2 NARTIs	1.8 logs	80%	57%	90
NFV + 2 NARTIs	1.6 logs	50%	32%	90
SGC SQV + NFV	1.5 logs	60%	28%	120
SGC SQV + NFV + 2 NARTIs	1.8 logs	85%	49%	110

SGC SQV = Soft Gel Caplet Saquinavir NVF = Nelfinavir

reasonably well to this combination with about a 1.5 log reduction in viral load and an 80 CD4+ cell increase after 12 weeks (though not as well as people using the same combination as their initial protease inhibitor). By that point, the majority had fewer than 500 copies of HIV RNA. People with advanced disease had less robust responses. Generally, after 12 weeks viral load began to increase toward earlier levels.

The second study followed 12 people who also had increasing viral loads while on nelfinavir. Six people switched to indinavir + NARTIs while the other six switched to ritonavir + saquinavir + NARTIs. Eight weeks after the switch, five had no response or increasing viral loads, four had only a transient response and three had a reasonable response sustained for 4 to 8 weeks.

Neither study gives much support for the claims by the manufacturer of nelfinavir, which has argued that people who fail on nelfinavir will still be sensitive to the other protease inhibitors. Best case reading of the two small new studies is that some people may have a modest response to a second protease inhibitor if they use an extremely powerful combination, like two protease inhibitors together. Even then, it seems unlikely to be as large or long lasting as the response seen when a dual protease inhibitor combination is used as a first-time therapy. A worse case reading would suggest that most people will have little or no response, and there is no evidence of a lasting benefit. Overall, the picture of protease inhibitor cross-resistance continues to suggest that all such drugs can induce cross-resistance to others of the same type.

Preliminary results from various studies of protease-protease combinations for people who are no longer responding to their existing protease inhibitor regimen have shown mixed results. Generally, factors which influence the outcome include:

the extent of prior therapy use; The greater and longer the history of prior therapy use, the weaker the response.

prior use of a protease inhibitor; With few exceptions prior use of another protease inhibitor results in weaker response to a dual protease combination.

how quickly a person switches when the initial therapy begins to fail; People who wait until viral load returns to pre-treatment levels fare less well than those who switch more quickly (however, those who switch more quickly also cycle through their remaining options more rapidly, perhaps hastening the day when no effective therapies remain).

what other changes are made when switching to a dual protease combination; People who switch without changing their RT inhibitors or adding new ones (either nucleside analogue or non nucleoside analogue reverse transcriptase inhibitors) fare less well than those who do make such additional changes.

Any of these factors can result in less effective and less durable response when switching to a dual protease inhibitor combination. For more discussion of this topic see the article *"Strategies for Protease Inhibitor Failure"* on page 4.

T-20 (pentafuside)

A study with the fusion inhibitor T-20 (pentafuside) has produced some encouraging news, even though it comes from a very short and very small study. Sixteen people who had either not been on prior antiretroviral therapy, or who had stopped all antiretroviral therapy for at least 15 days, participated in a small dose-escalation study. The doses studied were 3, 10, 30 and 100 mg (4 participants per dose group) given by intravenous infusion every 12 hours for 14 days. Little or no antiviral activity was observed at the first three doses. However, the four people receiving the highest dose had an average 1.5 log reduction in viral load and a 52 CD4+ cell increase after two weeks. Additionally, all four people on the highest dose saw their viral load drop below the limit of detection (less than 500 copies of HIV RNA). Of these four, two had previously used protease inhibitor therapy and had begun to see their viral loads increase before they switched to T-20. The other two in this group had not previously used antiviral therapy. There were no T-20 associated side effects reported, but after such a short study it would be a mistake to conclude that the drug has no side effects.

To reduce the inconvenience of standard infusion, T-20 is now being given by continuous subcutaneous (under the skin) infusion from a small, high-tech pump device that supplies a steady stream of the drug to the body. Though this drug delivery mechanism may sound unappealing, it is dramatically simpler than earlier infusion devices and many HIV-positive people who have seen the process say they believe it would be less intrusive than the mass of pills they must currently swallow every day. For more information on this and other alternative drug delivery methods, see the article *"Project Inform Drug Delivery Conference"* on page 7.

Commentary

Recent reports have shown that about 30% of people in large HIV clinics are starting to see their viral loads become detectable again or begin to increase while on protease inhibitor therapy. Adherence to complex treatment regimens may be one factor contributing to this, while another may be the inability to put together a truly highly active and potent regimen in the first place. This is usually because someone has previously taken most, if not all, of the available nucleoside analogues such as AZT, d4T, ddI, ddC and 3TC and thus gets little help from this class of drugs. Other reports, which are very preliminary, indicate that people who switch when their viral loads initially start increasing may have a better response to the new therapies compared to those who wait until their viral loads return to pre-treatment levels. But this approach is complicated by the possibility that it may cause people to use up all their treatment options too quickly. Still other physicians and researchers are beginning to recommend that people switch therapy only when they have a complete new regimen to switch to, such as a new protease inhibitor and two new nucleosides or one nucleoside and one non-nucleoside RT inhibitor. This approach is often recommended when a person is stable and viral load is not increasing rapidly, even if it has risen above the limit of detection. Clearly, new therapies with different mechanisms of blocking virus replication are needed for people who cannot tolerate or are breaking through on the protease inhibitors.

Research has shown that viral resistance to current therapies remains a complex problem but data have revealed some specific situations that contribute to therapy becoming less effective,

and these are sometimes avoidable with sufficient forethought. Among the situations to avoid are:

- following dosing schedules in a manner that allows blood levels to fall to the point that the virus is not sufficiently suppressed, allowing it to replicate and mutate (missing or seriously mis-timing doses);
- waiting until viral load returns all the way to pre-treatment levels before switching, rather than switching earlier, when viral load starts to increase from the lowest level, and viral replication is still fairly limited (admittedly complicated by the limited number of drugs which a person can switch to);
- switching to a new combination without switching to at least two new potent compounds.

The ease with which these situations can occur makes it clear that it is very important to develop a long-term personalized strategy around treatment decisions. Articles in past issues of *PI Perspective* and other Project Inform publications have described such strategies, and they have been featured in all Project Inform Town Meetings held around the country. Strategies should cover such points as when to switch, how to make that decision, what to take, how to ensure that the dosing schedule can be followed, and how to keep future options open.

Unfortunately, developing such an optimal strategy is much harder or even impossible for people who have already taken most or all the available therapies just to stay alive long enough to be confronted with this dilemma. It is no one's fault – least of all the patient's – when the struggle leaves a person without an ideal set of options. No amount of conceivable foreknowledge could have changed the situation. However, some compounds in development are likely be active against protease inhibitor resistant virus, and innovative ways of combining existing drugs may also shed light on how to delay viral resistance. The challenge for those who have limited choices is to develop a strategy that allows them to extend the effectiveness of their options long enough for at least two new potent drugs to become available. Sometimes, this goal conflicts with other goals of the strategy, such as changing therapy earlier rather than later once viral load begins to break through. Clearly, new therapies with entirely different mechanisms of blocking virus replication are needed for people for whom the currently available protease inhibitors are not an option.

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.

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PHS Guidelines on Opportunistic Infections

The US Public Health Service (PHS) recently issued new guidelines for the prevention (prophylaxis) and maintenance (to prevent recurrence) of opportunistic infections (OIs). The availability of highly active antiretroviral therapies (HAART) has significantly decreased the incidence of opportunistic infections, as these medications help the immune system recover or delay immune deterioration.

However, it is still not known whether increases in CD4+ cell counts as a result of HAART and/or an immune based therapies, like interleukin-2 (IL-2), can provide complete protection against opportunistic infections. There have been some reports that people whose CD4+ cells counts have increased, have stopped their maintenance therapies and have not yet had their OI reoccur. However, many researchers believe that the specific types of CD4+ cells, which provide protection against specific OIs, may be lost due to immune deterioration and these cells do not necessarily return, at least in the short term, as a product of HAART. Researchers agree that there is likely to be much individual variation in these regards, probably based on the degree of immune function which has been lost. Because of the many uncertainties in our current knowledge, the effect of HAART on the risk of opportunistic infections, for now, is not addressed as a factor in this revision of the Federal Guidelines on Opportunistic Infections.

Pneumocystis carinii Pneumonia

Prevention: The guidelines for preventing PCP remain unchanged. People with 200 CD4+ cells or less, people with unexplained fevers (greater than 100°F for 2 weeks) or a history of candidiasis in the throat (i.e. thrush) should start PCP preventative therapy. TMP/SMX (Bactrim or Septra) remains the drug of choice. However, the recommendations suggest that either one double-strength tablet or one single-strength tablet per day are equally effective and the lower dose may be better tolerated (see "*Update on Opportunistic Infections*" on page 16). Additionally, TMP/SMX may also be able to prevent other HIV-related infections such as toxoplasmosis and many bacterial infections. If TMP/SMX cannot be tolerated, dapsone, dapsone + pyrimethamine + leucovorin or aerosolized pentamidine can be used. Dapsone + pyrimethamine should also provide protection against toxoplasmosis, but not against bacterial infections.

Maintenance: To prevent recurrence of PCP, the guidelines recommend the same options as those for prevention.

Prevention in Children: Children who are born to HIV-infected mothers should start receiving PCP preventative therapy with TMP/SMX beginning at 4-6 weeks of age. If the child is subsequently found not to be HIV-infected, then the therapy should be stopped. However, if the child is found to be HIV infected, then the therapy should be continued for at least a year. Subsequent decisions on starting PCP prevention therapy should be based on CD4+ cell counts.

Prevention During Pregnancy: Pregnant women with 200 CD4+ cells or less should also start PCP preventative medication with a double strength tablet of TMP/SMX *after* the first trimester of pregnancy. However, if PCP prevention is felt to be necessary during the first trimester of pregnancy, aerosolized pentamidine should be considered as first option as TMP/SMX may harm the developing fetus.

Toxoplasmosis

Prevention: People should be tested for antibodies against toxoplasma after diagnosis of HIV infection. People who do *not* have antibodies against toxoplasma should take precautions to avoid infection by the organism. These precautions include: cooking meat so that the inside reaches at least 150°F; washing hands after handling raw meat, gardening, changing diapers, or litter boxes; and, for cat owners, keeping the cat indoors and not feeding it raw or undercooked foods.

People who have antibodies for toxoplasma should start preventative medication with TMP/SMX (Bactrim or Septra) if their CD4+ cell counts fall below 100. For people who cannot tolerate this drug, dapsone + pyrimethamine is recommended. Fortunately, most people with CD4+ counts below 100 are already using TMP/SMX for prevention of PCP. Therefore, no additional drug needs to be taken if they tolerate TMP/SMX well.

Maintenance: To prevent the recurrence of toxoplasmosis, the combination of pyrimethamine + sulfadiazine + leucovorin is recommended. For people who cannot tolerate sulfa-based drugs, pyrimethamine + clindamycin may be an alternative.

Prevention in Children: The guidelines for preventing toxoplasmosis in children are similar to those for PCP, with some minor differences. Children who are antibody positive for toxoplasma and cannot tolerate TMP/SMX should receive dapsone + pyrimethamine.

Prevention During Pregnancy: The guidelines for prevention of toxoplasmosis for pregnant women are also similar to those for preventing PCP. However, it is recommended that pregnant women defer taking pyrimethamine until after the pregnancy because of the low incidence of toxoplasmosis in the United States and because of potential harm to the developing fetus.

Mycobacterium avium Complex (MAC)

Prevention: People with CD4+ cell counts of 50 or less should start preventative therapy against MAC. Clarithromycin or azithromycin are the drugs of choice, but if they cannot be tolerated rifabutin should be considered. Before initiating MAC prevention, people should be tested to ensure that MAC organisms are not present in blood *and* that they do not have active tuberculosis. It is important to consider potential drug interactions with other medications when choosing a therapy. Many therapies to prevent and treat MAC have drug interactions with commonly used anti-HIV drugs.

Maintenance: For maintenance therapy, people who have not developed resistance to clarithromycin or azithromycin should use one of these drugs in combination with at least one other anti-MAC drug, such as ethambutol or rifabutin.

Prevention in Children: Children over 6 years of age with CD4+ cell counts of 50 or less, aged 2-6 years with CD4+ cell counts of 75 or less, aged 1-2 years with CD4+ cells of 500 or less and children under 12 months of age with CD4+ cell counts of 750 or less should receive MAC prevention therapy. Clarithromycin or azithromycin are the drugs of choice.

Prevention During Pregnancy: Pregnant women with CD4+ cell counts of 50 or less should receive MAC prevention therapy. Azithromycin is the drug of choice.

Herpes Simplex Virus

Prevention: Prevention against herpes simplex virus is not recommended. However, people should use latex condoms during sexual intercourse to reduce the risk of exposure to this virus.

Maintenance: Maintenance therapy for herpes simplex virus is not recommended. However, people with frequent or severe recurrences may consider acyclovir. People with herpes simplex virus that is resistant to acyclovir may consider either intravenous foscarnet or intravenous cidofovir.

Prevention in Children: Prevention of herpes simplex is not recommended for children.

Prevention During Pregnancy: Prevention of herpes simplex virus is not recommended for pregnant women. However, some researchers believe that prevention with acyclovir during the late stages of pregnancy may prevent transmission of herpes simplex virus to the child. For women with severe or frequent recurrences of herpes simplex virus, maintenance therapy with acyclovir may be considered.

Cytomegalovirus (CMV)

Prevention: People with CD4+ cell counts of 50 or less and who are CMV seropositive should consider oral ganciclovir for CMV prevention. However, there is considerable controversy over this because studies have drawn conflicting conclusions about the benefit of preventive therapy for CMV.

Maintenance: For maintenance therapy, lifelong treatment with intravenous (in the vein) ganciclovir, oral ganciclovir, intravenous foscarnet, intravenous cidofovir, intravenous ganciclovir + intravenous foscarnet or ganciclovir implants is recommended. Intravitreal injections (direct injection into the eye) of foscarnet or ganciclovir may also be considered.

Prevention in Children: Some researchers believe that children should be tested for CMV soon after birth. Some researchers also believe that children should be tested for CMV yearly. There are no recommendations of specific therapies for preventing CMV in children at this time.

Prevention During Pregnancy: Prevention of CMV disease for pregnant women is not recommended. People who conceive while receiving oral ganciclovir for prevention of CMV disease should stop this therapy. However, maintenance therapy is recommended for pregnant women.

Cryptococcal Disease

Prevention: People with CD4+ cell counts of 50 or less may consider preventing cryptococcal disease with fluconazole. However, some researchers believe that prevention of cryptococcal disease should not be recommended as the incidence of this disease is low and the use of fluconazole may result in drug resistant candida and cryptococcus. Avoiding areas where there are a lot of pigeon droppings may reduce the risk of cryptococcal disease.

Maintenance: For maintenance therapy, lifelong treatment with fluconazole is recommended.

Prevention in Children: There are no specific recommendations for children on prevention of cryptococcal disease, however lifelong maintenance therapy with fluconazole is recommended for children who have had cryptococcal disease.

Prevention During Pregnancy: Prevention of cryptococcal disease for pregnant women is not recommended. People who conceive while receiving either itraconazole or fluconazole as primary prevention for cryptococcal disease should stop these therapies, as they may be toxic to the developing fetus.

Histoplasmosis

Prevention: People with CD4+ cell counts of 100 or less should consider itraconazole as prevention therapy. However, itraconazole has not been conclusively shown to be effective in preventing some other fungal infections and the potential for drug interactions should be considered. People may reduce the risk of developing histoplasmosis by avoiding cleaning chicken coops, disturbing soil beneath bird-roosting sites and exploring caves.

Maintenance: For maintenance therapy, lifelong treatment with itraconazole is recommended.

Prevention in Children: There are no recommendations for preventing histoplasmosis in children, however lifelong maintenance therapy with itraconazole is recommended for those who have had the disease.

Prevention During Pregnancy: There are no specific guidelines for prevention during pregnancy.

Candidiasis

Prevention: Routine preventative therapy against candida is not recommended because of the potential to develop drug-resistant fungal infections.

Maintenance: There is considerable debate over the benefit of long-term maintenance therapy for candidiasis. Some researchers believe that long-term maintenance therapy will result in drug-resistant organisms while others believe that if candidiasis recurs frequently, then fluconazole can be used either intermittently or as long-term maintenance therapy. It is unclear whether resistance develops more quickly as a result of long-term maintenance therapy or frequently recurring intermittent therapy. Itraconazole and ketoconazole can also be considered alternatives to fluconazole.

Cryptosporidiosis

Avoiding Infection: To reduce the risk of cryptosporidial infection, people should wash their hands after contact with human feces, after handling pets and after gardening. Additionally, people should avoid oral-anal intercourse and should not drink water directly from lakes and rivers. Furthermore, newborn babies and very young pets may pose a small risk for cryptosporidial infection. Since tap water in some cities has been found to contain cryptosporidia, water filters capable of removing particles 1 µm (a thousandth of a millimeter) in diameter and larger, those that meet the NSF (National Sanitation Foundation) standard number 53 for "cyst removal," and those that use reverse osmosis technology should be considered. This information is typically advertised on the package when buying a water filter. Many bottled waters are also not free of cryptosporidia and only those that are distilled or filtered by reverse osmosis can be certain to be free of the organism. It is important to consider that ice from restaurants and bars may be made with water contaminated with cryptosporidia.

Prevention and Maintenance: There are as yet no proven preventative medications for cryptosporidiosis.

Varicella-Zoster Virus

Prevention: Adults and children who have not had chicken pox or zoster (shingles) in the past, or who have no detectable antibodies to zoster are at risk for zoster and should avoid exposure to someone who has zoster or chicken pox. However if they have come in close contact with someone who has zoster or chicken pox they should be given zoster immune globulin within 96 hours of the exposure.

Maintenance: No therapy has proven effective to prevent the recurrence of zoster.

Prevention in Children: There are no specific guidelines for prevention in children.

Prevention During Pregnancy: Pregnant women who are at risk for zoster should receive zoster immune globulin after exposure.

Tuberculosis

Prevention: People should receive a tuberculin skin test after diagnosis of HIV infection. People who receive a positive skin test result (a reddening of the skin greater than 5 mm around) should undergo chest radiography and clinical evaluation for active tuberculosis. People who are skin-test positive, but do not have active infection and have not been treated for or received preventative medications, should receive isoniazid + pyridoxine for 12 months. People who are skin-test negative but are at risk for tuberculosis (healthcare workers, people who work or volunteer in correctional facilities and homeless shelters, etc.) should consider isoniazid + pyridoxine for preventative therapy. Additionally, people who are skin-test negative should consider annual testing for tuberculosis.

Prevention in Children: Children who are born to HIV-infected mothers should receive a tuberculin skin test at 9-12 months of age. Children who are exposed to people with active tuberculosis should start isoniazid preventative therapy once it has been determined that the child does not have active infection.

Prevention During Pregnancy: Tuberculosis prevention therapy is recommended for pregnant women who have a positive skin test or if they have been exposed to people with active tuberculosis. Preferred therapies are isoniazid + pyridoxine, however many researchers believe that these medications should only be started after the first trimester of pregnancy to avoid potential harm to the developing fetus.

For more specific information on issues to consider for prevention, treatment or maintenance of any of these HIV-related infections, call the Project Inform hotline at 800-822-7422.

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Paclitaxel for Treating KS

Paclitaxel (Taxol®) received FDA approval as a second-line therapy for treating Kaposi's Sarcoma (KS). The bulk of the information supplied to the FDA referred to the use of paclitaxel in people who had previously treated KS with conventional therapy and had progressed in disease despite treatment, or who could not tolerate side effects associated with other therapies.

Paclitaxel is approved for use in combination with a growth factor called G-CSF, which stimulates neutrophil growth, important cells for fighting bacterial infections. The approval was based on two pivotal studies, including a total of 85 people with advanced HIV-related KS. One study evaluated a dose of 135 mg/m^2 administered every three weeks while the other evaluated 100 mg/m^2 administered every 2 weeks. In both studies volunteers were permitted to remain on antiretroviral therapy throughout the KS treatment. Of the 85 study participants, 59 had previously been on KS treatment and had either failed or were intolerant to therapy. Among this group, 2 people experienced a complete KS response to paclitaxel therapy. A complete response was defined as four or more weeks without detectable KS lesions, other than discoloration of the skin in the area where the lesion had been. Notably, 35 volunteers, or 59% of the total, achieved a partial response, which was defined as the absence of new lesions or symptoms of KS and a 50% or greater decrease in either the total number of lesions, number of elevated lesions, or the size of indicator lesions for at least one month. Those with higher Karnofsky scores, CD4+ counts and KS restricted to the skin had the best likelihood of favorable responses to therapy. Of the 37 participants who benefited from paclitaxel, the median time to response was about 2 months; the duration of response was a little over 9 months, with some sustaining responses for upwards of 2 years.

Paclitaxel is known to suppress neutrophils. Documented side effects in the combined studies included fever, hair loss, weakness, nausea, diarrhea, joint pain (arthralgia) or muscle pain (myalgia), peripheral neuropathy, mucositis, neutropenia, alterations in SGOT levels, kidney toxicity, anemia and thrombocytopenia.

KS is the most common AIDS-related cancer. While it affects men (20-25%) at much higher rates than women (1-3%), women can get KS as well. Early stage KS is often treated 'locally', meaning that lesions are treated directly with cryotherapy (freezing), surgical removal, laser therapy or chemotherapy injected directly into the lesions. It is important to remember that treating individual KS lesions might be appropriate for someone with disfiguring lesions, however, this is merely a band-aid approach as these treatments do not actually kill the cells at the root of the lesion. For KS that has progressed, a number of different chemotherapy approaches are used. Clinical trials have recently shown that treatment with chemotherapy which is encapsulated in fat (called liposomes) is more effective and seemingly less toxic than traditional combination chemotherapy regimens. Two such therapies are approved. The first is liposomal daunorubicin (DaunoXome®), which is approved as a first-line therapy for KS. The other is liposomal doxorubicin (Doxil®), which is currently approved as a second-line KS therapy but is pending review as a first-line approach. These approaches are becoming more widely used as new data support their use over more traditional 'cocktails', such as ABV, VV, and BV; regimens which include alternating or combining the chemotherapies vincristine, vinblastine, bleomycin and doxorubicin (Adriamycin). For more information on KS treatment, call the Project Inform Hotline at 800-822-7422. Recently there have been reports of people with HIV-related KS who have initiated therapy with potent protease inhibitor containing regimens and realized spontaneous remissions of KS. Studies are ongoing to examine this further.

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Resource Notes:

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

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

STEP Perspective is a newsletter produced by the Seattle Treatment Education Project. Call 800-869-STEP for information on their publications.

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

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

Update on Opportunistic Infections

The management of opportunistic infections (OIs) in the wake of HAART (highly active antiretroviral therapy) is a challenge for people living with HIV/AIDS and their clinicians.

Several clinical studies have reported that the use of effective antiviral therapy can reduce the first onset of opportunistic infections. Newer studies show that for a great number of people, HAART can also significantly delay or prevent the recurrence of opportunistic infections. These studies show that when HAART results in sustained increases in CD4+ cell counts and substantial decreases in HIV RNA levels there is a significant delay in recurrence of a number of opportunistic infections, but the risk is not wholly eliminated.

The correlation between HAART and delayed recurrence of disease is not fully understood since it seems to work for some people and not for others. Studies are ongoing to better understand the relationship and until more information is available, it is recommended that people continue on preventative and maintenance therapy drug regimens for opportunistic infections. Even though some people do report success in dropping preventive or maintenance therapy, doing so today may be an unwarranted gamble, one which is undertaken without any idea about the odds for winning or losing.

Pneumonia Vaccination

Bacterial infections are a major concern for people living with HIV disease, especially for people with CD4+ cell counts below 100. In recent years, pneumococci, a leading cause of bacterial pneumonia, have developed increasing antibiotic resistance making preventative therapy and an effective vaccine even more important. Fortunately, studies have demonstrated the benefit of pneumococcal vaccination for people living with HIV. However, a recent study compared a group of HIV-infected individuals who had been vaccinated with Pneumovax® (the preventative pneumococcal vaccine) more than 5 years before the study, with another group of HIV-infected individuals who had never been vaccinated. Those who had received the vaccine had no greater protective immune responses to pneumococcal infections than those who had never been vaccinated. Repeat vaccination improved immune responses modestly and there was no evidence that the vaccination had any harmful effect on the underlying HIV infection. The new Federal Guidelines recommend pneumococcal vaccination for people with HIV, repeated every five years. However, those with CD4+ cell counts of less than 100 should consider the vaccination optional, as it is less likely that their immune system will respond to infection even with vaccination, decreasing the likelihood of protection against pneumococcal infection.

PCP Prevention

Several studies comparing therapies and regimens for the prevention of Pneumocystis carinii pneumonia (PCP) have recently reported data. Together these studies help refine our understanding of PCP prevention. The largest PCP prevention study to date, with more than 2600 participants, compared a regimen of double strength TMP/SMX (Bactrim® or Septra®) daily to three times weekly for the prevention or recurrence of PCP. Interestingly, there were no significant differences between the two groups, but the trends consistently supported the daily regimen as more effective, with slightly lower rates of bacterial pneumonia and PCP among those receiving daily therapy. However, there were significantly more side effects among people receiving the daily dose compared to those receiving the three times weekly dose. Overall, 13.9% of people receiving daily TMP/SMX experienced any adverse event compared to 6.3% of people receiving the three times weekly dose. Although the rates of events were relatively small, there were more allergic/skin reactions, gastrointestinal upset, liver abnormalities and hematologic (blood markers) abnormalities among people receiving the drug daily.

Previous studies have shown that TMP/SMX is the drug of choice for PCP prevention, as it is more effective than the alternative options (dapsone or atovaquone). However, many people have difficulty tolerating TMP/SMX. Because it is such an important drug in managing HIV-related conditions, such as toxoplasmosis and PCP, even those who have initial bad reactions to the drug are often encouraged to find ways to try the therapy again. A new study reports that gradually increasing the dose may be the best way to 'rechallenge' with TMP/SMX. This study compared dose escalation (starting small and gradually increasing to the full recommended dose) to direct rechallenge (giving the full recommended dose again) in 191 people with prior treatment-limiting reactions to TMP/SMX. Results show that a six-day dose escalation is the superior method for re-introducing TMP/SMX to those with previous bad reactions to the drug. This is an important finding since 50% or more of HIV-infected people have an initial reaction to sulfa drugs, including TMP/SMX.

Finally, for those who simply cannot tolerate TMP/SMX, another study compared atovaquone to dapsone, both non-sulfa drugs, as alternatives for preventing PCP. A total of 1057 people were followed for an average of 2 years. The two compounds were found to be equally effective in preventing PCP. The only difference between the two groups was in the types of side effects experienced. People receiving atovaquone experienced more nausea and diarrhea while those on dapsone experienced more rash.

MAC Prevention

A study of 131 people who had never taken a protease inhibitor looked at the use of clarithromycin in a reduced daily dose of 500 mg once, rather than twice, daily for preventing MAC (Mycobacterium avium Complex) in people with CD4+ cell counts below 100. The study compared reduced dose clarithromycin to rifabutin dosed at the normal 300 mg a day, to no preventative therapy. Findings showed reduced dose clarithromycin is as effective as rifabutin in preventing MAC and improving survival. Both therapies showed better survival rates than no preventative therapy at all. Previous studies have shown that clarithromycin at the full dose of 1000 mg day (500 mg twice daily) is superior to rifabutin, however for people struggling with difficult treatment regimens or limited financial resources, reduced dose clarithromycin may be acceptable. Some researchers are concerned that the reduced dose of clarithromycin may lead to the organism becoming resistant to the drug which is generally preferred for treating MAC. How any of this translates into the current era in which almost everyone with MAC would also be using HAART with a protease inhibitor, is uncertain.

CMV and Kaposi's Sarcoma

Recent study results show that the level of cytomegalovirus (CMV) in blood is an important predictor of whether someone is at risk for developing CMV disease. In one study, people who had fewer than 100 CD4+ cells and who were positive for CMV by a polymerase chain reaction (PCR) test were 3.4 times more likely for developing the disease with a 2.5 times greater risk of death compared to those with no detectable CMV levels. The risk of CMV disease increases as CD4+ cell counts decline below 50. CMV retinitis (in the eye) is the leading cause of blindness among people with AIDS. This new CMV PCR test may help to determine who might best benefit from CMV preventive treatment, such as oral ganciclovir. The Food and Drug Administration (FDA) has not yet approved this new CMV PCR test. However, for those who are at risk and considering CMV

preventative therapy, blood samples can be sent to certain laboratories which are performing the test. For contact information on these labs please call the Project Inform hotline at 800-822-7422.

Results from a recent study comparing a number of different approaches for managing CMV disease has shown that the combination of a ganciclovir (GCV) implant (Vitrasert®) directly in the eye and oral GCV is more effective than the GCV implant alone in both preventing the spread of CMV to the unaffected eye or other organ systems and in prolonging survival. While intravenous GCV appears to be slightly more effective than the use of oral GCV in stopping the spread of CMV throughout the body, it was not as effective in prolonging survival as the combination oral and implant approach. This could be due to the added toxicities of the intravenous therapy and the associated risk of bacterial infections that accompany the surgically implanted port for intravenous (IV) administration of the drug.

Three hundred and seventy-seven people with CMV retinitis in one eye received (IV) ganciclovir (5 mg/kg every 12 hours for 14-21 days followed by 5 mg/kg once daily), a GCV implant alone or an implant + oral GCV (1500 mg three times daily). The results are shown in **Table 1.**

There was a lower incidence of Kaposi's Sarcoma (KS) among the groups that received IV ganciclovir and the implant + oral GCV compared to people on the implant alone, suggesting that systemic (throughout the body) ganciclovir may be able to reduce the risk of KS. For a more complete discussion regarding the issues to consider in the prevention, treatment and maintenance of CMV disease, call the Project Inform hotline for the *CMV Fact Sheet*.

Hepatitis C

Results from a small study shows that HAART can temporarily increase hepatitis C (HCV) viral load levels. Nineteen people who were co-infected with HCV and HIV were evaluated after starting HAART. HIV viral loads were significantly reduced after six weeks of HAART and CD4+ cell counts significantly increased, however, HCV viral load increased about 300% above pre-HAART levels. HCV levels returned to pre-HAART levels after 17-32 weeks while continuing on HAART.

HAART may result in a better immune response, destroying more HCV infected liver cells, which could result in the release of hepatitis C virus particles. Increasingly, providers are testing for HCV before starting an individual on HAART. If someone is HCV positive, careful monitoring of liver function is encouraged. If someone is HCV negative before starting HAART, but develops symptoms, treating HCV presumptively and testing for HCV with more sensitive tests (PCR) is encouraged. The common test for detecting HCV antibodies is not very sensitive and physicians have reported false negative test results that are clarified using tests which directly measure for virus (e.g., PCR technology). In instances where HCV disease emerges despite negative test results, it is not believed that HAART caused HCV infection, but rather that the test to detect HCV infection was inaccurate.

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Table 1: Ganciclovir (GCV) Treatment Methods

	Incidence of extraocular and second eye CMV after 6 months	Median survival times
IV GCV	17.9%	426 days
GCV implant	37.8%	388 days
GCV implant + oral GCV	22.4%	568 days

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 Project Inform's discussion paper *"Day One"*).
- **Get baseline CD4+ and HIV RNA tests, repeat quarterly**. Chart the trends. Women should get "gyn" exams and "pap" tests every six months.
- If the CD4+ trend is downward or already below 500, and HIV RNA above 5,000, **or** if HIV RNA is above 30,000-50,000, regardless of other factors, **optimize nutrition and consider combination antiviral treatment**.
- If viral measures do not decline below the limit of detection or at least below 5000, **consider a more aggressive antiviral regimen.**
- If the CD4+ trend stays below 300, **consider preventive treatment against PCP** (oral drugs if possible). If the count continues to fall below 200, **reconsider an antiviral regimen** if not already on one and **learn about preventive treatments** against other opportunistic infections. **Learn about drug interactions.**
- If you have begun preventative therapies and your CD4+ count rises as a result of antiviral therapy, **remain on any preventative treatments you have started.**
- If CD4+ count stays below 75, **intensify monitoring,** consider prevention against MAC/MAI and CMV infections. **Learn about preventive therapies.**

Immune Based Therapies Update

Several important studies of immune based therapies are ongoing and others are enrolling.

Thymus CT Scan

Project Inform previously reported on a thymus study at the Gladstone Institute in San Francisco. The thymus is an important organ in the development of new T-cells (CD4+ and CD8+ cells are T-cells) - it is unknown if immune reconstitution can occur without a thymus in severely immune compromised people. The study data show that people with CD4+ cell counts between 300 and 500 are more likely to have detectable thymic mass than people with CD4+ counts of either less than 300 or greater than 500. The detection of thymic mass among people with CD4+ cell counts ranging 300 to 500 was independent of age. In contrast, all HIV-negative volunteers over the age of 40 had *no* detectable thymic mass. These results are surprising, contradicting conventional wisdom that HIV targets and alters the thymus early in the course of HIV disease. Currently the therapeutic implications of these findings remain unclear.

For the time being, these results support using highly active antiretroviral therapy (HAART) well before progression to AIDS, while people still have CD4+ counts at least as high as the 300-500 range. Particularly among people with CD4+ counts between 300 and 500, thymus activity may increase to compensate for the progressive loss of immune cells. The thymus may start working overtime producing new cells as existing cells are destroyed by the virus. It is unclear if people who have undetectable thymus mass will regenerate thymic material when CD4+ cells rise as a result of HAART. Until this is understood, thymus transplantation in people with advanced HIV disease remains an important avenue of research.

Thymus Transplantation

Two studies are looking at the safety of thymus transplantation in people with HIV. Despite failed transplants in the early 1980s, researchers are encouraged by new technology to preserve the tissue for transplantation. Transplantation in children and adults with Di George's syndrome, in which children are born without a thymus, appears to have been successful, adding more optimism for applying the technique to HIV.

One study was funded by PI in collaboration with the Foundation for AIDS and Immune Research (FAIR). In this study, conducted through the University of Vermont, 8 HIV-positive volunteers with CD4+ counts below 200 have undergone the procedure, which involves implanting thymus tissue where the stomach muscles join. An additional plug of material is implanted in the arm so it can be easily accessed for biopsies to test whether the graft succeeded. After the procedure, volunteers are given an agent called anti-thymocyte globulin (ATG), to clear out any cells which might remain from the thymus donor. Side effects from ATG may include fevers, rigors and hives. Hives may persist for a few weeks. The side effects, which diminish over time, associated with the surgery are similar to those seen with any stomach surgery, like a hernia operation, and include muscle soreness, tenderness and gastrointestinal distress.

When the data was presented, 3 of the 8 volunteers had had biopsies of the material in their arms. Biopsies are being performed 8+ months after surgery. Researchers hope the results will show whether the tissue placed between the stomach muscles is viable and healthy. Two of the three biopsies found healthy tissue. In both volunteers with viable biopsies, there appeared to be increases in both CD4+ and CD8+ cells, as well as evidence of increases in 'naïve' cells, suggesting that some of these cells may have developed through the thymus tissue. Because all volunteers were encouraged to begin aggressive antiviral regimens before transplantation and most included a protease inhibitor in their regimens for the first time, it is unknown if thymus transplantation, or HAART, contributed more to increases in cell counts. Only further research will answer this question. At the least, the research proved that the transplantation is relatively safe and viable thymus material may be maintained in some people.

The second study, which includes 16 people with CD4+ cell counts between 200 and 500, is taking place at Duke University. Eight will receive AZT + 3TC + ritonavir (Norvir®) and 8 will receive the same anti-HIV therapy regimen *and* thymus transplantation. This study should clarify the relative contribution of transplantation vs. antivirals in improving immune parameters, including CD4+ and CD8+ cell counts and percentages of naïve cells. Thus far, four transplants have been completed and a total of 8 volunteers are being followed. All 8 have experienced decreases in HIV RNA levels to below the limit of quantification. All that can be concluded at this time is that the transplant does not appear to have negative effects on HIV RNA levels or cell counts. Preliminary data were presented about 2 months after the transplants; too early to see differences between the study groups. The effects of thymus transplantation in Di George patients take at least 6 months to be apparent, indicating that it will be some months before differences may emerge between the groups. Moreover, the study is very small and unlikely to yield data about the effectiveness of thymus transplantation. Rather, differences between the two groups and data on safety and feasibility of the procedure will inform the decision to move forward with more research.

Chinese Herbs Study Seeking Volunteers!

The Community Consortium in San Francisco is seeking volunteers for a study evaluating a Chinese herbal formula, Marrow Plus®, for treating HIV-related mild-to-moderate anemia. Anemia, a low red blood cell (RBC) count, is common in people with HIV and can be a side effect of many drugs. Standard treatment of mild to moderate anemia is either no treatment, or the use of an injected growth factor called Epogen. A number of the ingredients in the Chinese herbal formula are commonly used in China to treat low red and white blood cell counts.

Volunteers will receive either the herbal formula or an inactive formula for 12 weeks. The study is open to men and women above the age of 17 who have mild or moderate anemia, defined as a hemoglobin count between 9-12 g/dL (or between 9-11 g/dL for women). As part of the study, 20 participants can choose to receive Traditional Chinese Medicine (TCM) diagnoses at entry and at 12 weeks to help researchers understand how well TCM diagnoses correlates to clinical laboratory findings.

Volunteers will be reimbursed for participating and will receive the herbal formula free for a maximum of 12 weeks after the study ends, regardless of whether they received the formula or placebo during the study. For information call 415-502-0658.

CD8+ Cell Study Needs Volunteers!

A CD8+ cell therapy study at the Harvard Center for Blood Research needs volunteers with CD4+ cell counts greater than 400. Participants will receive AZT + 3TC + indinavir (Crixivan®), or the combination with cell therapy. The cells are called HIV-specific Cytotoxic Lymphocytes (CTLs), primarily CD8+ cells. They seek and destroy HIV-infected cells. The CTLs will be collected and "educated" to recognize the individuals' major HIV strains. Volunteers in the cell therapy group will receive 2 infusions of HIV-specific CTL (5 billion cells per infusion); one after participating in the study for 3 months and the second 3 months later. The second infusion will be given with a 5-day cycle of interleukin-2 (IL-2) delivered by subcutaneous (under the skin) injection. IL-2 may help support the cell's activity against HIV. For details on participating, call Susan Crockett at 617-278-3464.

HIV-specific CTLs may be very important in controlling HIV immediately after initial infection. Some studies suggest that people with initial strong and persistent HIV-specific cell responses are more likely to be long-term non-

progressors. Other studies, however, suggest that even though there is an increase in CD8+ cell number in people with HIV, these cells never control HIV well. Thus, capitalizing on what is known about the immune system's response to HIV and how it controls the virus, HIV-specific CTL therapy may provide the immune system with additional support by training the CD8+ cells to better control the virus.

Two previous studies, done before protease inhibitors became available, used smaller numbers of cells per infusion and no IL-2. Preliminary results from these studies show that there are no side effects associated with cell infusion, either during or following the infusion. Participants experienced increases in CD4+ cells and decreases in HIV RNA levels, but these changes were not sustained over time. Tests showed an increase in HIV-specific CTL activity which was sustained for up to 8 months, however. Side effects seen with IL-2 include fevers, rash and flu-like symptoms, and can be managed with the use of ibuprofen and antihistamines. For information on IL-2 and managing its side effects, call the Project Inform Hotline at 800-822-7422 for the new *IL-2 Fact Sheet*.

Educating Cells

A study at Stanford University is attempting to educate cells outside the body to recognize HIV. The study involves HIV-negative and positive family members. Cells are removed from HIV-negative volunteers and educated in a test tube environment to recognize HIV. Once they have been trained to be HIV-specific, they are infused into the HIV-positive family member. Preliminary data from the first 5 volunteers suggest that the procedure is safe, with no measurable side effects during or after the infusion of the HIV-specific cells. An increase in HIV-specific cell activity was seen in volunteers with CD4+ counts greater than 400, suggesting that the more intact the immune system the better the benefit of this approach. The study is enrolling people with CD4+ counts of greater than 300, who have willing HIV-negative family members with suitable cell types. While seemingly "high tech", most such studies are relatively easy to participate in. Both having the cells drawn, and having them infused, is similar to giving blood, and takes just a few hours.

IL-12 Study Enrolling!

A study to find the best dose for IL-12 is enrolling across the country. The first phase is open to people with CD4+ cell counts of less than 50. Later phases will be open to people with counts between 300 and 500. IL-12 may enhance macrophage function. These cells fight many of the infections associated with HIV-disease, particularly Mycobacterium avium Complex (MAC).

Oxandrolone for Weight Gain

Oxandrolone (Oxandrin®) is an oral drug used to promote weight gain in people experiencing weight loss for which there is no known cause (e.g. parasitic, viral, bacterial infections), including HIV-associated weight loss.

Oxandrolone is approved by the Food and Drug Administration although the studies which supported its approval were conducted upwards of 30 years ago and the usefulness of this drug in HIV is unknown and is only now being researched.

Oxandrolone is a synthetic (man-made), anabolic steroid. 'Anabolic' refers to the ability of this type of drug to promote lean body mass (anabolism). However, it is not recommended as therapy for treating low testosterone levels (hypogonadism).

Several small studies in people with HIV-associated weight loss have reported encouraging data when doses two to eight times higher than the approved dose were used. One study, conducted by Dr. Dietriech in New York, enrolled 21 people who had lost more than 5% their usual weight or who weighed less than their ideal body weight. This is not a standard definition for wasting syndrome, which is typically a weight loss of 5 - 10% below ideal body weight. The dose used was 10 mg twice daily, for a total daily dose of 20 mg. People treated for 30 days experienced a mean weight gain of 6.5 lbs, those treated for 180 days saw an 18.7 lbs increase. For those on therapy for 1 year, there was a mean increase in weight of 20.5 lbs. Those treated for 30 days saw an increase in the percent ideal body weight from 91.9% to 95.9% and those treated for 1 year went from 88.9% ideal body weight, to 102%, just slightly above 'ideal.' Because this study was not placebo-controlled, it is difficult to understand the contributions of antiretroviral therapy and other medications on the weight gain realized by the study participants. In previous studies of oxandrolone in people with HIV, lower doses showed no appreciable effect on weight gain.

Another study, still ongoing in Texas, has enrolled 20 women with HIV to evaluate two doses of oxandrolone, 10 and 20 mg daily, in conjunction with nutritional support and resistance training. Early data suggest that after 7 weeks there was an average increase in body weight of 7 lbs. Interestingly, nutritional assessments showed B vitamin and calcium deficiencies common among these women who either had wasting syndrome or classic body composition changes which indicate wasting syndrome. Again, this study is not controlled and other studies have shown that when nutritional support and weight maintenance programs are initiated, individuals tend to increase weight and have improved quality of life. The contribution of the drug to this improved weight gain is still unknown.

Side effects of anabolic steroids include breast enlargement, acne, prostate/urinary-tract infections, abnormal hair growth, excessive frequency and duration of erections, fluid or salt retention, nausea, jaundice, changes in sex drive, reduced fertility, hardening of the arteries, headache, anxiety, depression, shrinking of the testicles, and allergic reactions. There are many women-specific side effects associated with use of anabolic agents, including clitoral enlargement, menstrual irregularities, deepening of voice, hair loss, acne and changes in sex drive. While these side effects may also be associated with oxandrolone, they are seen less frequently than with testosterone and other non-synthetic anabolic agents.

Daily doses ranging from 20 to 80 mg may be ideal for treating HIV-associated wasting syndrome, and large studies evaluating different doses are currently ongoing. Despite aggressive advertising and marketing by the company developing this drug, the risks and benefits of oxandrolone therapy in HIV remain unknown. It would not be surprising, however, to see improved weight gain in HIV with these higher doses. The advantage of oxandrolone is that it is an oral anabolic agent and most other therapies (e.g., testosterone therapy, human growth hormone [Serostim®]) are injected. Also, liver toxicity seen with anabolic steroid use does not appear to be a problem with oxandrolone and the other synthetic injectable hormone, nandrolone. Other pharmaceutical weight gain therapies, including dronabinol (Marinol®) and megestrol (Megace®) seem to promote weight gain in the form of body fat, rather than lean body mass (muscle). For more information on devising a nutrition and weight maintenance strategy, call the Project Inform Hotline at 800-822-7422.

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Thus, IL-12 may be useful in preventing these infections. It may also be important in enhancing other types of immune function. IL-12 or a placebo will be given by an injection under the skin twice weekly for 4 weeks. Volunteers will be allowed to use anti-HIV therapy and will be required to be on preventative therapy for PCP. The goal is to find an optimal dose for use in larger trials, and volunteers will receive IL-12 doses of 30, 100 or 300 ng/kg (nanograms per kilogram of body weight), or placebo. The 30 ng/kg dose group has fully enrolled and new volunteers will receive the 100 ng/kg or 300 ng/kg dose, or placebo. For study locations, call 800-TRIALS-A and ask for information about ACTG 325.

WF-10 Studies

WF-10, a product of Oxie-Chemie (Germany), has shown interesting immunologic properties in a small study at San Francisco General Hospital. Earlier studies of the drug, which lacked adequate controls, suggested the drug may enhance protection against infections in people with advanced HIV disease. In this study, WF-10 appeared to provide a significant and substantial enhancement of macrophage function and activity, which might lead to better response against opportunistic infections. It also appeared to do this without stimulating T-cell activation or increasing viral load, two concerns which the FDA had raised earlier. Although how the drug does this is somewhat uncertain, these results suggest it may be a potent yet very selective activator of macrophages. If a planned additional study shows clinical benefit to this activity, WF-10 may find its place among immune-based therapies. It is sold in Germany and other countries to hasten healing of wounds.

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Expanded Access Programs Expanding

Three new drugs are currently available in expanded access programs – abacavir (formerly known as GW1592), adefovir (Preveon®, formerly known as bis-POM PMEA and GS 840) and efavirenz (Sustiva®, formerly known as DMP-266).

Although initial programs for these drugs are very small and constrained by limited drug supplies, they will soon be expanded to provide access to a wider group of people. The first step of expanding the efavirenz program is likely to be announced by the time readers receive this issue of *PI Perspective*, and a final form of the program should be in place early in 1998. Expansion of the program for abacavir should also take place early in 1998.

Efavirenz

This drug is a highly potent non-nucleoside analogue reverse transcriptase inhibitor (NNRTI), the same class of drug as nevirapine (Viramune®) and delavirdine (Rescriptor®). Although only preliminary information is available, the drug has shown fairly remarkable activity when used in combination with indinavir (Crixivan®). Additional clinical trials are studying its use in combination with a wide variety of other drugs, including AZT + 3TC, other protease inhibitors, and combinations employing one each of all three classes of drugs. Perhaps the most remarkable quality of efavirenz is that it remains stable in the body longer than almost any other currently available AIDS therapy. This quality permits the simplicity of once-daily dosing.

The initial efavirenz program was limited to people with fewer than 50 CD4+ cells with a history of failure on current regimens. The first stage expansion of the program extends the CD4+ cell limit to 200. The final stage of the program, if agreed to by the Food and Drug Administration, will eliminate CD4+ cell limits. For more on the efavirenz program call 800-998-6854.

Abacavir

This widely discussed drug, formerly known as GW1592, is a highly potent nucleoside analogue. It's highest level of potency, however, is limited to people who have not previously used other drugs of this class. New data shows that in general, the more drugs of this type a person has previously used to the point of failure, the less likely it is that this drug will work. Thus, its role will be limited, even though it is likely to make an excellent choice for first time therapy.

The current program for abacavir is limited to people who have CD4+ cell counts below 100, a viral load above 30,000 copies HIV RNA and who have failed at least one protease inhibitor regimen. The expansion of this program in early 1998 should at the very least remove these restrictions and make the drug widely available to people who need it to build an effective combination. For information on the program call 800-501-4672.

Adefovir

This is a nucleotide analogue which blocks HIV replication at the same stage of the virus life cycle as the nucleoside analogues and is dosed once daily. Results from earlier studies show modest anti-HIV activity when used alone. It is not known how well people who have failed on existing nucleoside analogue therapy will respond to adefovir. This drug also has activity against hepatitis B virus and cytomegalovirus (CMV) - however it is unlikely that adefovir can be used to treat CMV, although it may be effective in preventing the disease.

The current program is limited to those who have CD4+ cell counts below 50, a viral load above 30,000 copies HIV RNA and who have failed or are intolerant to a combination regimen containing two nucleoside analogues and a protease inhibitor. For more on the program call 800-445-3235.

Redefining Expanded Access

All previous expanded access programs for new drugs have been a product of the older era of AIDS therapy, which supplied one new drug at a time when earlier therapies failed. Today, we know that this model is ineffective and even harmful in the sense that it wastes the opportunity to truly benefit from the new drugs. But the same old rules continue to make the new drugs available in this fashion. This year, many treatment activists, as well the some of the manufacturers, are attempting to redefine the rules of expanded access to reflect the current recommendations for treating HIV disease. The key rules of current therapy call for avoiding the use of single drug therapy, and in general to avoid adding single new drugs one at a time to a failing regimen. The old expanded access programs, in effect, encourage such improper use of therapy by limiting access only to those people who have reached some arbitrary and often dangerously low level of CD4+ cells (or high viral load), and who are failing all existing regimens. In effect, the current system provides

the drug only when it is likely to be too late to be of benefit and when it can't be used properly.

New proposals are calling for elimination of CD4+ cell and viral load limits as entry criteria for expanded access. Instead, the recommended criteria will be to make the new drugs available to anyone who needs the drug to construct a viable treatment combination, as defined in the Federal Guidelines for the Use of Antiretroviral Therapy. In addition, the proposals will strongly encourage collaboration between programs so that people who need multiple new drugs can get them at the same time. By simplifying the entry criteria to these programs, the goal is to make it easier for people and their physicians to use the new drugs wisely, at a time when the patient is able to benefit most and when the drugs can be combined with one or two other new drugs the patient hasn't previously used.

Critics who fear that such a program might be too broad frequently don't understand that this design still imposes limits. For example, anyone who hasn't tried many of the available combinations would still be denied access because by definition, such people don't really need the new drug to create a viable combination. But the new program model would not deny the new drug or drugs to anyone who has cycled through the available combinations, regardless of CD4+ cell and viral load levels.

Despite wide community support, it is not clear at the time of writing whether the FDA has sufficiently advanced its own thinking to permit this approach.

Expanded Access Program Numbers:

Abacavir	800-501-4672
Adefovir	800-445-3235
Efivirenz	800-998-6845

Medicaid Managed Care: A System in Transition

Medicaid is the nation's primary health care safety net for low income people. Although Medicaid budget increases have slowed dramatically, the program's total operating cost for 1995 was $156.3 billion, making it a large target for cuts by policy makers and government officials seeking a "balanced budget."

The worst of the proposed reforms have been defeated *this* year, but the future of Medicaid remains a major concern because it is one of the most important care programs for people with AIDS. Roughly half of adults with an AIDS diagnosis and more than 90% of children with HIV depend on Medicaid. People with AIDS (and other chronic and life-threatening illnesses) need a high level of expert care. Medicaid recipients have had difficulty accessing that care in the past. If Medicaid fails to meet HIV health care needs, many people will suffer and fail to benefit from the recent advances in AIDS treatment research.

In addition to policy and funding changes, one of the most daunting challenges in ensuring appropriate HIV care is the rapid move into managed care. Ironically, this drive to lower costs by moving to managed care settings is occurring at the same time as the development of improved, but more expensive anti-HIV therapy. These treatment regimens not only cost more, but they also require more time, support and knowledge on the part of the healthcare provider and the patient. Complex needs are more difficult to meet in a managed care environment where monetary considerations often restrict access to expensive therapies and minimize the time healthcare professionals can spend with their patients. As a result, people with HIV may not be getting the appropriate diagnostic tests and may not get adequate information on drug adherence and potential drug interactions.

Movement into Medicaid Managed Care

Enrollment in Medicaid managed care is growing rapidly. Between 1993 and 1996, enrollment increased 170%, 33% of that growth happening between 1995 and 1996. As of June 30, 1996, 13 million Medicaid beneficiaries were enrolled in managed care plans, 35% of all Medicaid recipients. Forty-eight states offer some form of managed care (often called Health Maintenance Organizations or HMOs); some states have been able to use the savings to expand their Medicaid programs. As of 1996, Hawaii, Illinois, Kentucky, Minnesota, Ohio, Oregon, and Tennessee had received approval to enact Medicaid managed care programs that would mandate inclusion of people with AIDS.

Some HMOs have a good reputation for HIV care, and some physicians say they are able to provide quality HIV care in an HMO environment. However, this is not always the case and the incentive to deny access to care or to limit services has also resulted in many horror stories about managed care. At least one study has shown that people living with chronic or life-threatening illness do not fare as well under managed care, compared to in fee-for-service arrangements. For people living with HIV/AIDS the details and methods of implementation of their managed care program can mean a difference both in quality, and length, of life.

Since most HMOs are profit-oriented businesses rather than non-profit enterprises, their goal is to provide adequate service at the lowest possible cost. The lowered costs allow HMOs to "sell" health care packages to employers and government for a lower fee. Competition between HMOs to offer cost advantages is intense. Consequently, HMOs have a strong incentive to either carefully limit the number of high risk/high cost patients they accept, or to carefully constrain the amount of money spent on such patients. This makes people with HIV and other life-threatening illnesses a problem for most HMO's. Conversely, it also creates problems for people with HIV who must get their health care through HMO's and find themselves constantly confronting the drive to limit costs. Cost is understandably the last thing on the mind of a sick or dying person.

In the movement to Medicaid managed care there are both promises and challenges. The promises are largely directed to the employers and groups who purchase the service and to the stockholders, while the challenges are felt mostly by the patients. In theory, Medicaid managed care could provide more consistent levels of HIV care, ensuring coordinated care, a focus on prevention including early intervention, and reduced dependence on emergency room care. The overarching challenge is ensuring that such health plans are well constructed, fairly implemented, and appropriately regulated for patient protection. Additionally, individuals need to be educated about, and supported through, the more complex health delivery system. When it comes to shifting Medicaid patients into managed care, it will be critical that consumers and

advocates carefully evaluate the process and the protections provided for patients. The patient block represented by Medicaid in many ways is undesirable within the managed health care industry, since it includes people with the least resources and the greatest overall medical needs.

Changes in Federal Requirements

Before the Balanced Budget Act of 1997 states were required to apply to the federal government for a waiver of certain Medicaid requirements in order to move Medicaid recipients into managed care. Waivers articulate states' plans for moving people into the new system. The process the state goes through to produce the waiver typically gives consumers and advocates a chance to evaluate, critique and provide input into the state plan. The Balanced Budget act eliminated one of the required waivers. In some states this could mean that advocates and consumers have to look for other avenues to affect their state's move to managed care.

One place to look may be state plan amendments. Under federal regulation, states planning to shift to mandatory managed care are required to submit a plan amendment to the Health Care Financing Administration (HCFA) for approval. The plan amendment is another area where the state outlines its plans and may provide another chance for advocates to have substantive input. Because plan amendments have not been monitored very well in the past, advocates will have to make sure that states are using the amendment process, that the media is aware of this requirement, and that regional and central HCFA offices establish clear guidelines for plan amendments and review processes that include consumer participation.

The Balanced Budget Act also includes some consumer protections for Medicaid managed care at the federal level although the protections are broad and it is unclear as yet how they will be implemented. Patient protections should be built into state Medicaid managed care plans and monitored carefully.

What You Can Do

Medicaid is a joint federal and state health care program. It is overseen at the federal level by the HCFA and must provide certain benefits. However, states decide what options, such as prescription drug services, will be provided. As states move Medicaid further into managed care, much of the focus of advocacy efforts will now be forced to shift from the federal to the state level. One of the most important advocacy targets will be the contracts states develop with managed care entities serving the Medicaid population. However, there are steps to be taken at all levels.

At the personal level

Understand your state Medicaid situation. In most states it is not mandatory for people with HIV to enter into a managed care plan. If you receive enrollment information for Medicaid managed care do *not* assume you have to sign up. The standard Medicaid plan may be the better option for people living with AIDS. However, if your state does have mandatory managed care for people with HIV/AIDS you must make a decision regarding a plan, or you will be automatically enrolled in one of the participating plans.

Evaluate the plans carefully. It can be very difficult to determine plan benefits, so get help from local benefits counselors, AIDS service organizations or other people living with HIV already enrolled in one of the plans. You can also call the Project Inform Treatment Information Hotline (800-822-7422) for a discussion of issues that may be helpful in evaluating health maintenance organizations (HMOs).

Learn about all your options. Often there are ways to access benefits that may not be immediately apparent (e.g., sometimes a treatment may only be available through a prior approval process or another treatment access program). Work with benefits counselors, and local community based organizations to explore all of your options. Call the Project Inform Hotline if you are having a problem accessing a particular treatment.

Find, and get connected with, the best care provider you can. Your care provider can sometimes be your most effective advocate in the managed care environment.

Get involved with your HMO. Some managed care organizations include patients on the governing bodies or on boards of directors. This can be a very effective way to become involved with your managed care provider. Consumer boards and patient advocacy unions are effective if they go beyond merely advising and are given decision-making authority. Forming coalitions with other Medicaid patients with similar concerns will strengthen advocacy efforts.

At the State Level

Medicaid managed care plan development: People living with HIV/AIDS need to develop contacts with the governor and the state Medicaid director to learn about the state Medicaid program. Find out if your state is considering mandatory enrollment of people living with AIDS and how it will be soliciting public input. You can get help from elected officials if you have difficulty getting information from the state Medicaid office.

Contact the health committees in your state legislature to check on any legislation authorizing managed care, as well as any legislation mandating consumer protections in managed care. You can be a resource to legislators by telling your own story, relating Medicaid managed care experience in other areas of your state or the country, and by providing sample legislation. You can get copies of some state legislation by calling Project Inform.

Medicaid managed care contracts: It will be essential to monitor the development and imple-

Balanced Budget Act Protections

The consumer protections include:

- There must be a choice of plans (at least two); in rural areas, there must be an option of at least two primary care doctors.
- Individuals may change plans at any time with cause.
- Enrollment notices and information must be in a form which is easily understandable and include a broad range of information.
- Marketing materials must be approved by the state; door to door marketing and telephone marketing are prohibited.
- Emergency care must be reimbursed under any conditions that a "prudent lay-person" (meaning you) would reasonably expect to result in serious physical or mental harm without immediate medical attention.
- Health care plans must maintain a sufficient number, mix, and geographic distribution of providers with the ability to offer an appropriate range of services.
- The state must develop and implement a quality assessment and improvement strategy.
- There must be an external independent review of each plan including quality outcomes and timeliness of and access to services.

mentation of contracts between the state and the managed care entities that deliver medical care. The substance of the contract will determine the services that people are offered. The state must issue a contract with HMOs and sometimes will issue a request for proposal (RFP) from various HMOs in the process of setting up the managed care program. States use different processes. Some invite the public, consumers, physicians, etc. to review the proposed contract or RFP, others publish a RFP and ask for public comment. Find out how your state is handling these processes. If you can not obtain necessary documents, ask for help from a state legislator or file a Freedom of Information Act request.

Implementation: Once a managed care plan has started, expect problems with enrollment. Advocates should meet with the Medicaid Director or the person in charge of implementation to establish mechanisms to deal with problems quickly. The most common problem with enrollment is that clear, understandable information about the process and the plans are not available to people who are expected to enroll. Problems can also arise getting to a doctor with experience in treating HIV disease. Additionally, people may not understand what treatments are available and how to get them. Regular meetings with those responsible for oversight will be necessary to monitor the plans. If you are working with an organization, developing mechanisms so that individuals can report problems, while be important and can document ongoing concerns. Identify and join state level coalitions or create new reporting mechanisms. People living with HIV/AIDS share many of the same concerns as other people with disabilities, chronic illness, life-threatening disease, children, the elderly and other populations in the delivery of health care. Broad-based coalitions have much more power to advocate for change.

At the Federal Level

There is still much oversight needed at the federal level. Federal policy makers are often unaware of the real impact of their decisions. Advocates need to build a relationship with their HCFA Regional Administrators. If your state has an 1115 waiver or will be applying for one, HCFA will assign a project officer to that waiver. This person can be a valuable source of information. Call the HCFA Office of State Health Reform Demonstration Projects to get your project officer's name.

You can also work with national organizations, both AIDS organizations and other organizations addressing Medicaid such as Families USA. Submit comments and concerns regarding your state Medicaid program to Donna Shalala, Secretary of Health and Human Services, the Director of HCFA and your HCFA Regional Administrator. For information on how to contact these offices, please contact Ryan Clary at Project Inform's Treatment Action Network. Send copies to your governor, state Medicaid staff and state and federal legislators. If you need help identifying any of these people call TAN at 415-558-8669 or by e-mail Ryan at TAN@projinf.org.

Commentary

Although Medicaid has never been a perfect system, it provides necessary support for people living with AIDS and their children. There is currently a proposal at the federal level to expand the Medicaid program to cover low income people living with HIV who have not yet progressed to the disability status currently necessary to receive Medicaid benefits. If we are working to expand the Medicaid program and expect it to continue to be an effective safety net, we will have to closely monitor changes to the system. While it may be unclear whether Managed Care, as we know it today, will ultimately prove helpful or harmful to patient interests, it is a system we will have to deal with for several years to come. The AIDS epidemic affects many different populations including gay men and lesbians, women, people of color, substance users, people who need mental health services, people with hemophilia and many others. If we expect to reap the benefits of any new developments in treatment regimens, it will be essential to ensure that competent HIV care is delivered through both public and private insurance systems.

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Hormone Replacement Therapy

The use of hormone replacement therapy and hormonal contraceptives is a difficult issue for women living with HIV.

Advocates have battled for studies of possible interactions between HIV therapies and oral contraceptives (OC). However, it is not oral contraceptives (birth control pills), but the use of other hormonal therapies (such as implants and injections) that needs addressed. For many women with HIV, pregnancy plays little part in deciding on therapies, which are used to manage menstrual flow, menopause and premenstrual syndrome (PMS), or to affect body composition. These uses, as well as the impact of HIV therapies, are not addressed in simple oral contraceptive drug interaction studies.

HIV has an impact on hormone levels; in men, testosterone is often deficient and replacement therapy can increase energy levels, manage depression and promote weight. In women, abnormal menstrual cycles, weight loss, gynecological infections, headaches and fatigue are common and may relate to decreased estrogen. Estrogen supplementation is not a simple choice, as it can increase the risk of breast and endometrial (the membrane lining the uterus) cancers.

The issue of abnormal menstrual cycles and premature menopause in HIV positive women has been debated, and studies comparing menstrual cycle differences in HIV-positive and HIV-negative women have shown conflicting results. Many doctors view abnormal menstrual cycles as an inconvenience rather than a serious medical condition and thus don't address them aggressively. However, a recent study reported the use of hormone replacement in HIV-positive post-menopausal women predicted survival. This implies hormonal regulation may have broader health implications than previously assumed for women with HIV.

There are also questions about the relationship between hormone levels and the immune system, drug metabolism and body composition. Little is known about how hormonal therapies used by women interact with anti-HIV drugs. The few oral contraceptive studies done, have only looked at how HIV drugs and contraceptives affect the blood levels of one another. For instance, nelfinavir (Viracept®) decreases the levels of ethinyl-estradiol (a birth control pill) by 50% and some doctors suggest women double their dose to prevent pregnancy. What does this mean if ethinyl-estradiol (which contains, estrogen and progestin) is used for hormone replacement therapy rather than birth control? One concern is that a woman who doubles the dose may increase her risk of cancer. But the risk of cancer may be less when hormone therapy is used to resolve existing deficiencies, as opposed to boosting otherwise normal levels to prevent pregnancy. The reverse issue also exists; anti-HIV drugs may be metabolized differently in the presence of birth control medications. What are the interactions and effects of hormonal contraceptive or replacement therapies, such as the implants or injections, when used with anti-HIV drugs?

Replacement may also impact body composition changes and wasting. For instance, Depo-provera, an injectable synthetic hormone administered every 3 months, can increase body weight about 5 pounds per year. One study found that over 5 years, women gained 25 pounds on average, indicating that the weight gain is not transient. As with Megace, this weight seems to be primarily fat, not muscle. Injected once quarterly, Depo could be a simple, dual-use alternative to therapies like Megace for weight maintenance.

Research specific to hormone levels and the effects of hormone replacement therapy on women living with HIV is overdue. The better our understanding of the impact of hormonal imbalances on the immune system, drug metabolism and general health, the more effective women with HIV and their health care providers can be in addressing these issues.

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