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PERSPECTIVE

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

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Report from the Great Chicago Plateau

The 5th Conference on Retroviruses and Opportunistic Infections, held in Chicago in the first week of February, heralded few breakthroughs or surprises. Instead, it painted a picture of slow but steady progress following the advances seen with the advent of protease inhibitors and triple combination therapy beginning in 1996. This pattern of evolutionary change is likely to continue for the next few years, as the conference reports held out little hope for another major advance any time in the near future.

This issue of *PI Perspective* is dedicated primarily to the coverage of the recent conference and will highlight a number of the more significant findings in several areas, including: an overview of major trends and concerns in the use of therapy, new information about existing therapies, new drugs in the development pipeline and advances against opportunistic infections.

The Big Picture – Outcomes

The conference included presentations on the impact recent advances have had on the death rate and the incidence of opportunistic infections. In a word, all such studies could be described as positive. Reports from hospitals, medical groups and cohort studies report major reductions in the death rate compared to recent years. A typical example was a study entitled *"Accelerating Decline in New York City AIDS Mortality,"* prepared by the New York Department of Public Health. The study reported a 29% reduction in AIDS mortality between 1995 and 1996, and an additional 33% decline from the second half of 1996 to the first half of 1997. More importantly, the most recent figures show that groups which did not initially benefit in 1996 are now reporting major gains in 1997. The gap in response initially seen between white males and

Despite these limitations, the collective weight of new information about existing drugs, how to use them in combination, and new options discussed considerably in the first half of 1997, reflecting wider access to new therapies across all populations in the study area. Unfortunately, this pattern of improved access in places like New York is not always repeated in other regions for disenfranchised and impoverished populations.

Some people have questioned whether reductions in the death toll from AIDS can be attributed solely to new therapies. They have argued that the declining death totals simply mirror an earlier change in the epidemic, some ten years ago, when the total number of new infections began to decline. Epidemiologists, however, disputed such claims, arguing that the changes in the infection rate earlier were insufficient to account for the mortality reduction seen today. A clearer way to look at the issue is to examine what has happened to the incidence of opportunistic infections in recent years. Such infections, after all, are the final cause of most AIDS deaths. One particularly revealing study was presented by the Tulane School of Medicine in New Orleans. Because of its design, it eliminates any influence from changes in the infection rate a decade ago. This study simply looked at two large cohorts of HIV positive people with CD4+ cell counts under 200, one group of 1181 people in the 18 months before the availability of protease inhibitors and a second matched group of 1284 people in the first 18 months after protease inhibitors became available. The groups were compared for the incidence of opportunistic infections over the equivalent 18 month periods. The first period represented the era of two-drug combinations, such as AZT + 3TC, the second represented the initial availability of 3-drug protease inhibitor-based combinations. Incidence of PCP fell from 18% to 11.7%; wasting from 9.5% to 4.8%; KS from 4.3% to 2.5%; MAC from 8.5% to 6.1% and CMV from 4.6% to 3%. All changes favored the period in which protease inhibitors were available.

It should be noted that this study by no means represents the "best" possible picture of the new therapies, since there was no requirement that the people in the later group actually be on triple combinations. The only assumption that can be made is that *some* of them were, as compared to none in the earlier group. Additionally, many people who started protease inhibitors when they first became available in early 1996 merely added them to their existing regimen, potentially using them as just monotherapy, and almost certainly not getting the optimal response. We now know that to get optimal response, people should start at least two new therapies when they switch treatment regimens. Nonetheless, there were statistically significant reductions in the rates of all the most common HIV-related infections.

Side Effects

Other "big picture" news included clarification about two significant new side effects sometimes attributed to protease inhibitors, namely diabetes and body fat redistribution. Two studies which examined the diabetes question concluded that if protease inhibitors are responsible for new cases

of diabetes, it is at best a rare side effect with no evidence of wide-scale incidence. Researchers will continue to study individual incidences. The outcome is the opposite concerning fat redistribution (now being labeled as lipodystrophy), as several studies documented growing incidences of this problem. This side effect takes one of three common forms: (1) "buffalo hump" or an accumulation of fat at the back of the neck at top of the spinal cord; (2) "truncal obesity" or the accumulation of hard fat deposits in the abdominal area; or (3) wasting of the face, arms and legs. Incidence of these effects ranged from a low of 11% in one study to as high as 64% in another. Differences in the incidence rate may be attributed to differences in definition of the problem and differing levels of physical examination by physicians. The largest study concluded that these problems are not associated with any particular protease inhibitor but rather with all of them, perhaps in a potency-related fashion. For now, this problem does not yet appear to have any immediate clinical significance, but it does have a major cosmetic and body image impact for those suffering from it. No clear explanation yet exists of the mechanism. So far, the only known solution is to stop the use of a protease inhibitor. Some physicians anecdotally report success from changing the protease inhibitor regimen. Patients are encouraged to request careful physical exams by their physicians to look for the onset of this problem and keep watching for any new information about how to treat the condition. Some people are seeking help from endocrinologists, but so far, no one has claimed to have a solution.

Salvage Therapy

Salvage therapy remains one of the most important but understudied aspects of AIDS research. Most new drug studies focus on people who are just beginning therapy or who have limited prior use of anti-HIV drugs. If there is any clear message emanating from the Chicago conference, it is that people in these categories have a wide range of increasingly well proven options. In contrast, people who have experienced high level clinical and virological failure with existing drugs have few if any places to turn. A number of small studies labeled as "salvage therapy" were presented in Chicago, but they could all be summed up as a strategy of "try whatever's left" or "take everything at once." Small uncontrolled studies reported varying degrees of short-term success from 4-, 5-, and 6-drug combinations. Nothing, however, even hinted at an effective long-term strategy. Even if a 5- or 6- drug regimen works in the short-term, it seems unlikely that people could sustain such intensive therapy for long periods. Many people already have difficulty working with 3-drug combinations, so the challenges of adherence and toxicity in a 5- or 6-drug regimen may be overwhelming. Some of the small salvage studies reported in Chicago are described in *Antiviral Update* on page 4 of this issue of *PI Perspective*.

"is the restored level of immunity sufficient to lead a normal life?" The answer to this question increasingly seems to be yes...

Immune Restoration

Several key studies at the Chicago conference characterized the state of the immune system in people successfully treated for long periods with highly active antiviral therapy (HAART). In short, the studies show a surprising but still imperfect level of immune restoration. Progress or reversal seems to be occurring in nearly every documented defect of immunity associated with AIDS. The level of resulting immune response is still not comparable to uninfected controls, but this perhaps is too much to ask. Instead, the question might be *"is the restored level of immunity sufficient to lead a normal life?"* The answer to this question increasingly seems to be yes, with growing evidence that *some* people are able to successfully withdraw from the use of maintenance and preventive therapies against opportunistic infections. Even if the immune response remains imperfect, it may be adequate.

Some remaining important but unanswered questions about immune response include:

- ➔ Why do some people experience immune restoration but not everyone?
- ➔ What are the characteristics of the level of immune restoration needed to warrant withdrawal of maintenance or preventive therapies?
- ➔ Why doesn't the immune response return to a normal state, even in the presence of near-complete viral suppression?
- ➔ What can be done to augment the natural return of immunity?

These and related issues will be addressed extensively in the March 1998 meeting of the Project Inform Immune Restoration Think Tank (San Francisco, March 20 – 21).

Ease of Use – Adherence

The challenge of adherence to difficult therapy regimens remains a major roadblock to more wide-scale success with treatment. Several papers presented in Chicago demonstrated how truly difficult this challenge is, noting high levels of nonadherence even under the best of circumstances. While many behavioral programs are under development to assist people with adherence, the most fertile ground for attacking this problem is the development of better drugs that are less toxic and easier to use. Along these lines, reports at the conference noted the first therapy designed for "once a day" dosing (efavirenz), new ways to use existing drugs more easily (twice daily

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dosing for nelfinavir and indinavir; once daily dosing for nevirapine and ddI), as well as new drugs designed with ease of use in mind. Within a year or less, it will be common to see twice daily dosing regimens, and perhaps some complete combinations which require only a single dose period daily. Information on many of these simpler dosing regimens can be found in *Lower Dose Maintenance Therapy for HIV?* on page 9, while a wider discussion of the issues, challenges and strategies of adherence can be found in the "Adherence to HAART" presentation module on the Project Inform website (*www.projinf.org), also available through the Project Inform Hotline*. And lest people despair about their own inability to achieve perfect adherence, we should remember that all the good news about reduced death and opportunistic infection rates has come from a patient population which is imperfect in its adherence to therapy.

New Drugs in Development

New data were presented on a number of drugs expected to become widely available in the next 1 – 2 years. These are covered in detail in *New Drugs on the Horizon* on page 10. One important characteristic of most of the drugs expected in the near future is that they are unlikely to offer the necessary breakthrough needed by people with advanced disease and high level failure with current drugs. The immediate crop of new agents is composed largely of new and improved drugs of the same types as those previously offered. Thus, nearly all will suffer problems of cross-resistance with one or more existing agents. They may well be better choices for people just beginning therapy or those with only a modest history of therapy use, but will offer no panacea for the highly experienced patients. Drugs which fall into this category include abacavir, adefovir, amprenavir, FTC and efavirenz. A few additional new protease inhibitors are in early development which claim to overcome problems of resistance, but such claims should be viewed very cautiously until there are real data to support them. Though such claims have often been made before, it's hard to cite a single example in which they proved true.

What the advanced patient population needs are new types of drugs which react with entirely new targets on the virus. This includes such agents as zinc finger inhibitors (now in phase 1), fusion inhibitors (also in phase 1), and integrase inhibitors (struggling to get out of the laboratory). Unfortunately, there will be a considerable time gap before such compounds become routinely available.

In Summary

The Chicago conference stands largely as a model for where we stand in the course of the AIDS epidemic: resting on slowly rising new plateau. Advances of the size and quality seen in 1996 can't be expected every year, perhaps even every few years. Slow gradual improvement is taking place which will indeed make a difference, but it falls far short of a revolution or major step forward. For most people, this is more than sufficient, however, it remains sadly lacking for those people with the most advanced disease and those who have experienced high level failure on existing therapies. For them, the near future remains clouded with uncertainty. For their sake, we must all forsake the temptation of complacency and renew the demand for better therapy.❑

We should remember that all the good news about reduced death and opportunistic infection rates has come from a patient population which is imperfect in its adherence to therapy.

Antiviral Update

New results from studies offer people more information on how to use currently available drugs. It may be possible to use simplified dosing regimens which will make the drugs far easier to take and also likely to increase adherence. While imperfect, some small studies are starting to report information which may help guide those with extensive prior antiviral use. Together, this new information helps to round out our understanding of how to use the currently available options.

***Note: Most drugs are known by several different names, which is often confusing. See Drug Identification Chart (page 9) for a list of the names commonly used for HIV antiviral drugs.**

Indinavir

Preliminary results from a small study show no significant difference in antiviral activity between two triple-drug regimens. One hundred people with a mean viral load of about 35,000 copies of HIV RNA and a CD4+ cell count of 400 received either AZT + 3TC + indinavir (Crixivan) or d4T + 3TC + indinavir. There were no differences in side effects between the two groups. The most commonly reported side effects included increases in bilirubin levels and elevated liver enzymes. After 24 weeks of the study, the results are shown in **Table 1.**

Delavirdine

The first encouraging data on a study involving delavirdine (Rescriptor) shows that the drug, when used in an appropriate combination, can be quite potent. Three hundred and fifty-two people with CD4+ cell counts of about 350 and a viral load of 25,000 copies of HIV RNA received AZT + 3TC, AZT + delavirdine or AZT + 3TC + delavirdine. Results are similar to those seen with another NNRTI, nevirapine (Viramune), when used in combination with AZT and ddI. After 32 weeks of the study the results are shown in **Table 3**.

Table 1

	Viral load drop	CD4+cell change	% below 500 copies HIV
AZT + 3TC + IDV	1.6 logs	+145	80%
d4T + 3TC + IDV	1.9 logs	+170	85%

IDV = indinavir

Another small study also shows no difference in antiviral activity between two triple-drug regimens. One hundred people with a mean viral load of about 30,000 copies of HIV RNA and a CD4+ cell count of about 450 received either AZT + 3TC + IDV or d4T + ddI + IDV. There were no differences in side effects between the two groups. The most commonly reported side effects were nausea and vomiting. After 24 weeks of the study, the results were as shown in **Table 2**.

Table 3

	Viral load drop	CD4+ cell change	% below 400 copies HIV	% below 40 copies HIV
AZT + DLV	0.5 logs	+25	5%	0
AZT + 3TC	1.1 logs	+90	35%	15%
AZT + 3TC + DLV	1.5 logs	+130	65%	50%

DLV = delavirdine

Table 2

	Viral load drop	CD4+ cell change	% below 500 copies HIV RNA
AZT + 3TC + IDV	1.6 logs	+145	75%
d4T + ddI + IDV	1.6 logs	+210	70%

IDV = indinavir

Salvage Therapies

Preliminary data suggest that it may be possible to recycle drugs in order to put together a combination regimen. Twelve people who had failed regimens containing all the NARTIs and three protease inhibitors (hard gel (hgc) saquinavir (Invirase), indinavir and ritonavir {Norvir}) went on a 6- drug regimen consisting of d4T + 3TC + ddI + nevirapine + nelfinavir + hgc saquinavir. Only nelfinavir and nevirapine were drugs new to the participants and all the others were 'recycled'. After 12 weeks of the 6-drug regimen, 9 of the 12 participants had viral loads below 400 copies of HIV RNA and most had an increase in CD4+ cells (between 30 and 220 cells). This is a situation where the participants took all the drugs that were available to them and most had good anti-HIV responses, at least for the short-term. However, it is not known whether they could have gotten a similar response if they took fewer drugs. Moreover, it is not known how well people can sustain a 6-drug anti-HIV regimen especially if they also have to take medications to prevent or treat opportunistic infections.

Another study examined the use of ritonavir + hgc saquinavir + 2 NARTIs for people who have failed (increasing HIV RNA levels and decreasing CD4+ cell counts) either hgc saquinavir or ritonavir/indinavir. In this study of 43 people, 13 had failed saquinavir and 30 had failed ritonavir/indinavir. The average viral load at study entry was about 80,000 copies HIV RNA and CD4+ counts for the saquinavir group was 122 cells but only 69 cells for the ritonavir/indinavir group. The results were as shown in **Table 4**.

People who had previously taken saquinavir experienced a better response from ritonavir + saquinavir + 2 NARTIs compared to people

who had previously taken ritonavir/indinavir. This may be due to the fact that they retained some sensitivity to ritonavir while at the same time getting a much higher dose of saquinavir. Whereas people who had been on ritonavir or indinavir are unlikely to get any benefit from ritonavir and only short-term response from saquinavir.

Simpler dosing regimens

Preliminary results suggest that the antiviral activity of nelfinavir (Viracept) taken either twice daily or three times daily is similar. Two hundred and forty-one people with an average of about 100,000 copies of HIV RNA received d4T + 3TC and either the approved dose of nelfinavir (750 mg three times a day) or 750 mg, 1000 mg or 1250 mg of nelfinavir all taken twice a day. All participants who received either 750 mg or 1000 mg twice daily subsequently switched to the 1250 mg twice daily dose. Diarrhea and nausea were the most commonly reported side effects although they were not different between the two groups. The results after 32 weeks are shown in **Table 5**.

Similarly, preliminary results show the antiviral activity of indinavir taken either twice daily (BID) or three times daily (TID) are similar. Eighty-seven people with a average CD4+ cell count of about 275, a viral load of about 50,000 copies of HIV RNA and who had not previously taken 3TC or a protease inhibitor received AZT + 3TC + one of three different doses of indinavir: (1) 800 mg TID, (2) 1000 mg BID, or (3) 1200 mg BID. The side effects were similar between the three groups. The most commonly reported side effect was nausea/vomiting. The results after 32 weeks are shown in **Table 6**.

Based on the pharmacology of these drugs, there was always some belief that nelfinavir could be effectively used twice daily because of its long half life in the blood. But this was never the case with indinavir, which has a much shorter half life in the blood. Overall, the data from the indinavir study here seems a bit odd, in that all doses and schedules look surprising lackluster compared to other studies using the same drug. It remains to be seen based on longer-term studies with more people if twice a day dosing of indinavir and nelfinavir is truly comparable to three times a day dosing. However, if these longer-term studies truly show that twice a day dosing with the drugs are as good as three times a day dosing, then this will make these drugs far simpler to take and will most likely lead to better adherence.

Commentary

We still have only limited knowledge of how to treat people who have failed a first protease inhibitor regimen, and almost no knowledge of what to do after failing a second protease inhibitor combination. This must be a research priority as more and more people will undoubtedly begin to experience viral rebound while using these therapies. Some new drugs in development such as the fusion inhibitors and zinc finger inhibitors may be beneficial as part of a salvage regimen, however, they are still in very early clinical development and unlikely to be available to most people even if they do ultimately prove to have good anti-HIV activity. A simple way to summarize the current state of antiviral research is that things continue to look better and better for people just beginning therapy, with simpler and better regimens becoming routinely available. The outlook remains uncertain, however, for those who are most in need, the people who have already exhausted the current list of therapies.❑

Table 4

Viral load drop after starting ritonavir + saquinavir + 2 NARTIs

	Month 1	Month 3	Month 6	Month 9
Saquinavir failure	1.48 logs	1.84 logs	1.73 logs	2.08 logs
Ritonavir/indinavir failure	1.06 logs	0.58 logs	0.56 logs	0.00 logs

Table 5

	Viral load drop	CD4+ cell increases	% below 400 copies HIV RNA
NFV three times daily	2.3 logs	150	75
NFV twice daily	2.2 logs	170	75

NFV = nelfinavir

Table 6

Treatment: AZT+3TC+	Viral load drop	CD4+ cell increases	% below 500 copies HIV	% below 50 copies HIV
800 mg IDV, TID	1 log	150	50%	40%
1000 mg IDV, BID	2 logs	50	70%	60%
1000 mg IDV, BID	2 logs	50	70%	60%

IDV = indinavir TID = three times daily BID = twice daily

♀ Indinavir in Women

Little is known about the effects of hormones on the metabolism, potential effectiveness or side effects of drugs in women. A small study looking at the effects of the menstrual cycle on indinavir (Crixivan®) levels in the blood found dramatic differences in time to peak level and time to optimal therapeutic levels based on the various phases of the menstrual cycle over the course of a month. While the amount of indinavir in the blood appeared to change throughout the hormone cycle, it still remained broadly within the ranges observed in earlier studies that primarily included men. These monthly fluctuations need to be further studied to determine their implications on the durability of the regimen, resistance, dosing and possible long-term toxicity. Fortunately, there are several other studies looking at the use of antiretroviral therapy specifically in women, either in development or enrolling, that may have the opportunity to address these questions.

Double Protease Inhibitor Combinations

Dual protease combinations are of interest because some combinations offer the prospect of reducing the dose and dose frequency of the drugs compared to what is required when they are combined with the nucleoside analogue reverse transcriptase inhibitor (NARTI) drugs (such as AZT, ddI, ddC, d4T and 3TC). Another possible benefit of dual protease inhibitor combinations is to suppress virus replication for a longer period or to a deeper level than can be achieved with a combination using a single protease inhibitor. Initially, dual protease inhibitor combinations were most widely used in an effort to restore antiviral activity in people who experienced viral

Ritonavir plus Saquinavir

One European study examined the usefulness of adding nucleoside analogue drugs to a dual protease combination. Most earlier studies of protease combinations used only the two protease inhibitors. The study compared ritonavir (Norvir) + hgc saquinavir (Invirase®, the original version of saquinavir) to ritonavir + hgc saquinavir + d4T. Doses used were 400 mg ritonavir, 400 mg of saquinavir and 40 mg of d4T, all taken twice daily. Two hundred and eight people with an average CD4+ cell count of 260 and viral load of about 20,000 copies HIV RNA participated in this study. About half had been on prior NARTIs before joining in this study but all were using protease inhibitors for the first time. After 24 weeks, about 90% of the participants still remaining on the triple combination had viral loads below 400 copies HIV RNA compared to about 65% of people receiving the two-drug regimen. Both groups had about 150 CD4+ cell increases. Six people receiving the two-drug combination added d4T + 3TC after 18 weeks of the study because of increasing viral loads. All six participants subsequently had viral loads below 200 copies of HIV RNA. Mild to moderate diarrhea and tingling around the mouth were the most common reported side effects. In short, this study suggests adding one or more NARTI drugs provides a clear benefit over using a dual protease combination alone.

New data were presented from a long-running study of ritonavir + saquinavir (earlier reports of this study appear in prior issues of *PI Perspective*). Of importance is new information showing that 11% of the participants developed moderate to severe increases in triglyceride levels, but that drugs such as Lopid® and Atromid® were generally successful in reducing triglyceride levels. Another new finding concerned 27 people in the study who added up to 2 RT inhibitors (NARTIs) when their viral load began rising above the limit of detection. Most added d4T + 3TC. For 23 of the 27, adding the 2 nucleoside analogue drugs caused the viral load to fall back below the limit of detection (200 copies of HIV RNA) and this result has persisted through the study. These results are somewhat surprising as

HIV Eradication - Dead or Alive, or Even Necessary?

Because the concept of HIV eradication was new and sounded so exciting when first introduced two years ago, it was treated with great fanfare in the popular and community press. Eradication efforts were aimed only at people who were able to begin aggressive antiviral therapy within days or a few months of initial HIV infection, but the media often glossed over this distinction and made it sound like a cure was at hand. This year, the tables turned, with the popular and community media proclaiming the "end of eradication" and often accusing the researchers involved of "hyping" the concept. Our memory is that it was the media, if anyone, and not the researchers, who hyped the concept. Moreover, many commentators glossed over the fact that these initial efforts were solely raising the prospect of eradication in people who have the opportunity to initiate treatment extremely early in the course of disease, known as the "acute infection syndrome." In most cases, this means people who start treatment even before they experience seroconversion to HIV positive status, signaled by the development of HIV antibodies. No one has even begun to test the question of eradication for the chronically infected patient population, which makes up the vast majority of all HIV infected people.

Today, HIV eradication has neither been achieved nor has it been ruled out or declared a failure in people in these very early stages of HIV infection. While it is true that eradication efforts, such as those previously described by Dr. David Ho and others, have not yet completely eradicated all traces of HIV, a more honest way to describe the story is that they have come surprisingly close. (For background, see *PI Perspective* #19, *Eradication of HIV - Hope or Hype?*). HIV has, in a number of cases, been driven completely from the blood stream and most tissue reservoirs, while the remaining "hideout" of the virus has now been identified as "latently infected memory T-cells." It is in this class of cells that the last infectious virus or at least some remnants of the genetic material (DNA) of HIV can still be found – but only after an extraordinary search. By the techniques of just a few years ago, we would have considered HIV eradicated in such people.

Even when the most intense research methods find HIV DNA or tiny amounts of replication competent virus, it is not clear whether these remnants are adequate and sufficient to re-kindle a productive HIV infection. Work summarized by Dr. Bruce Walker of Massachusetts General Hospital raised the prospect that people treated in acute infection may be able to sustain effective suppression of virus without continuing treatment simply on the strength of their immune responses. His group reported that people treated in acute infection develop a very strong HIV-specific immune response, apparently identical to that seen in a small percentage of long-term non-progressors who seem capable of containing HIV infection without treatment. If the immune responses of these treated people are now truly the same as those seen in the exceptional long-term non-progressors, it might be possible to sustain control of HIV – without further treatment and without actually eradicating every last remnant of HIV.

In a closely related finding, Dr. Franco Lori (formerly of Dr. Robert Gallo's Lab in the US) reported on a patient treated with a unique combination of drugs, including hydroxyurea (Hydrea). After initial successful treatment and achievement of "undetectable" viral load in

most people believed that dose intensification with two NARTIs would not be sufficient to get viral replication under control and would result in only a transient viral load drop.

Nelfinavir plus Indinavir

A small study looked at the safety and antiviral effects of nelfinavir (Viracept) in combination with indinavir (Crixivan). Twenty-one people with a median CD4+ cell count of 259 and a viral load of about 50,000 copies of HIV RNA participated in this study. Approximately half of the participants had been on previous NARTIs but all were using a protease inhibitor for the first time. The doses studied were 1000 mg every 12 hours of indinavir and either 750 mg every twelve hours or 1000 mg every twelve hours. of nelfinavir. After 32 weeks of the study, 10 people experienced HIV RNA decreases to below the limit of detection (400 copies of HIV RNA) and of those ten, six had less than 50 copies of HIV RNA. Three people had to add NARTIs because they either had an increase in viral load or they did not have a sufficient antiviral response. There was a median increase of 133 CD4+ cells after 32 weeks of the study. This study found that indinavir did not increase nelfinavir levels in blood as much as anticipated and as a result future combinations of this regimen will use 1000 mg twice daily of indinavir and either 1000 mg or 1250 mg twice daily of nelfinavir.

Saquinavir plus Nelfinavir

A European study of the combination of soft gel (sgc) saquinavir (Fortovase®) plus nelfinavir (previously reported in *PI Perspective*) showed that this combination did not appear to offer any special or synergistic benefits. The dual protease combination may have about the same antiviral effects as either one of the two protease inhibitor combined with two NARTIs. Even the study group which combined both protease inhibitors plus 2 NARTIs did not appear to offer any advantage over the other combinations. The results after 32 weeks of the study are shown in **Table 1** (see next page).

Ritonavir Plus Nelfinavir

Preliminary results from a small study shows that the combination of nelfinavir + ritonavir has potent anti-HIV activity. Twenty people with a median CD4+ cell count of about 330 and a viral load of 33,000 copies of HIV RNA received 400 mg twice a day of ritonavir and either 500 mg or 750 mg twice a day of nelfinavir. None of the participants had previously been on a protease inhibitor. There were no differences between the two nelfinavir doses in antiviral response. After 12 weeks of the study, there was a 2 log reduction in viral load and over a hundred CD4+ cell increase. About 70% of the participants had viral loads below 400 copies of HIV RNA. Almost half of the participants had mild to moderate diarrhea. Despite the use of ritonavir, however, there did not appear to be any special benefit to this combination, perhaps because there isn't a strong interaction between ritonavir and nelfinavir. The preliminary results are good, but not of a higher order than typically seen of standard three-drug combinations.

The wider look at protease inhibitor combinations presented at the Retrovirus conference suggests that there are two general classes of protease inhibitor combinations. The first class describes combinations which produce some form of synergistic interaction when they are combined. The best example of this is the ritonavir and saquinavir combination, which greatly increases the activity of saquinavir because of drug interactions caused by ritonavir. The net result of this combination is the ability to achieve a very high level of antiviral activity while using lower doses of both drugs. Because of the lower doses, there is also a lower level of side effects from either drug and the net cost is lower than the standard cost of the two drugs combined. Almost all such synergistic combinations include ritonavir as one element, since this drug often has a profound effect on the way which other drugs are absorbed and metabolized by the body.

blood and body tissue, the patient removed himself from further therapy. Nearly a year later, no trace of HIV has yet reappeared in the patient using standard methods. It took a new level of amplification of the most sensitive known technique to find a single cell in 60 million that still contained a remnant of HIV. In this case, the patient's one year holiday from therapy did not result in renewed productive infection. Thus, the meaning and clinical significance of the one cell in 60 million containing HIV DNA is quite uncertain. More information about the study of this particular combination can be found in (*Hydroxyurea* page 15).

Considering these findings, it would seem premature to suggest that HIV eradication has proven a failure or to castigate its proponents as makers of hype. On the contrary, it's rather amazing how close the efforts have come to eradication or something functionally resembling it. Research on all aspects of eradication is continuing and has by no means ground to a halt or been declared a failure. The next step in this work is an effort to activate the few remaining cells that harbor HIV in the hopes of making the HIV in them vulnerable to the antiviral drugs and the immune response (they are protected from both as long as the cell remains latent or inactivated). Another approach calls for simply taking some volunteers, successfully treated since very early infection, off therapy to see whether the rekindled immune response is capable of containing the HIV infection. This entails very little risk to the volunteers since they could resume therapy easily if it fails.

These efforts at eradication should continue as an urgent priority. If it can be accomplished in a few people treated early under the most optimal conditions, researchers will learn a great deal which can perhaps later be applied to the more difficult question of people with chronic infection. Few people believe it will be possible to keep today's patients on aggressive chemotherapy for the rest of their lives, so sooner or later, better and more lasting solutions will be critically needed (as they are already for people failing current therapy). Instead of faulting researchers for raising and pursuing the prospect of eradication or its functional equivalent, we should be applauding their progress and asking how we can help.

If and when eradication happens, it will first happen in a single person or a very few who have had the most optimal care and treatment from the moment of initial infection onward. Certainly, it would be a mistake to think that this could quickly be applied to people with chronic infection. But it would also be a mistake to declare it impossible. As we learn more about the immune responses that are capable of controlling HIV infection in a small percentage of people, we may also learn what it will take to restore them in all the rest of those infected with this daunting virus. We are only at the very earliest stages of understanding what it means to have "undetectable" levels of virus for years on end, or what possibilities are created when we see the return of missing cells and cell function in both acute and chronic infection. Only fools would pretend to think we know the answers to these questions in advance.

Table 1

	Viral load drop	CD4+ cell increase	% below 400 copies HIV RNA
SQV + 2 NARTIs	1.96 logs	92	70%
NFV + 2 NARTIs	1.77 logs	73	55%
SQV + NFV + 2 NARTIs	1.75 logs	134	83%
SQV + NFV	1.86 logs	161	69%

SQV = saquinavir NFV = nelfinavir

The second class of combinations are those in which there is no particularly advantageous interaction. In this case, the net result at best some modest additive advantage in potency, if any. In some cases, there seems to be little obvious gain from using such combinations. Combinations of this type typically do not include ritonavir and thus they lack any special advantages from drug interaction.

While most of the double protease inhibitor combination studies are relatively small, they suggest that these combinations can be safely used and are sometimes quite potent. Some such combinations offer a significant benefit over standard triple combinations, while others do not. Whether dual protease inhibitor combinations should be used as a first-line therapy is still a matter of debate. Clearly, longer-term studies need to be conducted comparing dual protease inhibitor therapy to what is now considered first-line therapy (a protease inhibitor and 2 NARTIs). Additionally, it is not known which double protease inhibitor combination will be the best tolerated and most potent. Generally, double protease inhibitor regimens can be taken twice versus three times a day when they are used in combination with NARTIs. However, the potential downside might be that if someone were to fail a double protease regimen, chances are they will be cross-resistant (where resistance to one drug results in little or no benefit when switching to another) to all other available protease inhibitors.❑

In Memory

We dedicate this issue of the PI Perspective to:

Curtis Rood

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

(Beginning with this issue) we also honor friends and supporters who died of causes other than AIDS

Lyle Hawk.

Their memory lives on in the work that remains.

Protease Paunch and "Buffalo Hump"

While there have been many reports of lipodystrophy (changes in fat distribution) after long-term protease inhibitor therapy, so far, there are no widely accepted explanations of its cause. "Protease paunch," once mistakenly called "crix-belly" because people thought it was uniquely caused by indinavir (Crixivan), describes a condition in which body fat is redistributed from other areas and accumulate in hard, fatty layers around the abdomen. One study found that 11% of people developed 'protease paunch' or 'truncal obesity' and that it was more common in older people and those who were on prolonged antiviral medications. Another study by an Australian group found that lipodystrophy affected up to 64% of people on protease inhibitors. They found a loss of body definition around the face, arms and legs, and a corresponding accumulation of fat around the abdomen and/or behind the neck. This study also noted that the median time to onset of lipodystrophy was about 10 months. Additionally, the Australian group noted that a certain portion of the HIV protease enzyme was structurally similar to a naturally occurring enzyme in the body, the role of which is to go around the body and gather up and destroy lipids (fatty substances). They hypothesize that this portion of the protease enzyme may therefore be attracting lipids resulting in lipodystrophy. However, it is not clear why the build up of fat is found around the neck, resulting in a buffalo hump, or around the gut.

The wide differences in the reported frequency of occurrence of lipodystrophy may be attributed to varying definitions of the problem or to differences in how carefully patients and physicians look for it. Most researchers reporting on the problem believe that it is not unique to any particular protease inhibitor. The lead researcher of the Australian study believes that the frequency of occurrence is related primarily to the overall potency of the protease inhibitor regimen, with the greatest risk for people using the most potent dual protease combinations and the least for people using the least potent single protease inhibitor (hard gel capsule saquinavir). No one has reported any solution to the problem other than to stop the use of protease inhibitors, not a very practical suggestion for many people. Some individual physicians anecdotally report achieving some success simply changing the protease regimen, but without a controlled study, it is difficult to interpret this phenomenon. For example, they might simply be changing from a more potent to a less potent regimen. For people who have previously developed resistance to drugs like nevirapine and delavirdine, one possible solution might be to switch to a three-drug combination based on efavirenz and two NARTIs, thus eliminating use of a protease inhibitor. In preliminary studies at least, such a combination appears to equal the potency of most three-drug regimens based on a protease inhibitor.

Lower Dose Maintenance Therapy?

Two recent studies asked whether it is possible to switch to a "less potent" maintenance anti-HIV regimen after sustaining HIV RNA levels below 200 copies for at least 2 months. The hope would be that once initial HIV RNA levels are brought under control, "maintaining" viral suppression with a less potent antiviral approach could offer the potential to decrease the complexity of regimens that people are taking for the long-term.

Overall, the "less potent" maintenance regimens were not as effective at sustaining viral suppression compared to a 3-drug, highly active antiretroviral therapy regimen. One study followed 509 people with a median CD4+ cell count of 450 and a median viral load of about 20,000 copies HIV RNA who had not previously been on 3TC or a protease inhibitor. Forty-three percent had previously been on AZT. All participants received AZT + 3TC + indinavir for 6 months. If the participants had HIV RNA levels decrease to below 200 at 16, 20 *and* 24 weeks, they then received either AZT + 3TC, indinavir alone or stayed on AZT + 3TC + indinavir as a maintenance regimen. At the time of the preliminary analysis, 316 people were on the maintenance phase. Viral rebound was defined as any return of viral load above 200 copies HIV RNA. The results were as shown in **Table A**.

Table A

	# with viral rebound on maintenance Rx
Indinavir	16/101
AZT + 3TC	18/104
AZT + 3TC + indinavir	3/104

Table B

	# with viral rebound on maintenance Rx
AZT + 3TC	22/92
AZT + IDV	16/93
AZT + 3TC + IDV	6/92

A European study, known as TRILEGE showed similar results. Three hundred and seventy-one people with an average CD4+ cell count of 363, and a viral load of about 30,000 copies of HIV RNA, who have not been on any prior anti-HIV therapies participated in this study. Volunteers received AZT + 3TC + indinavir for three months and then either AZT + 3TC, AZT + indinavir or AZT + 3TC + indinavir if they had fewer than 500 copies of HIV RNA after the second month of the induction phase. Two hundred and seventy-seven people went onto the maintenance phase of the study. The results were as shown in **Table B**.

These results raise as many questions as they answer. They must be taken at face value, namely that switching to maintenance therapy after 24 weeks (the US study) or after as little as 12 weeks (the European study) greatly increases the risk of viral rebound. However, it would be a mistake to believe that these studies answer the broader question of maintenance therapy. Other studies have shown that the peak level of viral response is seldom reached in 8 weeks, and not always even in 24 weeks, and that the peak response cannot be measured solely in the bloodstream. Tissue reservoirs of HIV take longer to clear. Moreover, these studies did not use the newer, more sensitive viral load tests which can distinguish between people with hundreds of copies of HIV RNA and people with less than 50 or 20. People who become "undetectable" on the more sensitive assays respond differently over time than those who never reach such levels. Finally, other studies have shown that the peak level of immune restoration in response to HAART is seldom if ever reached in 6 months. Taken together, these considerations argue that the switch to maintenance therapy in these studies occurred far earlier than it should have. For now, all that can be said is that an early switch to maintenance therapy is not warranted. Whether switching at a later time will work, after peak responses to HAART are attained, is uncertain, but it is not ruled out by the current data. Further study is warranted.❑

Drug Identification Chart

Protease Inhibitors

Initials	*Generic name*	*Trade name*	*Manufacturer*
AMP	amprenavir		Glaxo Wellcome
IDV	indinavir	Crixivan ®	Merck
NFV	nelfinavir	Viracept ®	Agouron
SQVhgc	saquinavir	Invirase ®	Hoffman-La Roche
SQVsgc	saquinavir (new) *soft gel capsule*	Fortovase ®	Hoffman-La Roche
RTV	ritonavir	Norvir ®	Abbott Labs

NARTIs (Nucleoside Analogue Reverse Transcriptase Inhibitors)

Initials	*Generic name*	*Trade name*	*Manufacturer*
ABA	abacavir	Ziagen ®	Glaxo Wellcome
ADF	adefovir	Preveon ®	Gilead Sciences
AZT	zidovudine	Retrovir ®	Glaxo Wellcome
ddC	zalcitabine	Hivid ®	Hoffman-La Roche
ddI	didanosine	Videx ®	Bristol-Myers Squibb
d4T	stavudine	Zerit ®	Bristol-Myers Squibb
3TC	lamivudine	Epivir ®	Glaxo Wellcome
ATZ+3TC		Combivir ®	Glaxo Wellcome

NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors)

Initials	*Generic name*	*Trade name*	*Manufacturer*
EFV	efavirenz	Sustiva ®	Dupont Merck
NVP	nevirapine	Viramune ®	Boehringer Ingelheim
DLV	delavirdine	Rescriptor ®	Pharmacia & Upjohn

New Drugs on the Horizon

Recent advances in anti-HIV treatment have primarily come not from new therapies but from better understanding in how to use existing drugs, such as new combinations and simplified dosing regimens. While there are new drugs in development, most are simply improved versions of existing drugs or new drugs of the same type as those currently available. These new therapies are likely to only offer incremental benefits in the form of simplified dosing and reduced side effects but seldom with better activity against HIV. As such, new drugs in the pipeline will offer more and better choices for people starting therapy or those with limited prior use, they are unlikely to offer any substantial benefits for people who have developed high level resistance to most of the currently available anti-HIV therapies. Consequently, the people with the greatest need for new therapies are still left with limited options.

Most studies continue to test new drugs primarily in people who are relatively healthy and with little or no prior use of anti-HIV therapies. Manufacturers focus on this group because it is much easier to show good antiviral activity in such people. In contrast, people who have been on extensive prior therapies usually respond less well to new drugs and have a higher risk of developing side effects. As a result, there is little information to guide the choice of a second or third treatment regimen after an initial combination loses its ability to suppress viral replication. Moreover, there is almost no reliable information on how to treat people who have been on all or almost all of the existing therapies.

New Drugs in Development
Efavirenz

Efavirenz is likely to be the next anti-HIV drug to be approved by the Food and Drug Administration (FDA) and is expected to be in pharmacies by the fall of 1998. Results from studies are very encouraging. Efavirenz was previously shown to work well in antiviral naive patients in a two-drug combination with a protease inhibitor. A new study suggests that it is equally effective in the same population in three-drug combinations with AZT + 3TC. The study compared a three-drug efavirenz combination to a two-drug combination with NARTIs, mimicking similar studies done with 3-drug protease inhibitor based combinations. One hundred and thirty-seven previously untreated people with a mean CD4+ cell count of 370 and viral load of about 50,000 copies of HIV RNA were assigned to receive either AZT + 3TC or AZT + 3TC + efavirenz. Participants received 200 mg, 400 mg or 600 mg of efavirenz once daily. After 24 weeks of the study, the results are shown in **Table 1.**

The three-drug combination here appear to be as potent as most 3-drug combinations employing a protease inhibitor. All three doses were generally well tolerated with nausea, headache, fatigue and dizziness being the most commonly reported side effects. The dose of efavirenz that is currently used in the clinical studies is 600 mg once daily. Efavirenz should be taken before going to bed to reduce the likelihood of developing neurological side effects, such as mania, depression and other mood disorders. Efavirenz is currently available under an expanded access program for most HIV-infected people who require a new drug to build an effective combination.

Table 1

	% with less than 400 copies HIV RNA	% with less than 40 copies HIV RNA*	Mean CD4+ increase
AZT + 3TC	65%	15%	90
AZT + 3TC + 200 EFV	96%	83%	170
AZT + 3TC + 400 EFV	91%	68%	175
AZT + 3TC + 600 EFV	100%	67%	110

EFV= efavirenz

*week 16 results

Comment: While the results of the triple combination study with efavirenz and AZT plus 3TC must be considered somewhat preliminary, they strongly support the notion that many people can achieve the goal of effective therapy – sustained viral suppression below the limit of detection – using a three-drug combination anchored by a non-nucleoside RT inhibitor (NNRTI). The rationale for using such a combination is that it preserves the use of a protease inhibitor for use in a different combination. In effect, using such a strategy would give a person two Highly Active Antiretroviral Therapy (HAART) regimens which could be used one after the other. The current standard approach, as recommended in the Federal Guidelines, is to initiate therapy with the standard approach, a three-drug combination including a protease inhibitor. The problem with the standard approach is that it leaves a person with few effective options if and when it fails since all studies to date agree that switching to a second protease inhibitor after the first one fails seldom produces a strong and durable response. Using an approach based with initial therapy based on a drug in the NNRTI class should have little or no effect on one's later ability to use a protease inhibitor combination.

Another theoretical but practical advantage of initiating therapy with a NNRTI-based combination using a drug like efavirenz is this type of drug has generally fewer and less severe potential side effects than protease inhibitors. People who are asymptomatic and just beginning therapy tend to be less willing to put up with side effects. Thus, such a combination might lead to better adherence to therapy, especially when one of the main drugs is used only once a day.

It may take more than a year before these new approach is addressed clearly in the Federal Guidelines, but this new data on an efavirenz-based triple combination is difficult to ignore. On the surface, it would appear to offer a superior approach to treatment strategy. For now, it is important to note that such a strategy is not right for everyone. It should be limited to the kinds of people who were actually treated in the studies. Thus, initial therapy based on a 3-drug combination including a NNRTI and two NARTIs makes sense primarily for people who (1) have not used any prior antiviral treatment, (2) who are essentially symptom free, and (3) have a viral load below 50,000. A better level of response might be seen if a lower viral load limit were employed. People who do not meet this description should continue to employ the standard three-drug combinations including a protease inhibitor.

Some voices may still argue that it is best for

everyone to begin with the combinations which include a protease inhibitor and no one can say that this is wrong. However, it fails to address the question of long-term strategy, and fails to recognize how effective some of the three-drug NNRTI-based combinations have proven in clinical trials. The best NNRTI data, exemplified by the current efavirenz study described above, seems equal to the responses seen in most three-drug protease inhibitor based combinations, and it is in fact superior to the response shown for some standard combinations. It is too early to know whether a NNRTI-based combination will be as durable and keep people below the limit of detection for as long as a good standard combination, but the results have continued to look good after 1 year in at least one such study (a 3-drug combination which included nevirapine (Viramune)).

One question which cannot yet be clearly answered is whether all of the current NNRTIs (delavirdine (Rescriptor), efavirenz, and nevirapine) are equally effective for use in such a strategy. The answer is uncertain because the three drugs have been studied in very different ways. In terms of raw numbers, the combination with efavirenz does appear to be somewhat more potent than the others, but it is hard to say if this is true reflection of the power of the drug or the way in which it was used.

Three alternative ways have been suggested to employ a drug like efavirenz in clinical strategies. One is to use it in a three drug combination along with one NARTI and one protease inhibitor. Surely, this will produce a highly potent response. Many researchers are concerned, however, that if the regimen fails, the patient will have exhausted not one but both classes of highly active drugs (protease inhibitors and NNRTIs) in a single step because there is such a high level of cross-resistance within these two categories of drugs.

A second approach would employ a drug like efavirenz in a simple, two-drug regimen along with a potent protease inhibitor. Studies of efavirenz have shown this approach to be at least equal to most three-drug regimens which include a protease inhibitor. The main advantage gained here would be simplicity of use and thus better compliance. However, the same objection applies, in that failure would harm both classes of drugs.

A third alternative is to add or switch to a NNRTI based combination after a patient has failed an initial protease inhibitor. So far, no study has shown this to be an effective strategy. Many physicians have already employed this strategy by default, since there were few other choices left for many people. As a general rule, however, the more antiviral drugs people have used previously, the less responsive they are to the next drug or drugs. If researchers believe that protease inhibitors are the most potent drugs presently available, then there would be little reason to expect a NNRTI to work well after a patient fails on a protease combination. In contrast, in earlier stages of HIV infection, all drugs tend to be at their best. Thus, if researchers believe that NNRTIs are inherently any less potent than protease inhibitors, an argument can easily be made that suggests that if a person intends to use a NNRTI, it may be best to use it earlier, rather than later, in the course of disease.

Using an approach based with initial therapy based on a drug in the NNRTI class should have little or no effect on one's later ability to use a protease inhibitor combination.

These are difficult questions for which hard answers do not yet exist. The Federal Guidelines Panel will undoubtedly struggle with them for much of the next year or two. No one can say with absolute certainty which strategy (start with NNRTI vs. start with protease inhibitor) will produce the overall best response. The probable answer is that "it depends." Factors to consider include a patient's initial viral load, stage of disease progression, tolerance for side effects, etc. But for now, it seems clear that at least for some people, an initial therapy strategy based on a drug like efavirenz plus two NARTI's may make good sense. Researcher and clinicians need to be careful to avoid setting up any particular approach to therapy as hard dogma. New information must be allowed to lead to new strategies.

Abacavir

Abacavir is a new drug of the NARTI class. Preliminary results from a study combining abacavir with various protease inhibitors show good anti-HIV activity in almost all combinations tested. Seventy-eight people with an average CD4+ cell count of 349 and viral load of about 55,000 copies of HIV RNA, who have not been previously treated with any anti-HIV drugs, received abacavir + amprenavir (a new protease inhibitor described later in this article), abacavir + indinavir, abacavir + nelfinavir, abacavir + sgc saquinavir (Fortovase) or abacavir + ritonavir. The doses used were 300 mg twice daily of abacavir, 1200 mg twice daily of amprenavir, 800 mg three times daily of indinavir, 1200 mg three times daily of saquinavir and 600 mg twice daily of ritonavir. Results after 16 weeks were as shown in **Table 2**.

Table 2

	Median viral load reduction	% below 400 copies HIV RNA
ABA + amprenavir	2.42 logs	11/13 (85%)
ABA + indinavir	1.83 logs	7/10 (70%)
ABA + nelfinavir	2.49 logs	7/9 (78%)
ABA + saquinavir	1.98 logs	7/13 (54%)
ABA + ritonavir	1.63 logs	9/12 (75%)

ABA = abacavir

The most commonly reported side effects included nausea, vomiting, diarrhea and headache. Serious adverse events reported include fever, skin rash, diarrhea and drug reaction. Four people had to discontinue treatment due to hypersensitivity to abacavir. In all of the abacavir studies conducted so far, between 2 to 5% of the participants have developed hypersensitivity to the drug. This reaction is usually systemic (throughout the body) and includes fevers, malaise, nausea, vomiting and sometimes rash. The hypersensitivity appears relatively soon after starting abacavir (3-42 days) and resolves one to two days after stopping the drug. It is important NOT to try and take abacavir again (re-challenge) if there was hypersensitivity to the drug, as the subsequent reaction is potentially fatal.

Additional studies of abacavir have attempted to define its level of cross-resistance to other drugs in its class. These studies suggest that the drug will be most potent in people using therapy for the first time, but that the drug will still have a significant level of activity for people who developed resistance to only one or two other drugs of this type. However, its activity drops strongly in people who have developed resistance to two or more NARTI drugs.

Amprenavir

Results from a small study show that a combination of amprenavir and other protease inhibitors offers significant anti-HIV activity. Thirty-four people with an average CD4+ cell count of 393 and a viral load of about 44,000 copies of HIV RNA received either amprenavir + indinavir, amprenavir + sgc saquinavir (Fortovase®), amprenavir + nelfinavir or amprenavir + AZT + 3TC. The doses used were 800 mg three times daily of amprenavir, 750 mg three times daily of nelfinavir, 800 mg three times daily of indinavir and 800 mg three times daily of saquinavir (note

Expanded Access

Three new drugs are currently available in expanded access programs – abacavir (Ziagen ®, formerly known as GW1592), adefovir (Preveon®, formerly known as bis-POM PMEA) and efavirenz (Sustiva®, formerly known as DMP266).

Program Numbers:

Abacavir (NARTI) 800-501-4672
(for anyone failing current therapy and requiring an additional new drug for treatment strategy)

Adefovir (NARTI) 800-445-3235
(for anyone failing current therapy and requiring an additional new drug for treatment strategy)

Efavirenz (NNRTI) 800-998-6854
(for anyone failing current therapy whose CD4+ has ever gone below 400 and requires an additional new drug for treatment strategy)

whether antiviral activity might be restored in such people by putting them a combination of amprenavir, abacavir, and efavirenz. Results are not yet available from this study. For now, it seems unrealistic to expect this drug to be a remedy for people who have exhausted the previously available protease inhibitors.

Adefovir (formerly bis-pom PMEA) and Bis-Poc PMPA

No new data have been recently presented from studies of adefovir, even though the manufacturer hopes to see the drug approved in 1998. The drug, of a slight different class called Nucleotide Analogue Reverse Transcriptase Inhibitors offered only modest potency against HIV in earlier studies, showing an average viral load reduction of ½ log or less. However, since it may also have activity against CMV infection, it's dual activity may yet make it desirable, pending the outcome of the current studies.

Bis-Poc PMPA is another drug of the same type and from the same manufacturer, Gilead Sciences. Early studies have suggested that bis-poc PMPA is considerably more potent than its older brother, adefovir. Thirty-six people participated in a study of bis-poc PMPA (75, 150 or 300mg once daily orally). Most of the participants had previously received anti-HIV therapies (mostly nucleoside analogues, however about a third had been on a protease inhibitor). The design of the study was such that people had to discontinue taking their current medication before starting this study. Participants received a single dose of bis-poc PMPA followed by no drug for seven days and then drug for the next 28 days. The results at the end of the 28 days of therapy were as shown in **Table 4**.

The most common side effects reported in the study included elevated creatine kinase levels (an enzyme that measures muscular function) and elevated liver function tests. Previously we reported on the results of a study using intravenous (direct injection into the vein) PMPA. Studies to evaluate higher doses of bis-poc PMPA are planned for the future.

Table 3

	Median viral load drop	% below 400 copies HIV RNA	% below 20 copies HIV RNA
AMP + IDV	3.75 logs	5/6 (83%)	4/6 (67%)
AMP + SQV	2.94 logs	5/5 (100%)	2/5 (40%)
AMP + NFV	1.84 logs	3/6 (50%)	3/6 (50%)
AMP + AZT + 3TC	2.79 logs	2/3 (67%)	2/3 (67%)

AMP = amprenavir

that this is less than the recommended standard dose of saquinavir). None of the participants had previously taken a protease inhibitor. The results, after 16 weeks of the study are shown in **Table 3**.

Side effects noted in the study included diarrhea, tingling, numbness, nausea, vomiting, abdominal pain, flatulence and headache. Some preliminary drug interaction results shows that indinavir increases amprenavir levels by about 30-40% in blood. Amprenavir had no effect on indinavir levels.

The manufacturer reports that amprenavir does not appear to share patterns of resistance with other protease inhibitors and thus might still prove useful after other protease inhibitors fail. However, at least one major university disagrees with the finding. Moreover, an initial small NIH study in people who had failed prior protease therapy was discouraging, even though amprenavir was used in combination with abacavir and other NARTIs. An ongoing study is testing

FTC

Results from a small study of FTC (which is chemically similar to 3TC) shows very potent short-term anti-HIV activity. This study enrolled 10 people who had not previously taken 3TC and received 25 mg twice daily of FTC or 200 mg once daily of FTC for 14 days. At the end of the 14 day study, the results were as shown in **Table 5**

Both doses were very well tolerated with no significant side effects reported. One interesting observation from this study was that people on the low dose had no viral load reduction on the first three days of therapy while people on the higher dose had an immediate viral load reduction. Furthermore, the rate of reduction in viral load was greater in the group that received the higher dose. These are clearly very impressive results, especially since this study only looked at FTC alone. Furthermore, FTC has activity against hepatitis B virus and the possibility that FTC may be able to be taken just once a day makes this drug particularly attractive. However people who have developed resistance to 3TC are unlikely to benefit from FTC.❑

Table 4

	Viral load drop
Placebo	0.06 logs
25 mg PMPA	0.32 logs
200 mg PMPA	0.44 logs
300mg PMPA	1.22 logs

Table 5

	Viral load drop
25 mg FTC twice daily	1.4 logs
200 mg FTC once daily	2.1 logs

Interleukin-2 (IL-2)

Several studies confirmed the ability of interleukin-2 (IL-2, Proleukin®) to induce substantial CD4+ cell increases in HIV-infected people receiving antiviral therapy. Conflicting reports remain regarding the ability of IL-2 to effect changes in the rate of clearance of HIV, particularly HIV lurking in quiet reservoirs.

Dr. Fauci, the Director of the National Institute of Allergy and Infectious Diseases, echoed a theme heard throughout this year's Retrovirus conference - despite aggressive anti-HIV therapy a group of cells persists which are capable of producing viable and infectious HIV. These cells, it appears, are predominantly inactive or latent CD4+ memory cells in the lymph nodes and they may live for years. This reservoir of HIV remains an obstacle, requiring lifetime treatment to control HIV. There has long been an untested theory that activating these specific infected cells of the immune system, in the context of successful highly active antiretroviral therapy (HAART), could help flush out this reservoir and perhaps complete the elimination of HIV from the body. One way to do this might be by using IL-2, which activates CD4+ cells, in conjunction with HAART. Dr. David Ho's team is currently planning to test this approach in a group of people who have been successfully treated since the stage of acute infection. In a supportive finding, Dr. Fauci presented data from a laboratory experiment where infected cells were examined with or without IL-2 in the presence of anti-HIV therapy. When IL-2 was added, the reservoir of latent cells was activated and the result was a reduction in the number of infectious virions in the culture. Fauci's group is now going back to look at stored samples from a study of people receiving IL-2 in combination with HAART and comparing them to samples from people using HAART alone, to see if this same phenomenon happens in people.

Using IL-2 in eradication experiments in combination with anti-HIV therapy in treating people with acute infection certainly needs to be explored. This approach might be the extra push that helps the immune system clear or prevent the establishment of infections. Whatever the results of such an experiment, however, they cannot readily be transferred to people with established infection. The use of IL-2 therapy as part of an eradication regimen in the setting of established infection needs to be researched methodically and wisely. Simply adding IL-2 to an existing anti-HIV regimen is not likely to result in eradication. Whatever hope there is for eradication in people with established infection, it will obviously require the most optimal imaginable conditions, beginning with a perfect response to HAART, sustained long enough for all other reservoirs of infection to clear. Certainly we know that there are people using IL-2 in combination with potent anti-HIV regimen, whose virus is still measurable. This tells us that adding IL-2 therapy can't overcome imperfect viral suppression. We already know that antiviral therapy is not sufficient to achieve complete viral clearance. It is possible that there are some long-term HAART and IL-2 users whose virus has remained undetectable for many years at the most sensitive levels of detection. Such people should be sought out and offered intensive further laboratory work to see if clues about eradication can be learned from their immunologic and virologic experiences. If any such people are reading this and don't know where to turn for further investigation, call the PI Hotline for a referral. Several prominent laboratories

*Starting **January 1st 1998** you can still phone, fax or e-mail us at our old numbers, but our new street address will be:*

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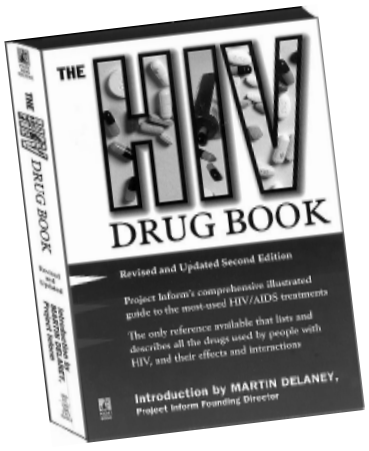

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A discussion of adherence to HAART...
And more.

are anxious to study people with such extremely positive experiences. The implications of Dr. Fauci's findings is simply that this issue needs to be explored, and strategies to purge the reservoir of infected cells needs to be made a priority if eradication is ever going to become a reality, either in acute infection or chronic infection.

An Italian study of varying doses of IL-2 in people with CD4+ cell counts ranging from 200 to 500 confirm the value of IL-2 in effecting substantial CD4+ cell increases when used in conjunction with anti-HIV therapy. The Italian study included 60 people who had never previously received a protease inhibitor. Volunteers included 35 men and 22 women who received varying doses and routes of administration of IL-2 with a 3-drug protease inhibitor containing regimen, or triple-drug therapy alone. Fifteen people were included in each group. A schematic of the study design is shown in **Table 1**.

After 6 months of therapy the mean percentage increase in CD4+ cell count over baseline values were 122% in group I, 96% in group II, 129% in group III and only 8% among those receiving only the 3-drug anti-HIV regimen. Viral levels decreased in all groups, as a consequence of 3-drug therapy, and no viral 'rebound' was noted among those receiving IL-2. The unusually poor CD4+ response among those receiving only 3-drug therapy may be a product of the protease inhibitor used in this study, which was the old formulation of saquinavir (Invirase®). This version of saquinavir maybe taken off the market in the United States due to absorption problems, and replaced with a new and improved version, called Fortovase®. The pop-ularity of Invirase® in some European countries continues to mystify most US researchers, since its inferiority compared to other protease inhibitors has been confirmed repeatedly. With those receiving IL-2, regardless of dose or route of administration, all had significant CD4+ cell increases to their pre-study levels.

A study in Spain looked at the use of IL-2 among people with CD4+ cell counts less than 250. Among a group of people initiating triple-drug therapy including a potent protease inhibitor, 21 people who had achieved viral suppression below the limit of detection of standard available tests, and sustained this reduction for at least 24 weeks, were given IL-2 or no IL-2. All study participants had previously been on NARTIs (e.g. AZT, ddI, ddC, d4T and 3TC) prior to initiating therapy with the protease inhibitor-containing regimen. Of the 21 people enrolled in the study, 11 received no IL-2 and 10 received IL-2 therapy. IL-2 was administered subcutaneously (by injection under the skin) at a dose of 3 MIU, once daily, for 5 consecutive days every 4 weeks for at least 6 cycles. The results from immunologic monitoring are shown in **Table 2**.

In this study, IL-2 in combination with a 3-drug anti-HIV regimen effected a greater increase in CD4+ cell counts then those observed among people receiving triple-drug therapy alone. Moreover, those receiving IL-2 experienced more pronounced rises in CD8+ cell counts. No significant changes were observed in viral levels. Side effects associated with IL-2 use were experienced by 70% of IL-2 users, but at this low dose were relatively mild, primarily fever and fatigue. Side effects were controlled with aspirin.

Table 1

Group	Therapy
I	3-drug protease inhibitor containing regimen in plus: 1) 12 MIU (million international units) IL-2 for 5 days, delivered intravenously (in the vein) every 8 weeks for 2 cycles followed by: 2) 7.5 MIU twice daily (total 15 MIU daily) for 5 days, delivered subcutaneously (injection under the skin) every 8 weeks for 4 cycles
II	3-drug protease inhibitor containing regimen plus: - 7.5 MIU twice daily for 5 days, delivered subcutaneously every 8 weeks for 6 cycles
III	3-drug protease inhibitor containing regimen in addition to - 3 MIU twice daily (total 6 MIU daily) for 5 days, delivered subcutaneously every 8 weeks for 6 cycles

Table 2

	IL-2 (Pre-study)	IL-2 (Week 24)	No IL-2 (Pre-study)	No IL-2 (Week 24)
CD4+	152	299	122	165
CD4%	11	17	10	12
CD8+	843	1086	841	825
CD8%	55	53	58	58
Memory Cells	432	486	582	592
Naïve Cells	774	996	530	644

Commentary

These two studies are among the first to address the use of IL-2 in people with lower CD4+ cell counts. Heretofore, information has been limited to very few studies, most of which were conducted in the pre-protease inhibitor era. Previous studies, not including protease inhibitor anti-HIV regimens, showed that people with low CD4+ cell counts did not appear to realize CD4+ cell increases with IL-2 and that stimulating the immune system with IL-2 may result in increases in HIV replication. The risk of increased HIV

replication, coupled with side effects associated with IL-2 use, resulted in a recommendation that people with CD4+ cell counts below 200 do not use IL-2. With the advent of more potent anti-HIV therapies, IL-2 is now being reexamined as an option for people with low CD4+ cell counts. The first study of this nature was conducted at the National Institutes of Health (NIH). Study results, reported a few years back, showed that in the context of protease inhibitor therapy, IL-2 appeared to be useful in bolstering CD4+ cell increases. In the NIH study, however, IL-2 was administered intravenously (continuous 5 day infusions, directly into a vein). The studies presented at this conference showed that IL-2, delivered subcutaneously (through injection under the skin), could effect positive CD4+ cell increases, and HIV replication was not impacted significantly. This is important information, as people can self inject IL-2 after being trained by their health care provider, increasing the ease of administering the drug. Moreover, side effects associated with subcutaneous administration are less dramatic than side effects seen when IL-2 is administered intravenously.

A large Phase III study, which will include people with CD4+ cell counts greater than 350, is expected to begin enrolling soon. This study will evaluate use of 2 different doses of IL-2, administered subcutaneous (by injection under the skin), delivered for 5 consecutive days, every 8 weeks. Volunteers will receive either IL-2 or no IL-2 and be allowed to take any anti-HIV regimen they and their doctor deem appropriate. Volunteers in this study may also elect to participate in a sub-study that will look at the effect of IL-2 on immune tissues, including the effect of IL-2 on the reservoir of quiet cells harboring HIV. To participate in this sub-study, individuals will be required to fly to the National Institutes of Health's (NIH) campus, in Bethesda, MD. As with most NIH-sponsored studies, airfare and accommodations will be supported by the NIH. ❑

Hydroxyurea - New Observations

Using drugs that inhibit HIV in different ways, and at different places in the virus' reproductive cycle may be important to maximally suppress HIV replication. Hydroxyurea appears to work against the virus differently than the currently available anti-HIV drugs, and thus it is particularly interesting.

This drug has been used in people for many years and is approved for the treatment of several types of cancer and is now "off patent" and thus relatively inexpensive. About five years ago Dr. Gallo and his group at the National Cancer Institute (NCI) found that hydroxyurea had activity against HIV. The drug inhibits factors made by human cells that HIV needs in order to reproduce, rather than directly inhibiting viral factors. All currently approved anti-HIV drugs target viral factors. The NCI group found that the anti-HIV activity of the nucleoside analogue reverse transcriptase inhibitors (NARTIs), such as AZT (Retrovir), ddI (Videx), ddC (Hivid), d4T (Zerit) and 3TC (Epivir), was significantly enhanced when they were combined with hydroxyurea. Additionally, because hydroxyurea targets cellular rather than viral factors, it may be more difficult for the virus to become resistant to this drug. Whereas HIV mutates very rapidly with each replication cycle, cells are much more stable. In fact, there have been no reports of resistance to hydroxyurea to date.

HIV more readily infects activated CD4+ cells which in turn produce more virus than resting or 'latent' cells. HIV can also infect resting CD4+ cells, however. These infected resting cells die off more slowly than the activated cells and act as a reservoir for HIV infection. Most of the approved anti-HIV therapies, with the exception of ddI, have better activity against HIV in activated cells. Hydroxyurea is more active against resting cells, however, making the combination of hydroxyurea and ddI attractive for targeting a reservoir not addressed by other anti-HIV drugs. Furthermore, recent studies have shown that virus is present, for many years, in people with viral loads below the limit of detection of currently available tests. In those studies, virus was still found in this resting pool of CD4+ cells that hydroxyurea and ddI are especially good at targeting.

If you think of the HIV replication process is similar to that of building a house using 2 by 4 wooden planks, then the NARTIs would be defective 2 by 4s, where if they are used in the building of the house the house would collapse (i.e. new virus will not be produced). But because of toxicity issues with the NARTIs, where you can only reach a certain dose before developing serious side effects, only a limited number of defective 2 by 4s will be in the wood pile and the odds of the construction worker picking up a defective 2 by 4 is small. Hydroxyurea, on the other hand, can be thought of as a shipment of functional 2 by 4s not showing up at the construction site. The house still has to be built but now the number of functional 2 by 4s available has decreased whereas the number of defective 2 by 4s remains the same. Therefore, the chances of the construction worker picking up and using a defective 2 by 4 have increased resulting in many more houses collapsing.

Recent reports on hydroxyurea in combination with other anti-HIV drugs have stirred interest in the research and HIV-affected communities. Most of the excitement has centered on observations in three people receiving hydroxyurea in combination with other anti-HIV drugs who subsequently have stopped all anti-HIV therapy. After attaining "undetectable" levels of HIV RNA, these people discontinued anti-HIV therapy for a variety of reasons. Normally, withdrawal of therapy results in renewed viral activity, but these three individuals have showed no signs of viral rebound (renewed viral replication). After as much a one to two years, they have continued to have HIV RNA below the limit of detection on the currently available tests.

One of these three people was a recent seroconverter (he had been infected for approximately 6 months at the time treatment was begun) and reported a viral load of about 85,000 copies of HIV RNA prior to initiating therapy which included ddI + hydroxyurea + indinavir (Crixivan). The individual's viral load quickly went below the limit of detection (500 copies of HIV RNA) after starting the 3-drug regimen. Subsequent tests also found him below the limit of detection of HIV RNA in bodily fluids and lymph tissue. This person developed hepatitis A and had to stop all three drugs after about 5 months. During the three weeks that the hepatitis A was active, the individual's viral load remained below the limit of detection despite having stopped anti-HIV

therapy. After the hepatitis symptoms resolved, the patient restarted the 3-drug regimen, but discontinued again two months later, choosing to forgo therapy altogether for the time being. Surprisingly, his viral load has remained below the limit of detection, despite stopping anti-HIV therapy, for over a year. Tests looking for viral DNA (virus already integrated into the cells) also proved negative in the blood stream. Additionally, it was very difficult to detect the presence of HIV in the lymph tissue of this individual. Only by using an extremely sensitive test was HIV genetic material (HIV DNA) found – one cell contained HIV among 60 million. It remains unclear whether the presence of HIV DNA in such a small proportion of cells is capable of rekindling productive HIV replication. Certainly for the time the patient has been followed, it has not been able to do so.

The other two people had very low viral loads when they initiated a regimen of ddI and hydroxyurea. They received this combination for about a year at which time they chose to stop taking the medications. Two years after stopping their anti-HIV medications, viral load remains below the limit of detection. However, HIV in the lymph tissue of these two individuals was much more easily detected.

While these reports are very unique and intriguing, they are not the result of controlled studies and almost certainly do not reflect a common experience among people using hydroxyurea. Controlled studies of hydroxyurea have not shown quite as dramatic anti-HIV responses, although none of the other studies used the drug in a three-drug combination with a protease inhibitor.

One of the largest studies of hydroxyurea to date involved 142 people with CD4+ cell counts between 200 and 500, who received ddI + d4T or ddI + d4T + hydroxyurea. The dose of hydroxyurea used was 500 mg twice daily. Most of the participants had received no previous ant-HIV therapy. The results after 12 weeks are shown in **Table 1**.

Another large study involved 80 people with a median viral load of about 58,000 copies of HIV RNA and CD4+ cell counts of about 300. Volunteers had either received no prior anti-HIV therapies or had received prior AZT or d4T. Participants received ddI + hydroxyurea or ddI alone for 12 weeks and then added hydroxyurea. The dose of hydroxyurea used in this study was 500 mg twice a day. The results after 24 weeks are shown in **Table 2.**

This study found that generally, people on the ddI + hydroxyurea combination had better antiviral responses than people receiving ddI alone. Additionally, people who started on ddI and added hydroxyurea after 12 weeks had an additional antiviral boost when hydroxyurea was added.

Table 1

Regimen	Viral load decrease	CD4+ cell count increase	% below 200 copies HIV RNA
ddI + d4T	1.6 logs	91	32
ddI + d4T + HU	1.9 logs	10	55

HU = hydroxyurea

More recently a study of 24 people, 10 of whom had primary HIV infection (were newly infected with HIV), received ddI + hydroxyurea + indinavir (Crixivan). The average duration of therapy so far is about a year. In all 24 people the combination effected viral load decreases to below the limit of detection (400 copies of HIV RNA). This finding itself is rather unusual, as few, if any, studies have reported 100% success rate in reaching "undetectable" levels of HIV RNA. On average CD4+ cell counts increased by 168. This finding too is unusual because most other studies of hydroxyurea reported little if any gain in CD4 counts. In fact, the lack of a CD4+ response has commonly been seen as direct consequence of the unique activity of hydroxyurea. However, this is the only study which employed the drug in a combination that included a protease inhibitor. This study group included the exceptional case of the person described above who has had no return of viral activity a year after stopping therapy.

Table 2

Regimen	Viral load decrease		CD4+ cells change		% below 500 copies HIV RNA	
	Week 12	Week 24	Week 12	Week 24	Week 12	Week 24
ddI	0.82 logs	1.2 logs	+48	+27	7/35 (20%)	10/33 (30%)
ddI + HU	1.13 logs	1 log	+11	-6	10/30 (33%)	13/30 (43%)

HU = Hydroxyurea

The optimal dose of hydroxyurea is still unknown. Studies have used hydroxyurea ranging from a low dose of 500 mg once a day to as high as 400 mg three times a day. The most studied dose is 500 mg twice a day, which is shown to have relatively few side effects. Studies are now planned to determine the optimal dose and dose scheduling for this drug. A small Canadian study enrolled 26 people with CD4+ cell counts between 100 and 300 , who had been on ddI for at least 6 months prior to enrolling Participants received one month of ddI alone and then received one month of ddI plus hydroxyurea (either 500 mg once a day or 500 mg twice a day) followed by one month of ddI alone. People receiving the twice daily dose of hydroxyurea had greater decreases in viral load, with an average drop of about 0.6 logs after four weeks on the combination therapy, compared to 0.02 log reduction for people on the once daily dose. There were no changes in CD4+ cell counts with either dose. When hydroxyurea was discontinued, viral load increased. Based on results from this study, the 500 mg daily dose of hydroxyurea is considered inadequate. Whether dosing needs to go higher than 500 mg twice daily remains to be seen. Because of it's unusual design and the lack of any 3-drug combination arms, this study can tell us very little about the ideal way to use hydroxyurea. New studies will explore more optimal uses of the drug.

The primary side effects noted with hydroxyurea have been bone marrow suppression which has led to decreases in neutrophils (neutropenia), red blood cells (anemia) and platelets (thrombocytopenia). Other side effects have been nausea, vomiting and rash, though these are uncommon. As with many drugs, people who start hydroxyurea therapy with a low absolute neutrophil count (less than 1500 cells/µL) were more likely to develop neutropenia, which can result in increased risk of developing bacterial infections. High dose hydroxyurea (doses used for treating cancer is about twice as high as that used for HIV) can suppress white blood cell production (in fact, that is what it is intended for – to suppress the excessive replication rate of cancerous T-cells).

Most hydroxyurea studies have been in people who have relatively intact immune system. While use of the drug in people with advanced disease has not been studied as extensively, there

♀ Self-Controlled HIV Prevention?

For women who have been following the development of microbicides for self-controlled methods to prevent infection from HIV and other sexually transmitted diseases, data were reported on PRO 2000 Gel, a virucidal (kills the virus) topical gel that does not appear to significantly disrupt or inflame the cells of the vaginal tract. This has been one of the hurdles in the development of these compounds because the irritation caused by some gels increases the risk of infection rather than decreasing it. PRO 2000 Gel will be moving into larger clinical studies to determine its effectiveness in preventing HIV transmission.

have been many anecdotal reports of people using hydroxyurea as part of a salvage regimen with good results.

It is very likely that hydroxyurea will play a useful role as part of a combination therapy against HIV. However, the optimal way of using this drug has still not been determined. Laboratory studies suggests that a combination of hydroxyurea and either ddI, abacavir (1592) or possibly f-ddA (a new nucleoside analogue currently in development) may result in better antiviral activity than when combined with AZT, ddC, d4T or 3TC. However, these are laboratory studies and the best NARTIs to use with hydroxyurea is still unknown. Hydroxyurea is clearly a drug that should be researched further, with its novel mechanism of action against HIV, added anti-HIV effect when combined with some, if not all, of the nucleoside analogue drugs and good side effect profile, it is likely to be a useful therapeutic option for people living with HIV. The sad thing is that has taken so long to discover and develop the useful properties of this drug against HIV disease, when it has been readily available from the earliest days of the HIV epidemic. Because the drug is "off patent," and will likely be offered generically once approved for HIV disease, this lack of clear financial opportunity has undoubtedly slowed its development.❑

Opportunistic Infections Update

The overall incidence of opportunistic infections (OIs) has significantly decreased since the availability of highly active antiretroviral therapy (HAART). While there is evidence that HAART results in significant and clinically relevant immune recovery in many people, it is not immediate and not complete.

Although the improved immune response associated with HAART has been shown to delay progression and relapse of various HIV-related infections, it may not control infections that have already started, and are just beginning to establish themselves, at the time that HAART is initiated. While the use of HAART has dramatically decreased the overall incidence of OIs, HAART doesn't work for everyone, for a variety of reasons. Thus, it has not eliminated all OIs nor has it eliminated the need for preventative or maintenance therapies in all cases. More research is clearly needed to determine the appropriate use of preventative and maintenance medications in this new era of anti-HIV treatment.

Mycobacterium Avium Complex (MAC)

A study recently provided insight into something being termed "MAC reversal syndrome." The study showed that individuals who already have MAC when initiating HAART sometimes have an unusual inflammatory response due to increased immune function. This syndrome involves fevers and the growth of a mass or masses usually around the neck or spine. The addition of prednisone appeared to lessen the inflammatory reaction. Over time, these individuals still benefited from HAART with dramatic decreases in HIV levels and increases in CD4+ cell counts and their MAC infection stabilized. Thus, HAART does not necessarily prevent MAC in persons fostering infection, but ultimately seems to be beneficial whether or not MAC occurs. While this study is small, it suggests that people who have active manifestations of MAC, such as fevers and other symptoms, should remain on HAART and anti-MAC therapies during such an episode.

Tuberculosis (TB)

A recent multinational study of 1583 people who were both HIV-positive and PPD-positive (positive for TB) found that 2 months of rifampin (600 mg once a day) + pyrazinamide (20 mg/kg once a day) was just as effective at preventing active TB as 12 months of isoniazid (INH) (300 mg once a day). INH has long been considered the gold standard for preventing TB. There was no difference in the magnitude of side effects between the two regimens. As expected, adherence in the 2 month regimen was significantly better, with 80% of people completing the 2 month regimen compared to less than half completing the INH regimen. This shorter course of therapy is particularly interesting because HIV infection is known to hasten the progression of TB disease as well as increase the rate of activation of latent TB infection. Furthermore, some studies have found that TB can further stimulate HIV replication. Therefore, a shorter course of therapy which might improve adherence would be particularly beneficial for people who are co-infected with HIV and TB. Additionally, this short-course regimen is likely to be less expensive than a year of INH–perhaps allowing countries which cur-

rently cannot afford the use of INH to start TB prevention campaigns. The rifampin + pyrazinamide combination provides a safe and effective regimen for the prevention of TB, however, there are significant potential drug interactions associated with the use of rifampin which may impact a person's decision to opt for this regimen.

Pneumocystis Carinii Pneumonia (PCP)

Several studies looking at PCP preventative regimens in the era of HAART still show occasional breakthrough cases of PCP. All studies confirm the use of TMP/SMX (Bactrim or Septra) as the first line preventative therapy. For those who are intolerant to TMP/SMX, data from two studies covering a total of 1057 people compared dapsone (100 mg once a day) and atovaquone suspension (Mepron) (1500 mg once a day) for the prevention of PCP. Results from the combined studies showed the two therapies to be equally effective. Additionally, there was no difference in the incidence of toxoplasmosis between the two groups. This was somewhat of a surprise since dapsone has been the drug of choice for those who can not tolerate TMP/SMX. Additionally, there has been concerns that the original version of atovaquone was not absorbed well into the bloodstream resulting in insufficient blood levels of drug to prevent PCP. The new studies used an improved formulation of atovaquone. People receiving dapsone were more likely to develop rash and anemia (a decrease in red blood cells) while people receiving atovaquone were more likely to experience gastrointestinal side effects. In this large study, people receiving atovaquone had fewer drug discontinuances than people receiving dapsone, suggesting that atovaquone may be preferable to dapsone for people who cannot tolerate the standard therapy (TMP/SMX).

A second study also confirms atovaquone as a useful second line therapy for PCP prevention for people who can not tolerate standard therapy (TMP/SMX). Four hundred and seventy-six people received aerosolized pentamidine (Nebupent) (300 mg monthly) or one of two doses of atovaquone suspension (either 1500 mg or 750 mg once a day). There were no differences in the number of PCP cases between the three groups. People receiving either dose of atovaquone were significantly more likely to develop rash while people receiving aerosolized pentamidine were more likely to develop bronchospasms.

Candidiasis

As with all other OIs, the rates of candidiasis or thrush have decreased. Several studies have looked at the role of maintenance therapy (to prevent the recurrence of thrush) for people who have a history of recurrent thrush but are responding well to HAART. One study found that withdrawal of azole-suppressive therapy, such as fluconazole (Diflucan) and itraconazole (Sporanox), for maintenance of recurrent thrush in people responding to HAART did not result in significant relapse. Only two of twenty people had any recurrence of candidiasis after withdrawal of maintenance therapy. In both cases, it was a single episode controlled with a short course of fluconazole and there was no further recurrence during the median 5 months of follow-up. This would suggest that for those people experiencing immunologic and virologic responses to HAART, need for maintenance therapy may lessen over time, as the immune system recovers.

For people with candidiasis not responsive to standard therapy, a small study found that 3 people resolved their disease with the use of GM-CSF (Leukine, 300 micrograms/subcutaneous (under the skin for 14 days) as an adjunctive therapy to fluconazole (400 mg/once a day). While the numbers here, again, are quite small, further investigation into the use of GM-CSF in this setting is warranted.

Cryptosporidiosis/Diarrhea

Nitazoxanide (NTZ) is an anti-parasite compound currently in tration for consideration for approval for its antidiarrheal activity. In studies, NTZ has been shown to decrease stool frequency by at least 50% in about 40% of people who have thus far received the drug. About 20% of people have had a complete response with no cryptosporium eggs (oocysts) detectable. NTZ is dosed at 500 mg twice a day and escalated to 1000 mg twice a day if no response is seen in a minimum of 4 weeks. This is the first evidence of a single drug having activity against cryptosporidiosis. It is likely that NTZ in combination with other antiparasitic drugs may have even better activity against cryptosporidiosis.

A recent study showed that paromomycin (Humatin) (1 gram twice a day) and azithromycin (Zithromax) (600 mg once a day), used in combination, may also be an effective treatment for cryptosporidiosis. This is important as neither drug alone has shown efficacy against this organism. In this study, volunteers experienced marked reductions in oocysts, 40% reduction in the number of stools per day and a reduction in overall stool volume per day.

CMV

In the search for new classes of drugs, fomivirsen (formerly known as ISIS 2922), an antisense drug against CMV, was studied in 28 people with newly diagnosed CMV retinitis. People received either immediate or deferred therapy. Participants were given 150 µg by direct injection into the eye once weekly for three weeks, and then put on maintenance therapy at 150 µg once every other week. The deferred therapy group had progression of their CMV retinitis in a median time of 13 days compared to 71 days for the immediate treatment group. The most common side effects were increased pressure in the eye. This study shows that fomivirsen may be a useful drug for the treatment of CMV retinitis. Additionally, laboratory studies show that fomivirsen is active against CMV which is resistant to other commonly used anti-CMV therapies such as ganciclovir (Cytovene), foscarnet (Foscavir) and cidofovir (Vistide). However, these results do not compare favorably with those seen from some other treatments for CMV, most notably the ganciclovir implants, which offer a much longer "time to relapse" than that cited here. Other new drugs under study for CMV include valgan-ciclovir, a new and much more potent form of oral ganciclovir. All studies of new drugs for CMV remain hampered by slow recruitment rates caused by the success of HAART in preventing new incidences of CMV.

Kaposi's Sarcoma

At last year's conference there were several anecdotal reports of resolution of Kaposi's Sarcoma (KS) occurring concurrent to viral load

♀ Cervical Cancer and Viral Load

Several studies looking at the role of HIV viral load as a predictor for disease progression and death have recently been reported. These studies confirm that high viral load is a predictor for disease progression. One study focused on the role of viral load in predicting an increased risk of pre-cancerous or cancerous cervical abnormalities. In this study of 2,000 women, those with viral loads greater than 50,000 copies of HIV RNA were at greater risk for developing squamous neoplasia (cancer) than those with lower viral loads. This risk for cervical cancers and pre-cancerous conditions also appear to be increased among women with lower CD4+ cell counts who have a history of human papilomavirus (HPV) infection. In addition, data from the Women's Interagency HIV Study (WIHS) have shown that women with CD4+ cell counts below 50 and viral loads greater than 500,000 copies of HIV RNA have the greatest risk of death. Although this may not be a surprise, it is another reason to consider treatment strategies to suppress viral activity and boost CD4+ cell counts.

decreases observed as a result of highly active anti-HIV regimens that included a protease inhibitor. This year a French group reported on 13 people with KS, 8 had cutaneous KS (skin lesions) and 5 had pulmonary (in the lung) KS. Participants were followed for 1 year after initiating a highly active protease inhibitor containing regimen. Study participants were also allowed to employ conventional chemotherapy for treating KS in concert with a 3-drug regimen. Among those with pulmonary KS, 3 of 5 experienced a complete response (i.e. resolution of KS) and 4 of the 5 are still alive 15 months after the initiation of the study. This type of response, particularly among people with pulmonary KS, has not been previously observed with chemotherapy alone. Among those with cutaneous KS, 4 of 8 experienced a complete response. Remission of KS, in this study, is also associated with a decrease in levels of HHV-8 (also known as KSHV), a herpes family virus believed to be associated with Kaposi's Sarcoma.

Another study showed a correlation with increases in viral levels and KS disease progression. A Chicago group presented information on 27 people with KS, identified between January 1996 and October 1997. In this group, rises in HIV RNA levels (greater than ½ log increase) proceeded KS disease progression. Of the 18 individuals who experienced a greater than ½ log increase in HIV RNA levels, all experienced KS disease progression within 2 months. The other 9 individuals observed had stable HIV RNA levels and only 2 of these individuals experienced KS disease progression within the study period. This would suggest that persons with KS who experience rises in viral levels should consider more frequent monitoring of viral load (e.g. repeat test within a few weeks) and consider making changes in their anti-HIV regimens. The flip side of this coin, in this study, is that KS improvements following decreases in HIV RNA levels were much more variable.

Commentary

Several of the studies described above suggest that we are entering a new era in the treatment and prevention of opportunistic infections. Although the data are not yet complete, it is becoming clear that when HAART is successful, it has a major impact on the occurrence of new opportunistic infections and on the need for continued maintenance therapy for those who had such infections previously. Under the best of circumstances, it appears that HAART results in a strengthened immune response which is sufficiently potent to allow discontinuation of OI maintenance therapies. Similarly, when HAART is effective, it sometimes eliminates the need for the preventative therapies previously employed at certain set CD4+ levels. However, how this applies to individuals is not at all clear. Studies have not yet provided enough information to predict who can and cannot safely forego preventative or maintenance therapies. In theory, there may someday be a measure of the strength of immune response which would make it easy to know who can and cannot forego these therapies. For now, it seems largely a matter of guess work, and thus, a decision which comes with considerable risk.

While we lack precise knowledge on how to make decisions about OI prevention and maintenance today, we do know a few things which might help guide such decisions:

➔ First, it is clear from a number of current studies that restored immune response is not an immediate consequence of HAART,

While we lack precise knowledge on how to make decisions about OI prevention and maintenance today, we do know a few things which might help guide such decisions

but rather one which develops slowly over time. Thus, it would seem prudent for people to wait at least months to a year while maintaining a strong HAART response before making any changes in preventative or maintenance therapy.

➔ Secondly, it seems logical that the risk of withdrawing preventative therapy would be lowest in people who never had any kind of an OI prior to their use of HAART.

➔ Third, it is also logical to expect that those people who have the strongest and best sustained immune response to HAART, as measured by CD4+ cell increases and level, stand the best chance of successfully foregoing OI preventative or maintenance therapy.

➔ Finally, an individuals tolerance for the risk of getting an OI must be measured against each individuals tolerance for taking additional drugs and coping with additional drug side effects.

Over time, better measures of immune response, including perhaps tests which might predict an individuals capacity to response to specific OIs might become routinely available. Until such time, the issue of OI preventative and maintenance therapy will be a highly individualistic matter, one which must be decided very carefully by each individual and his or her physician. In extreme examples – people with the best and worst responses to HAART – the decisions are relatively easy to make. For those who fall between, however, it remains a subject which must be addressed with great care. Each significant OI, if and when it comes or recurs, has the potential to do serious and lasting harm, as well as to derail otherwise stable treatment with HAART. ❑

HIV Surveillance Discussion Paper

Concerned about HIV reporting requirements? New thinking has led some AIDS agencies, as well as the CDC, to reconsider the question of whether HIV status should be reported, by name or by number. Project Inform's Public Policy Department has created a new, in-depth analysis of the issues. Too large to fit in the *Perspective*, instead find it on the PI Website or call the Hotline and ask for "*The HIV Surveillance Discussion*

Hepatitis in HIV disease

Liver problems are a frequent cause of disease and sometimes death in people with HIV. Technically, any significant irritation or inflammation of the liver is called "hepatitis," but the term is more commonly used to refer to several infections of the liver. The majority of such liver diseases in people with HIV are caused by viruses, especially hepatitis B virus (HBV) and hepatitis C virus (HCV). Other organisms that may cause liver disease include cytomegalovirus (CMV), Epstein-Barr virus (EBV), mycobacterium avium complex (MAC), toxoplasmosis and histoplasmosis. Studies have shown that almost a quarter of people with HIV is also co-infected with HBV. Additionally, many drugs used in the treatment of HIV disease can also cause forms of liver disease or hepatitis as a side effect of their activity.

This article focuses on the most common forms of viral hepatitis – those that are induced by an infectious agent. More than five types of hepatitis (A-E) have been identified. Hepatitis A and E are mainly transmitted through sexual contact while hepatitis B, C and D are primarily spread through blood or other body fluids. This article will deal primarily with hepatitis A, B and C. The symptoms of the various hepatitis viruses are quite similar, with all causing elevated levels of liver enzymes. Hepatitis A virus (HAV) most commonly causes high fevers, jaundice (yellowing of the skin and eyes), nausea, diarrhea, fatigue, abdominal pain, dark urine, vomiting and loss of appetite. HBV most commonly causes fatigue, jaundice, vomiting, abdominal pain, nausea and anorexia. HCV most commonly causes fever, appetite loss, jaundice, nausea, diarrhea and vomiting. Diagnosis of the various hepatitis viruses is usually done by a blood test. It is important to get an accurate diagnosis so that sex partners and people living in the same household can take appropriate preventative measures. Recent advances have led to the development of technologies, such as polymerase chain reaction (PCR) tests and branched DNA (bDNA), to monitor hepatitis levels in blood. These are the same technologies currently used to measure HIV RNA levels (viral load). Currently, these tests are available for investigational use to measure HBV and HCV levels.

Hepatitis A

Travelers who visit countries where HAV is common and sexually active gay men are particularly at risk for developing hepatitis A. The virus can be contracted through contact with infected people, by drinking contaminated water or by eating contaminated food. Additionally, gay men are most often infected through sexual contact, especially through oral-anal contact with infected persons. A person is most infectious about 2 weeks before the onset of jaundice. Although HAV can be found in saliva, it is very unlikely that it can be transmitted by saliva. HAV very rarely results in chronic liver disease.

Prevention

Hepatitis A can be easily prevented. Vaccination is the most effective method of preventing HAV infections, however, maintaining good personal hygiene, such as routinely washing hands, has also been shown to be successful in interrupting outbreaks when the mode of transmission is from person to person, including sexual contact. Hepatitis A vaccines (Havrix and Vaqta) are 94%-100% effective in preventing HAV infection. An initial injection with the vaccine protects adults for up to a year and a second booster shot is given 6 to 12 months later. The second dose provides long-term protection against the virus. Immune globulins (IG) are also sometimes used to prevent hepatitis A. IG is over 85% effective in preventing HAV infection, however, the period of protection is relatively short (usually between 3 and 6 months depending on the dose of IG used).

Post Exposure Prevention

People who have recently been exposed to HAV (household or sexual contact with someone who has hepatitis A) should consider post exposure prevention. People who have not been vaccinated against HAV should receive IG within 2 weeks of exposure. People who were vaccinated at least a month before exposure do not need IG.

Treatment

There are no treatments for hepatitis A. Most people clear the infection on their own (without medication) and usually people will only develop hepatitis A once. Therapies that may cause liver damage or which are metabolized (broken down) in the liver should be used with caution.

Hepatitis B

Almost everybody is at risk for developing hepatitis B. This includes health care workers, people who are sexually active, injection drug users, people who require blood or blood products, prisoners, infants born to mothers who are infected with HBV and people who have intimate

♀ HIV and the Genital Tract

The presence of HIV in the genital tract has been previously reported, with several studies showing that reductions in viral load in this compartment correlate with decreases in blood for individuals on highly active antiretroviral therapy (HAART). However, recent studies have shown that HIV is also produced in cells in the genital tract and can have unique resistance mutations compared to those in blood. In addition, viral load can sometimes be measured in the genital tract in the presence of infections or invasive procedures, even when it is not measurable in blood. This is important because many have assumed that undetectable virus levels in blood, using the currently available tests, automatically means undetectable virus levels in the genital tract. These findings have implications for both perinatal and sexual transmission, but further research is required.

Project Inform Hot Line!

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:

1-800-822-7422

contacts or live with people with chronic HBV. Most cases of HBV (30%-60%) are believed to be sexually transmitted. Infection with HBV virus often induces a temporary stage of acute infection when a person feels seriously ill with fevers, liver pain and swelling and severe fatigue. This period usually lasts from as little as one week to as long as month, after which the patient recovers symptomatically. However, some people go on to develop a chronic form of HBV infection. Chronic HBV infection develops in up to 10% of people infected as adults, which increases their risk of developing chronic liver disease as well as transmitting HBV to others. Additionally, people who are co-infected with HIV and HBV are more likely to develop chronic HBV infection. Chronic HBV infection can take two general forms. In most people who develop chronic HBV, the disease is largely benign and without significant symptoms. It's presence is detected only through blood tests. In a small percentage of people, chronic HBV takes an aggressive form, producing bouts of symptomatic illness. Over time, this aggressive form of chronic HBV can lead to liver failure and liver cancer. Regardless of which form chronic HBV takes, chronic carriers are believe capable of transmitting the disease to others.

Prevention

Vaccination is the most effective method of preventing hepatitis B infection. However, most researchers recommend that gay men and injection drug users be screened for hepatitis B antibodies (evidence of previous HBV infection) before being given the vaccine. Hepatitis B vaccine (Engerix-B and Recombivax HB) is usually given in a three dose cycle. The first dose is about 50% protective, the second dose 85% protective and the third dose is typically 90% protective. The second dose of the vaccine should be given at least one month after the first and the third dose should be given at least 4 months after the second dose. It is important to complete the entire regimen, as the third dose is required to provide long-term protection. Some studies suggests that people with HIV may not get the same response to the vaccine as someone who is not infected with HIV. Therefore, it is currently recommended that people with HIV who are vaccinated check for hepatitis B surface antibody levels (an indicator of how protective the vaccine might be) 1-2 months after the third vaccine dose. People should consider revaccination with three more doses if no or very low levels of antibodies are detected.

Post Exposure Prevention

People who have sexual contacts with someone who has acute hepatitis B should receive hepatitis B immune globulin (HBIG) and hepatitis B vaccine within 14 days after the most recent sexual contact. Adults who live in the same household as someone with acute hepatitis B are generally not at risk for infection. However, it is recommended that children and adolescents be vaccinated against HBV. Furthermore, if the person still has detectable hepatitis B surface antigen (a marker of hepatitis B infection), then everyone in the household should be vaccinated. Hepatitis B vaccine is currently recommended to prevent HBV transmission for people with casual/household and sexual contact with people who have chronic HBV infection.

Treatment

No treatment is approved for people with acute HBV infection. Interferon alfa-2b (Intron A) is the only therapy currently approved for the treatment of chronic hepatitis B. Studies have shown that it is about 40% effective in eliminating chronic HBV infection, with people who were infected during adulthood more likely to respond to this treatment. Some studies suggest that people with HIV have a lower response rate

♀ AZT and Mother to Child Transmission

The reduction in HIV transmission from mother-to-infant with the use of anti-HIV drugs has been a remarkable success story. However, it has not been a reality for many nations where the complexity of the therapy regimen, along with poor access to the necessary drugs, inadequate prenatal care, wide scale malnutrition and the potential for transmission through necessary breast feeding, has blocked the ability to share in this major advance. Results from a new study in Thailand show the success of a simplified regimen of AZT which reduced by 51% the mother-to-child transmission among women who are not breast feeding (from 18.6% without AZT to 9.2% with AZT). In this study, women were given 300 mg. AZT twice a day orally starting approximately 26 weeks after conception through birth. Unlike the standard US regimen, the babies were not given AZT after birth, nor were the mothers given AZT intravenously during labor.

This greatly simplified regimen offers a more viable possibility for women in developing countries, even if it is slightly less efficacious (the US regimen produced a 66% drop in transmission, versus 51% for the simplified regimen.) This simplified AZT regimen will be less costly, potentially allowing many developing nations to implement a useful campaign to reduce mother-to-child transmission of HIV. Further research will need to be done to determine the effectiveness for women who are breast feeding and whether still simpler regimens might be found for women who do not access care until delivery.

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, **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, **consider a more aggressive 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 for at least six months.**
- If CD4+ count stays below 75, **intensify monitoring,** consider prevention against MAC/MAI and CMV infections. **Learn about preventive therapies.**

to interferon therapy than people who are not HIV infected. Interferon alfa-2b is usually given three times a week for 16 weeks or longer, subcutaneously (under the skin) or intramuscularly (into the muscle). A significant number of people develop side effects while on this therapy, with fevers, fatigue and headaches being the most commonly reported.

Several therapies are currently being studied for the treatment of HBV, including interferon alfa-2a (Roferon-A), interferon alfa n3 (Alferon N), lamivudine (3TC, Epivir), famciclovir (Famvir), lobucavir, thymosin alpha, adefovir dipovoxil (Preveon) and FTC. Preliminary results have shown that lamivudine, famciclovir and adefovir dipovoxil are all effective in reducing hepatitis B levels (HBV DNA levels) in blood with some normalization in measures of liver function.

Hepatitis C

Hepatitis C is mainly contracted through body fluids, primarily blood or blood products, sharing needles, mother-to-child transmission and through sexual contact. Only about 25% of people infected with HCV develop symptoms after the initial infection. These symptoms, usually flu-like such as fever, fatigue, muscle and joint pain, nausea and vomiting, appear within 2-8 weeks after exposure. Because the symptoms of HCV are usually milder than those of HAV and HBV, they often go undiagnosed. Furthermore, because most people infected with HCV do not have symptoms, they are more likely to become chronic carriers of the virus and unknowingly infect others. Chronic HCV develops in up to 85% of HCV infected people and about 70% develop some form of chronic liver disease. While the total incidence of HCV is lower than that of HBV, it is spreading more rapidly and the severity of the disease is far worse. For instance, end stage HCV infection is now the leading indicator for liver transplantation and chronic HCV also increases the risk of liver cancer. Recent studies suggest that the course of HCV-related liver disease is accelerated among people who are co-infected with HIV and HCV. Another study found that people who were co-infected with HAV and HCV were significantly more likely to die from sudden liver failure. Often times, by the time HCV is diagnosed, the liver is already severely damaged. The concurrent use of alcohol considerably increases the risk of progression of liver disease. HCV, like HIV, is a very difficult virus to treat because it can mutate quickly and develop many different quasi-species (slightly different than the original virus) which escapes the immune response.

Prevention

There is no effective vaccine against HCV. Because of the numerous subtypes of HCV, the development of an effective vaccine is especially difficult. Currently, the only method to prevent transmission of HCV is to practice safe sex and to make sure that needles are sterilized (this includes needles used for tattooing, body piercing and acupuncture).

Treatment

The only approved treatments for hepatitis C is interferon alfa-2b and interferon alfa-2b. Since most people relapse after therapy is stopped, treatment may need to be continued indefinitely. However, the current recommendation is to use interferon alfa three times a week for at least a year. There is also preliminary evidence that treating acute hepatitis C may reduce the risk of developing chronic disease. Some preliminary results also show that the combination of interferon alfa-2b with ribavirin (Virazole and Rebetol) is more effective than either drug alone. Preliminary results from other studies have also shown that interferon alfa-n3 may be more effective than interferon alfa-2a and –2b, while yet another interferon – consensus interferon – shows promising activity. Because of the rapid rate of mutation seen with HCV, it seem logical to expect that combination therapy may be more effective and more durable than monotherapy.

Several studies have shown that people who are co-infected with HIV and HCV have significantly higher HCV levels (HCV RNA levels) than are seen in people who are infected with HCV alone. One small study also showed that hepatitis C viral load levels temporarily increased significantly after starting highly active antiretroviral therapies (HAART). However, HCV levels returned to pre-HAART levels after 17-32 weeks while continuing on HAART. The researchers speculated that HAART results in a better immune response, destroying more HCV infected liver cells, which could result in the release of HCV particles. Many researchers are now measuring HCV levels before initiating HAART and closely monitoring that level after starting HAART as there have been a few reports of reactivation of hepatitis C. Currently, there is no good data to guide physicians in making treatment decisions for HCV based on HCV viral load, since no long-term natural history studies have yet been conducted. What constitutes a "high" or "low" HCV viral load has not yet been determined, nor do we know how various viral load levels correlate to outcomes of disease and death. Several other therapies are being studied for the treatment of hepatitis C including thymosin alpha, interferon beta, oral alpha interferon and amantadine (a common flu drug).

Summary

A vaccine and treatments for hepatitis C are desperatley needed. An effective public health campaign needs to be implemented to alert the public about the dangers of hepatitis, especially hepatitis C. Since the route of transmission for HAV, HBV and HCV is similar to that of HIV, many people are co-infected with these viruses. It is important for people to find out whether they are co-infected so that an appropriate treatment strategy can be put together. People co-infected with HIV and HBV should talk to their physicians about the various treatments for HBV and HIV. Some therapies are active against both viruses. Combination therapy will likely result in better activity against hepatitis B

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**

and hepatitis C. However, some therapies may be broken down in the liver and may cause liver enzymes to increase, potentially aggravating the hepatitis. On the other hand, for someone who is HIV infected but not infected with HAV or HBV, then vaccination should be considered.❑

Progressive Multifocal Leukoencephalopathy (PML)

PML is a rare AIDS-related condition, caused by the JC Virus. Between 80 to 85% of all adults, world wide, are exposed to this virus at some time in their lives, but it only appears to cause disease in people with a weakened immune system. Prior to AIDS, PML was rarely seen except in people with cancer or who received bone marrow transplants. Today, the majority of all PML cases occur in HIV-infected people, primarily those in advanced stages of disease with very low CD4+ cell counts. It can occasionally appear in people with CD4+ counts as high as 400, however, and is the first AIDS-defining condition diagnosed in about 1% of people with HIV. Because it is so rare and because it affects the brain, an organ that is difficult to study, its diagnosis and treating are poorly understood.

Treatment

Heretofore, a diagnosis of PML was quite grim. The one therapy used for treating it, a toxic antiviral called ARA-C (cytosine arabinoside, Cytosar-U®), delivered through a shunt directly into the brain, has shown marginal, if any, evidence of benefit. The average time from diagnosis of PML to death, prior to the availability of highly active anti-HIV therapies (HAART) including a potent protease inhibitor, was 1 to 3 months. It is unclear why, if the majority of people with HIV are infected with the JC virus, the incidence of JC virus-related disease remains so low. When it does strike, however, the disease course can be quite rapid. The infection rapidly forms lesions on the brain and begins affecting various functions controlled by the brain and nervous system. The most frightening aspect of PML is that there is no "usual" course of disease. Whatever functions are controlled in the area of the brain being ravished by the JC virus will determine the manifestations of PML. For example, if the virus strikes the part of the brain that controls sight, vision could be lost. If it strikes the part of the brain that controls speech or motor skills, one could lose the ability to talk or walk. There is no predicting where or how the virus will attack, and thus what functions will be impaired.

Prior to the availability of HAART, there has been little encouraging news with regard to PML. But several groups at the recent Retrovirus Conference reported symptom-free survival after a PML diagnosis of over two years and counting for some patients using HAART. An Atlanta group reported on factors associated with survival among 375 people with HIV and PML. The median survival after a PML diagnosis was 1 month, overall (including people with PML in the pre-protease inhibitor era). Additionally, about 85% of those diagnosed with PML had died within 6 months of diagnosis. Prolonged survival (greater than 6 months) was associated with use of protease inhibitors and other anti-HIV therapies.

In a study reported by a French group, 71 people diagnosed with PML between January 1990 and September 1997 were observed for factors influencing survival. Many were diagnosed in the pre-protease inhibitor era. PML was the first AIDS defining event for about half of the study participants. It was the event that led to an HIV diagnosis in 8 of the volunteers, suggesting it was the first serious symptomatic illness they experienced. A little less than half of the individuals had been on anti-HIV therapy prior to PML diagnosis. This study showed that of those participants who had previously been on anti-HIV therapy, those who modified their regimen after the PML diagnosis, had a longer survival (10 months) than those who did not change therapies (3 months). Moreover, those individuals employing an anti-HIV regimen that included a potent protease inhibitor had prolonged survival (12 months compared to 3.5 months among those not using protease inhibitors). Among those using a protease inhibitor containing regimen since their broadened availability in 1996, over half (54.2%) are still alive. Seven people have survived more than two years after their PML diagnosis.

A second French group looked at the use of cidofovir (Vistide) for PML. People received cidofovir through an expanded access program and all were receiving HAART. While this observational group is quite small, a preliminary look at survival rates suggests that cidofovir may be useful PML therapy for some people. A prospective study to evaluate this effect is underway. Cidofovir is an approved treatment for CMV retinitis.

In Spain, another group studied use of HAART in 13 people with PML (12 of 13 also received Ara-C). The median survival time post PML diagnosis was 273 days. Historical results suggest that in this particular population, survival is typically about 72 days. Thus, triple-drug therapy nearly quadrupled survival time post PML diagnosis.

Diagnosis

Diagnosing PML is tricky. Many HIV-related conditions produce similar initial symptoms.

PML, toxoplasmosis, and even herpes virus infections in the brain can have similar appearances on an MRI scan, which is equivalent to an X-ray of the brain. Because the lesions can look similar, it's important to pursue definitive diagnosis by means of a brain biopsy so that the cause can be determined appropriately. A small hole is drilled in the skull and a piece of tissue is collected and analyzed. If the JC virus is found in the tissue, a diagnosis of PML is made. A brain biopsy is quite invasive, however, and therefore less invasive diagnostic techniques need to be developed. A lumbar puncture (i.e. spinal tap) is hardly non-invasive, but compared to a brain biopsy it's far more palatable for many people. The use of polymerase chain reaction (PCR) technology, the same technology used in the new tests to measure HIV levels, to look for the presence of the JC virus in cerebral spinal fluid is currently under investigation.

Among people with HIV, about 30% without and 70% with PML have detectable JC virus in the blood circulation. Given the large percentage of people with measurable levels of JC virus without PML, using blood as a source for diagnosing PML is not practical. Far too many people without PML could be misdiagnosed as having PML. Exploring the use of cerebral spinal fluid (CSF) to diagnose PML may provide a median ground. Dr. Major, of the National Institutes of Health, has presented data showing that 80% of people with PML confirmed by brain biopsy have JC virus in the CSF. While this provides a step toward a simpler diagnostic tool, it's still not without problems. Dr. Major presented information showing a very small number of people with other (not PML) neurological conditions who also had the JC virus measurable in the CSF. When it comes to neurological manifestations, appropriate diagnosis is critical. For example, herpes infections in the brain can produce symptoms similar to those of PML, yet these infections may be readily and easily treated with a 21-day course of intravenous acyclovir (Zovirax). Until the technology is further refined, using CSF as a primary mode of diagnosis may lead to misdiagnosis. The beginning of research into this field is long overdue, however, and these first steps toward less invasive diagnostic techniques are extremely important.

While there are no standard of care guidelines regarding anti-HIV therapy and PML, the numerous reports outlined above suggest it would be fair to make a few assumptions. After presumptive diagnosis with PML, regardless of whether an individual elects a brain biopsy for definitive diagnosis, initiating or changing a HAART regimen seems advisable. The studies outlined above, in conjunction with anecdotal reports of complete resolution of PML lesions after initiating HAART are extremely encouraging. Survival after PML diagnosis among those initiating HAART, in a number of reported cases, is 2 years and counting.❑