

Report from the HAARTland

This year's Sixth Conference on Retroviruses and Opportunistic Infections, held in Chicago January 31 to February 4, presented a mixed bag of new data on the treatment of HIV disease. Depending on whose needs were at stake, conference presentations provided either encouragement by offering a number of potentially improved first line therapy options, or frustration by showing few prospects for people who have already exhausted current therapy options. If there was any bottom line message appropriate for everyone, it was that making the best possible use of currently available therapies remains the most important challenge faced by every HIV-infected person.

Options for "Third Line" Therapy?

Good news at the far reaches of the HIV therapy experience—for people who have become unresponsive or intolerant to all currently available therapies—was limited perhaps to one small study of a single drug. An initial dose-ranging study of the new fusion inhibitor, T-20 (pentafuside), gave the drug to one of the most difficult patient populations ever treated in a clinical trial setting. Volunteers in the study had previously used an average of nine drugs, including three protease inhibitors. Despite the high level of resistance to previously used treatments, people using T-20 showed at least some significant suppression of HIV, even when it was used alone (i.e. not in combination with other anti-HIV medications). There were, of course, serious limitations to this finding and no one suggests that the drug should be used alone. The details of the success and tribulations of the T-20 study are described

in *Third Line Therapy Options* on page 9.

The next glimmer of hope for people losing their response to current therapies involved a surprising finding in a French study. The study suggested that the new protease inhibitor, amprenavir, might work better than other protease inhibitors in people who previously developed resistance to another drug of this class. The usefulness of this finding, however, may be limited to people who have had prior experience with only one other protease inhibitor. Data from studies with people who had become unresponsive to multiple protease inhibitors weren't nearly as encouraging. More about amprenavir can be found in the box *Expanded Access Programs* on page 13.

Most other news for people in need of third line therapy (people who have failed two or more previous treatment combinations) centered on the use of a combination of a large number of drugs. While typical antiviral regimens use three or at most four drugs, new third line regimens

employ anywhere from five to nine drugs. While a few small studies employing this methodology reported seemingly encouraging results, many scientists and clinicians remain skeptical about long-term tolerance and adherence to the extremely complex dosing requirements the drugs require. Still, it's nice to know that something appears to work. More information can be found in *Third Line Therapy Options* on page 9.

Beyond these meager examples, hope for the person with extensive prior use of anti-HIV therapy came only from a sprinkling of reports about new drugs in early stages of development, most commonly new protease inhibitors and new non-nucleoside reverse transcriptase inhibitors (NNRTIs). The sponsors of these experimental drugs often assert the hope that the drugs will be active despite prior resistance to other drugs in the same class. However, history suggests that such claims are all too easy to make in early stages of drug development and vastly more difficult to prove in later clinical applications.

"Class-Sparing" Initial (First Line) Therapy

For people just starting therapy, the outlook is somewhat improved. Debate continues about the various "protease inhibitor-sparing" regimens and the even newer "NNRTI and protease inhibitor-sparing" regimens. In general, the goal of these "class-sparing" regimens is to save one or more classes of antiviral drugs for later use, hopefully delaying side effects and achieving a longer period of effective treatment. The first protease inhibitor-sparing regimen was described nearly two years ago at the Vancouver conference. A study of nevirapine (Viramune) plus two older nucleoside drugs, AZT (zidovudine, Retrovir) and ddI (didanosine, Videx), appeared to sup-

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press virus to below the limit of detection of HIV RNA tests for about a year. Though this early study used a less than ideal combination, it clearly demonstrated that three-drug combinations without a protease inhibitor could be effective, at least for a number of people just beginning therapy. The concept was bolstered by reports the following year of an ongoing study of efavirenz (Sustiva) plus two nucleosides (AZT and 3TC). After 48 weeks, this combination now appears to be roughly equivalent in potency to a typical protease inhibitor-based three-drug combination.

This year, additional studies with nevirapine-based or delavirdine-based (Rescriptor) three-drug combinations seemed to confirm the picture. Due to differences in how the studies were run and analyzed, however, it is not currently possible to say whether any one NNRTI makes a better basis for combinations than others. Even more importantly, each of the three NNRTIs differs somewhat in side effects, drug interactions and cost, which suggests that choosing one will always be a somewhat individual choice.

Why would anyone want to use a NNRTI combination instead of protease inhibitor combination? Proponents of this approach hope to solve three problems. First, the NNRTI class is generally easier to use than protease inhibitors (PIs), making adherence easier and more likely. Second, there is a growing concern about long-term side effects associated with protease inhibitors, such as the various forms of fat redistribution. If these problems are truly caused by PIs, then it might make sense to use an alternative regimen as first-line therapy. That way, the side effects of PIs could be delayed. Third, preserving the use of potent PIs for later use might offer a better long-term strategy, allowing people to fully utilize the benefits of two other classes of drugs before moving to the PIs.

However, not everyone agrees that starting treatment with a NNRTI-based combination is the wisest approach, even if it seems to work fairly well. Critics point out that only protease inhibitor-based combinations have thus far demonstrated long-term viral suppression for three years or more, while PI-sparing regimens have only been tested for a year. Another concern is that us-

ing a NNRTI as first line therapy will probably eliminate this whole class of drugs later in the course of HIV infection. This is particularly a concern if a person needs third line therapy after protease inhibitors have begun to fail. For people at this end of the treatment spectrum, often the only thing that works is a combination of many drugs, including first time use of the NNRTI class of drugs. If the NNRTI drugs were used earlier (to the point of failure), there is almost nowhere else to turn for third line therapy. Therefore, many physicians and researchers believe it may be more important to preserve the NNRTI class for later use. The arguments on both sides of the issue seem reasonable.

So if using a NNRTI combination to "spare" the protease inhibitor for later use might not be the wisest strategy, what about combinations that spare both the NNRTI and PI classes for later use? If sparing one class of drugs has some advantages, why not spare two classes? Studies have already begun to test this approach. These NNRTI and PI-sparing regimens employ three-drug regimens made up entirely of nucleoside analogue drugs (NARTIs), or two NARTIs plus hydroxyurea. Some of these studies have shown fairly impressive success in suppressing virus below the limit of detection in a majority of users. None, however, have yet reported results beyond 24 weeks. If this kind of regimen can effectively keep viral levels below the limit of detection in most people for a year or more, this may present an important option for wringing the longest possible period of success from the currently available drugs. These studies are described in *Class-Sparing Treatment Therapies* on page 5.

Of course, no strategy satisfies everyone. Still another group of researchers wonders whether the best overall approach might simply be to combine all three current classes of drugs into a single, highly potent mix. Theoretical arguments suggest this approach might lead to the best and longest suppression of HIV. But when such a regimen fails, it runs the risk of using up all three classes of drugs at once.

Whatever the answer, the overall message here seems to be that there are now several viable approaches for starting first line therapy. Each

In Memory Of . . .
 We dedicate this issue of the
PI Perspective to:
Bob Chapman
Paul Joseph Corser
Jeff Jones
Reggie Williams

Their memory lives on in the
 work that lies ahead of us all.

has theoretical advantages and disadvantages, but there are no long-term studies which can tell us which makes for the best long-term strategy. Read more about these and other initial therapy options in *Options for First Line Therapy* on page 7.

Coping with Long-Term Therapy

Many patients and physicians had high hopes that the Chicago conference would provide greater understanding of the side effect problems facing people on aggressive combination therapy. Concerns have reached a serious level about a class of side effects generally referred to as metabolic complications in therapy. The most widely discussed complication is the syndrome of effects sometimes called lipodystrophy, simply translated as a disturbance in the way the body processes fats. The effects of lipodystrophy include obvious physical effects such as the following:

- the accumulation of hard fatty deposits at the top of the spine (*buffalo hump*),
- loss of fat or wasting in the face and limbs (facial/limb wasting),
- accumulation of fat in the abdomen (or *protease paunch*, though it may not be strictly related to PIs),
- breast enlargement, in both women and men.

Related phenomena detected by lab tests include elevated cholesterol and triglyceride levels, insulin resistance and diabetes.

Despite an entire symposium devoted to these troubling issues, most people came away from the Chicago Conference disappointed since so little new information was offered. For the most part, presentations were simply updates or restatements of others made last summer in Ge-

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neva. There was still no agreement about the exact cause or mechanism of the problems and widespread disagreement on how often they occur.

Little encouraging treatment information was offered. A few very small studies suggested that switching from protease inhibitors to NNRTI-based combinations might help, but the data were scarce and over-promoted. The long delay in addressing these concerns points to a possible problem in the current oversight of newly approved drugs: no one seems to be responsible for tracking the consequences of unforeseen side effects.

Perhaps the only positive note on this subject came from a very preliminary laboratory study at Glaxo Wellcome. Their initial data seem to define a mechanism faulting some, but not all, protease inhibitors. If their data are correct—and this is a large *IF*—they suggest that at least one protease inhibitor [theirs, amprenavir (Agenerase[®])] might not contribute to lipodystrophy. But this is exactly the rub: it's too early to know if they are right and too easy to question their objectivity until further data is available. Nonetheless, hints in their early data support the possibility that there may be a difference with this drug. Time will tell.

There was considerable discussion about another aspect of long-term therapy, namely how to get people off therapy altogether. The reason for addressing the topic seem clear: it is highly unlikely that people will be able to remain on the current drugs for a lifetime. Aside from the accumulation of side effects, large numbers of people report great weariness with constant adherence to drug regimens. A few years may be possible, but more and more people are pessimistic about their ability to "stay with the program" for the rest of their lives.

Two different discussions are underway among researchers about the issue of "going off therapy." Unfortunately, media reporting on the subject has lumped the two very different concepts together. In fact, they are two entirely separate theories that apply to different patient populations. For a more thorough discussion of pulsed therapy and strategic interruptions of therapy, see *Pulsed Therapy and Structured Interruptions of Treatment* on page 12.

Yet another concern associated with long-term therapy is the broad question of how long it will continue to work, even under the best

circumstances. A positive note was sounded in recent data from an early study of indinavir (Crixivan[®]). After three years, about two-thirds of the study participants were able to stay on therapy and maintain viral load levels below the limit of detection. Although most researchers saw this as surprisingly good news, at least one major media outlet chose to characterize it as a sign of failure, proclaiming instead that one-third had failed therapy after three years. Certainly, the glass is more than half full, so the media pessimism was surprising. It is highly unlikely that any researcher in recent years would have been sufficiently confident to predict continued success for three years for two-thirds of people using the new drugs. Apparently, the media expected 100% success.

Perhaps more encouraging was the finding that even though an increasing number of people were "failing" on therapy—defined today as having detectable viral load—most continued to do well clinically. In fact, many of the people "failing" based on viral load measures actually saw their CD4+ cell counts continue to rise long afterward. Whether this is a unique property of protease inhibitors or an indictment of our

current definition of "failure" is unclear. It is likely some of both.

A final but sobering note on long-term therapy was the widely discussed—but still anecdotal—observation that the rate of new opportunistic infections was indeed increasing,

and in all likelihood, so too is the death rate. Current public figures do not yet reflect these apparent trends, but public figures tend to lag nearly a year behind.

Impact on Treatment Strategies

The current state of knowledge of HIV treatment, as presented at the Sixth Conference on Retroviruses and Opportunistic Infections, raised more questions about treatment strategy, but did little or nothing to answer them. People just beginning therapy for the first time clearly have the greatest number of options ever available. Yet selecting among those options impacts all future choices for second and third line therapy.

The most obvious dilemma centers around the optimal time to use the NNRTI class of drugs represented by efavirenz, nevirapine and delavirdine. Data suggest that they can be used

effectively in first line therapy, but that doesn't necessarily mean this is the best time to use them. For now, they also play a critical and unique role for people who have become resistant to a first or second line protease inhibitor regimen. If the NNRTIs are used in early, first line therapy, by definition they won't be useful later. Just which strategy results in the longest possible life is unclear and there are no data to guide this decision.

It is also unclear whether the best initial overall strategy, is (1) a three-drug, all-nucleoside (NARTI) regimen; (2) a mix of a NNRTI and two NARTIs; (3) a protease inhibitor and two NARTIs; or (4) a regimen which combines one or more classes of drugs. There is logic, if not data, to support all these choices. Yet each has different consequences later on down the line. Please refer to the *Drug ID Chart* on this page for assistance.

People struggling with lipodystrophy problems face similar, uncharted courses of action. Should they abandon an effective PI regimen for an alternative based on a NNRTI or three NARTIs? What about switching to a different protease inhibitor, such as amprenavir?

Another strategy question looms over the fundamental issue of when to start therapy in the first place. The "hit it hard, hit it early" mantra of 1996 looks increasingly naïve today in light of the long-term complications of therapy and the lack of new treatment options that work well after initial therapies fail. Knowing what we do today, a reasonable case can be made for delaying therapy somewhat to avoid starting people on the cycle of potential side effects and drug resistance any earlier than necessary. In truth, the actual data from 1996 never recommended treatment for all HIV-infected people, nor did any other guideline. Yet many physicians interpreted the

words of researchers to suggest exactly that. This question is further complicated by recent data demonstrating that men and women tend to have somewhat different levels of viral load at equivalent CD4+ cell counts. That leads to debate about whether there should be gender differences in deciding when to start therapy. For more information on *Gender Difference in Viral Load* on page 18.

For the foreseeable future, there is no reason to expect clear answers to any of these questions, since little is being done to answer them. The lack of long-term "strategy" trials—proposed here and

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by other activists many years ago—continues to haunt the field of HIV research, forcing people with HIV/AIDS and physicians to make no more than *best guess* decisions about many critical issues. In this context, it is far too easy to have

decisions influenced by drug company promotions, advertising and simplistic physician preferences.

Perhaps more than at any other time in the history of the epidemic, people today need to be as well informed as possible about the issues they face. There is no one right answer for

everyone, and everyone must understand the implications and long-term consequences of the choices they make. Clearly, patient empowerment and knowledge may be more important today than any individual medication offered for the treatment of HIV disease.

Drug Identification Chart

INITIALS	GENERIC NAME	TRADE NAME	MANUFACTURER
Protease Inhibitors (PIs)			
AMP	amprenavir	Agenerase*	Glaxo Wellcome
IDV	indinavir	Crixivan*	Merck
NFV	nelfinavir	Viracept*	Agouron
SQVhgc	saquinavir hard gel capsule	Invirase*	Hoffman La Roche
SQVsgc	saquinavir soft gel capsule	Fortovase*	Hoffman La Roche
RTV	ritonavir	Norvir*	Abbott Labs
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
DLV	delavirdine	Rescriptor*	Pharmacia & Upjohn
EFV	efavirenz	Sustiva*	Dupont Pharma
NVP	nevirapine	Viramune*	Boehringer Ingelheim
Nucleoside Analog Reverse Transcriptase Inhibitors (NARTIs)			
ABC	abacavir	Ziagen*	Glaxo Wellcome
AZT	zidovudine	Retrovir*	Glaxo Wellcome
AZT+3TC	---	Combivir*	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
Nucleotide Analog Reverse Transcriptase Inhibitor (NtARTI)			
ADV	adefovir	Preveon*	Gilead Sciences
Ribonucleotide Reductase Inhibitor (RRI)			
HU	hydroxyurea	Hydrea*	Bristol-Myers Squibb

Class-Sparing Treatment Therapies

The latest buzzword of HIV treatment is the so-called “protease inhibitor-sparing” regimen. This concept describes an effective three-drug treatment combination that does not use a protease inhibitor (PI). At its simplest, the goal of such a regimen is to preserve or “spare” the protease inhibitor option for later use. There are now reports of similar regimens that spare two classes of drugs, withholding the use of protease inhibitors and non-nucleoside RT inhibitors (NNRTIs) for later use.

There are a number of advantages and disadvantages of this approach. Typically, a PI-sparing regimen substitutes one of the NNRTI class of drugs [delavirdine (Rescriptor), efavirenz (Sustiva), or nevirapine (Viramune)] for a protease inhibitor, while still using two of the nucleoside class of drugs (NARTIs), such as AZT and 3TC or ddI and d4T. Another option, which spares both the PI and the NNRTI classes, creates a three-drug treatment regimen made up of three NARTI drugs, or two NARTIs and a member of yet another class of drug, such as hydroxyurea.

A logical case can be made for both of these class-sparing approaches. It is now possible to achieve good suppression of virus in a majority of people just starting treatment without using either a protease inhibitor or a NNRTI. But it is far from clear which of the many possible combinations or types of regimens will actually help an HIV-infected person live the longest and most comfortable life. Just because a class-sparing regimen can suppress virus adequately, even for a year or more in a majority of people, doesn't necessarily mean that such regimens are the optimal methods of treatment or that they are fully equivalent to a protease-containing regimens.

Arguments For and Against Class-Sparing Regimens

The idea of substituting a NNRTI drug for a protease inhibitor in a typical three-drug combination in initial therapy offers a few theoretical advantages. First, it may allow a person to avoid or at least delay particular side effects usually associated with protease inhibitors. If the regimen can be as effective in suppressing virus as a PI-based regimen, then it might make sense to delay exposing people to protease inhibitor side effects. The limitation to this, however, is that the NNRTI drugs used instead have side effects of their own. Moreover, it is not yet entirely clear whether their use will always prevent the more troubling side effects of combination therapy, such as lipodystrophy (see *Lipodystrophy* on page

14). At least one NNRTI, like almost all protease inhibitors, can raise cholesterol and triglyceride levels. All NNRTIs, in varying degrees, can produce a troublesome rash, and one produces unique and often disturbing effects in the central nervous system and brain. In short, replacement of the PI with a NNRTI does not eliminate side effects, but quite likely changes them and, for some, reduces their severity.

A second motive for using PI-sparing regimens is to use a regimen that suppresses HIV for a prolonged period of time but does not contribute to the development of resistance to protease inhibitors. This would make it possible for people to effectively use a PI later, if the first combination regimen fails. Proponents argue that by sequencing the NNRTI and PI classes of drugs in this fashion, therapy overall will remain effective for a longer period. Not everyone agrees, however.

Critics point out that the most effective second or third line therapy for use after a protease inhibitor regimen fails is a new regimen that includes both a previously unused protease inhibitor and first time use of a NNRTI drug. If the patient has already used an NNRTI to the point of failure due to resistance, then this option is closed off for them, leaving them with few if any combinations likely to be effective when protease inhibitors begin to fail. Additionally, critics point out that the NNRTIs require only one mutation to render that entire class of drug ineffective. For instance, many believe (and some new data support) that when a person fails a NNRTI-containing regimen, such as AZT + 3TC + efavirenz, they will be resistant to both

3TC and the NNRTI. They counter that when a person fails a protease inhibitor-containing regimen, they may only be resistant to one of the nucleoside drugs and still are sensitive to the protease inhibitor for later use.

Either way, a person has only one shot at using the NNRTI-based regimen. There are no data at all that proves using it early or using it later results in the best durability for therapy overall. Both arguments about when to use the NNRTI regimen are theoretically valid, but neither is backed by results of research from well-designed studies. Simply put, anyone's view about when best to use this class of drugs is merely a matter of opinion.

Finally, some researchers argue in favor of using both the PI class of drugs and the NNRTI class, along with a NARTI or two, all together, concurrently in hopes of achieving the most intense and longest lasting viral suppression possible. The counter-argument, of course, is that when such a regimen fails, the patient has virtually nowhere left to turn, possibly having developed resistance to all classes of drugs at

once. Again, there are no data showing that any of the three approaches leads to the longest possible life span or even the longest possible suppression of HIV.

NNRTI- and Protease-Sparing Regimens

The most recent theory of class-sparing

regimens argues that if preserving the protease inhibitor for later use is a good idea, then why not spare both the PI and the NNRTI class, if that can be done without sacrificing effective viral suppression. This line of thinking leads to the use of three-drug regimens made up entirely of NARTI-class drugs. The most successful of these so far has included AZT and 3TC plus the new, highly potent NARTI, abacavir (Ziagen). It is not as clear whether similar results can be achieved with all possible combinations of NARTIs, since abacavir represents newer and more potent generation of this class. There are a number of similarly potent new NARTIs in clinical studies. Another possibility is to combine two NARTI-class drugs plus an “outsider” drug like hydroxyurea (HU, Hydrea), which doesn't fit into any of the common classes but has been shown to have good anti-HIV activity. Recent studies have shown results ranging from good to very good from such combinations, though longer-term

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data are still lacking.

What's to be gained by such an approach? In theory, it might be possible to extend the overall durability of treatment by using the available drug classes in three effective stages, applied sequentially. An example of this might begin therapy with a three-drug NARTI or NARTI plus hydroxyurea regimen, followed by a regimen made up of two NARTIs and a NNRTI, followed ultimately by a PI-based regimen. Believers suggest this might lead to the most extended period of effective therapy. Such an approach would also delay the various side effects associated with NNRTIs and PIs for later, while hopefully preserving long-term viral control.

A number of other sequences are also possible, such as starting on three NARTIs followed by a PI plus NNRTI plus NARTI combination. In effect, this approach argues that the class of drugs used isn't as critical as once thought, and that it is really the total number of drugs used in combinations that is responsible for their effectiveness.

Each class of drugs has its strengths, weaknesses and side effects, but what matters most is always using at least three drugs together, of which at least one or two should be drugs considered to be "highly active." Again, critics of this approach point out that there are only 5 NARTI drugs presently available and they have some degree of cross-resistance (where resistance to one drug results in resistance to another in the same class) to each other. As a result, they feel that it may be difficult to put together a potent follow-up treatment regimen.

Regimen Limitations

Proponents of new class-sparing regimens base their claims of legitimacy on the belief that the "sparing" regimen will work as well as a PI regimen, at least for the majority of people starting therapy for the first time. This is fairly well established for some of the "sparing" regimens, but not as well for others. However, no such regimen has yet demonstrated the long-term durability proven for protease inhibitor regimens. This doesn't mean they have failed in this regard, but only that the studies have not yet run for as long as the best protease inhibitor studies (now out to three years for small groups).

There are at least theoretical reasons to question whether NNRTI combinations will last as long, but there are no hard data either way. NARTI combinations do not share this theoretical weakness, but are generally not perceived to be quite as potent overall.

One other issue clouding the comparison of PI regimens and PI-sparing regimens is a unique, recent research finding. People on protease inhibitors tend to experience continued benefits in terms of CD4+ cell counts and overall health

well after a person develops resistance to the protease inhibitor and virus levels begin to rise. This is quite different from the experience with older drugs. In the past, when a person developed resistance to NARTI drugs such as AZT or ddI, CD4+ counts generally fell and overall health declined.

The fact that many people seem to have the opposite experience with protease inhibitors suggests that PIs may continue to provide some kind of benefit not yet understood. This phenomenon is referred to as a "disconnect" between a protease inhibitor's effect on HIV and its effects on the immune system. It is considered to be a good thing, but so far, there is no evidence that a similar "disconnect" happens with NNRTI-based regimens or all-NARTI regimens. So this may represent a unique benefit of PI-based therapy, one that should not be discounted too easily.

On the other side of the coin, it certainly seems that PI-based regimens present the most complex mix of side effects and drug interactions. These two must be weighed in the decision about what to use when starting therapy.

Commentary

In short, there is no clear winner in this race as yet, and reasonable arguments can be made for all three approaches. People should view with skepticism any claims that one approach is necessarily better than the others. We don't know what will last longest, and we don't know all the consequences of each choice.

It is clear, however, that whatever choice is made for first line therapy it will definitely impact choices and outcomes of subsequent therapy. Therefore, it is important that such a choice be made only after full and careful examination of all the facts. The challenge is to understand the ups and downs of each approach and choose the one best suited to the individual's preferences, lifestyle and beliefs.

Class-Sparing Regimen Limitations

Regimen	Possible Advantages	Possible Disadvantages	Drug Interaction Complications	Impact on Future Options
Three-drug PI-based regimen	Best proven long-term viral suppression. Continued immune and general health benefits even after viral "failure."	Generally harder to use and adhere to. Long-term side effects might include (lipodystrophy, diarrhea, kidney problems, diabetes).	Mild to severe (ritonavir is the biggest problem; but its activity can also be exploited positively).	Preserves NNRTI for use in treatment failure. Usually leads to cross-resistance with other PIs.
Three-drug NNRTI-based regimen (PI-sparing)	Alleviates fears of PI-related side effects*. Generally easier to use and adhere to.	Not yet proven in long-term setting (limit, 1 year). No evidence of continued benefit after viral failure. Unique "neurological" side effect (feelings of disorientation) with efavirenz.	Delavirdine: effects can be exploited positively. Efavirenz: moderate problems. Nevirapine: minor problems. No major problems.	Preserves PIs for later use. Consumes NNRTI class, making it unavailable for use in later treatment failure.
Three drug NARTI or NARTI plus -regimen (NNRTI- and PI-sparing)	Saves PI and NNRTI for later use. Generally easier to use and adhere to.	Alleviates fears of PI and NNRTI-related side effects. Introduces few if any new side effects (most are present in other combinations anyway).		Preserves both PI and NNRTI classes for later use. May hasten resistance to other NARTIs.

*Note: some side effects attributed to protease inhibitor therapy, such as lipodystrophy, have not been proven to be strictly associated with the use of protease inhibitor-containing regimens. One NNRTI, efavirenz, has been shown to result in increases in cholesterol and triglycerides, which some believe is related to the risk of developing lipodystrophy.

Options for First Line Therapy

The widespread availability of the next generation of new anti-HIV therapies is still at least a year or more off. However, most of them are currently in, or will soon be in, small studies; a few are already moving into large-scale studies.

Abbott Laboratories Study of ABT-378

One new drug under study is Abbott Laboratories' new protease inhibitor (PI), ABT-378. Preliminary results show ABT-378 is very potent and well tolerated, at least as first line therapy. In the main study reported so far, 101 people who had never received prior anti-HIV therapies participated. They were given a combination of ABT-378 and a small amount of ritonavir (Norvir). ABT-378 will always be combined with some dose of ritonavir because ritonavir helps keep high amounts of ABT-378 active in the body for longer periods.

Volunteers began the study with an average viral load of about 70,000 copies HIV RNA and an average CD4+ cell count of about 350. Three different doses of ABT-378/ritonavir (Norvir) were used (200/100mg, 400/100mg and 400/200mg), all of which were taken twice a day in combination with d4T (stavudine, Zerit) + 3TC (lamivudine, Epivir).

After 24 weeks, the drug combination suppressed viral load to less than 400 HIV RNA copies in about 85% of the participants. The ultrasensitive viral load test was performed in a smaller group of participants; and among that group, 89% had less than 50 copies HIV RNA. No one has dropped out of the study because of side effects. Most side effects noted to date have been mild to moderate in severity, with abnormal stools (less than three loose stools per day) and diarrhea (more than three loose stools per day) being the most commonly reported.

Abbott had high hopes for ABT-378, thinking it would be effective for people who have experienced renewed viral activity or breakthroughs despite using numerous protease inhibitors. More recently, they have become more realistic about how this drug will fare in the multi-protease resistant population. However, Abbott is starting new studies, including some for people who developed resistance to a single protease inhibitor.

Planned studies will test the drug in people who are resistant to several available protease inhibitors but who have not yet taken a non-nucleoside reverse transcriptase inhibitor. A

committee of activists is working with Abbott to propose other study designs for third line use. Together, these studies will help determine where and how to best use the ABT-378/ritonavir combination. For now, it looks like the best-proven use will be as first line therapy.

The ATLANTIC Study of Two Class-Sparing Regimens

The ATLANTIC study compared two class-sparing regimens (one of which spared both the PI class and the non-nucleoside class of drugs) to a standard PI-containing regimen. The two studies enrolled 298 participants each. Volunteers had an average viral load of 16,000 copies HIV RNA, CD4+ cell count of 418 and had not previously been on anti-HIV therapy. People receive d4T + ddI (didanosine, Videx) + 3TC, d4T + ddI + nevirapine (Viramune) or d4T + ddI + indinavir (Crixivan). After 24 weeks the results, in terms of viral suppression, were as follows:

These results suggest that a number of possible three-drug combinations are likely to be effective in suppressing HIV levels at least for the first 24

ATLANTIC Study Results

Treatment Regimen	Percent <500 copies HIV RNA	Percent <50 copies HIV RNA
d4T+ddI+3TC	71%	56%
d4T+ddI+NVP	69%	67%
d4T+ddI+IDV	78%	71%

weeks of use. There does not appear to be a great difference whether the combination is anchored by a PI, a NNRTI [e.g. nevirapine, delavirdine (Rescriptor) or efavirenz (Sustiva)] or even simply a highly potent nucleoside analogue, like abacavir. It doesn't tell us, however, which strategy or combinations will last longest or prove easiest to use and tolerate over the long haul.

Additional PI-Sparing Regimen Studies

Another study looking at a PI-sparing regimen compared AZT (zidovudine, Retrovir) + 3TC + abacavir (Ziagen) to AZT + 3TC + indinavir. Five hundred and sixty-two participants in the study had an average viral load of about 65,000 copies HIV RNA, CD4+ count of 360 cells and had not previously received anti-HIV therapies.

About 65% of the participants in both groups achieved HIV RNA levels below 400 copies after 24 weeks of the study. Approximately 45% of the participants had HIV RNA levels below 50 copies based on the ultrasensitive viral load tests after 16 weeks of the study. People with high HIV levels (over 100,000 copies HIV RNA) at study entry seemed to respond just as well as people who started with lower HIV levels. A similar percentage in each group achieved HIV levels below 400 copies HIV RNA.

It is disturbing, however, that about a third of the participants in both groups discontinued their treatment regimens. About half of those who discontinued treatment did so because of side effects, the most common of which were nausea, fever (only among people receiving abacavir), vomiting, fatigue and skin rashes. There were 13 cases of abacavir-related hypersensitivity (5% of the group receiving abacavir) including one death reported as a result of restarting abacavir after the hypersensitivity reaction. One interesting observation showed that people receiving the indinavir regimen had significant increases in cholesterol levels compared to their pre-study levels, whereas the group receiving abacavir had no significant changes in cholesterol levels.

Another study looking at a PI-sparing regimen enrolled 152 people who had not previously received anti-HIV therapies and who had a mean viral load of approximately 200,000 copies HIV RNA and a CD4+ cell count of 200. Participants received AZT + 3TC or AZT + 3TC + delavirdine (Rescriptor). The percentages of people who achieved suppression of viral load below the limit of detection after 24 weeks follows:

These results are reasonably good given that the viral load at study entry was so high. People who entered the study with either high or low HIV levels (above or below 100,000 copies HIV

PI-Sparing Regimen Study Results

Treatment Regimen	Percent <400 copies HIV RNA	Percent <40 copies HIV RNA
AZT + 3TC	10.3%	2.6%
AZT + 3TC + DLV	56.8%	47.3%

RNA) were equally likely to achieve viral levels below 400 copies HIV RNA. However, far fewer people who started with higher HIV levels were able to get their HIV levels below 40 copies HIV RNA compared to people who started with lower HIV levels.

Approximately 15% of the people receiving delavirdine discontinued their regimen because of side effects. The most commonly reported side effect was rash (reported in 23% of those receiving delavirdine), but only three people (4%) had to discontinue delavirdine because of this side effect. Results from this study suggest that a combination of AZT + 3TC + delavirdine may be another reasonable “PI-sparing” option for people choosing a first line regimen.

What Do These Results Mean?

A person may get a potent and long-lasting response from his/her first line therapy but may not be able to put together a potent second line regimen (due to cross-resistance to the other drugs or because the first line regimen used up too many treatment options). As a result, HIV levels might soon increase after starting this second regimen. Another person may have a reasonably long lasting response to both his/her first and second line therapies and end up with an overall longer-lasting response.

Many researchers believe that the first treatment regimen is the most important. Similarly, many researchers believe that it is important to drive HIV levels down as far as possible, preferably below 40 copies of HIV RNA (using the ultrasensitive viral load tests). Several studies suggests this result in a longer lasting response to therapy that people who are not able to attain this kind of viral suppression.

While all recent data are encouraging and suggest that people who have not previously received anti-HIV medications have numerous treatment options, there are little data to help determine which options may be most beneficial over the long-term. The fact remains we only have information on people who have been on these regimens for a relatively short period of time. Only results from long-term treatment strategy studies—finally just starting—will enable us to know if people should start with a regimen that contains a protease inhibitor, a non-nucleoside reverse transcriptase inhibitor or neither. For a thorough discussion of the advantages and disadvantages of class-sparing drugs, see *Class-Sparing Treatment Therapies* on page 5.

The Power of Words

Beginning with this issue, Project Inform will change some words commonly used in HIV/AIDS newsletters and presentations. Constituent feedback remind us that words can convey unintended meanings. At their worst, seemingly innocent words can lead to discouragement, or they can insult the listener or reader. They can also carry the wrong message.

An early example of this was the media’s use of *AIDS victim*. Though it intended to provoke a sympathetic response, it typically was heard as disempowering or assuming weakness in people with AIDS. Today the phrases in question come from within the community concerned with AIDS—researchers, educators, activists and healthcare workers.

Drug Cocktails

Some people protest calling today’s powerful and often toxic drug combinations, *cocktails*. They are right. A cocktail is a drink and not always something seen as *good*. Drug combinations, however, are powerful, serious therapies and are not to be made light of or associated with “party-ing.” Also, people in recovery programs resent the term. Project Inform stopped using this phrase several months ago.

Treatment Failure

Treatment failure is a loaded and overused phrase in today’s vocabulary. Scientists used it to describe a situation in which a person had regained any level of detectable viral load. This grossly overstates medical reality. The only *failure* involved is making viral load completely undetectable. This hardly qualifies as meaningful *treatment failure*, which implies dire medical consequences.

People with modest levels of detectable viral load often do well for many years by clinical measure. They are sick of being told their treatment efforts have *failed*. Project Inform will now use an alternative term, *viral breakthrough*. This describes a situation when viral load becomes detectable at some level after a period of undetectability. It clearly reflects that something has changed and avoids drawing inappropriate conclusions about the overall effectiveness of a person’s current therapy.

Salvage Therapy

The third phrase, *salvage therapy*, describes a wide and loose group of situations. The intention behind it comes from the efforts employed when a person is not responding to conventional

treatment. Patients and their physicians in these situations talk about *salvaging* something for the patient, often through extreme measures.

By definition, cancer patients in this situation are generally considered a lost cause. In AIDS, salvage therapy was first used to describe experimental treatment efforts for people who had lost response to all available drugs and had run out of options. Over time, the definition has grown even wider. Now it refers to any treatment effort for people who lose responsiveness or become resistant to even their first treatment regimen. The phrase disturbs many people when applied so widely.

People who lose response to a single treatment regimen frequently have a number of options left, including several new drugs and new *classes* of drugs. These people resent being described as a basket case or at the end of the line. *Salvage* usually refers to grasping anything of value from a sunken ship or fire-ravaged building. It’s no wonder people find it inaccurate and offensive. People truly running out of options are by no means in need of salvaging.

Project Inform will replace *salvage* with a system for describing stages of treatment:

FIRST LINE THERAPY: the first and highly potent regimen a person utilizes, usually three drugs, one a protease inhibitor.

SECOND LINE THERAPY: the regimen a person chooses after losing responsiveness or experiencing viral breakthrough on an initial regimen.

THIRD LINE THERAPY: in short, anything that comes next, the regimen(s) utilized after first line and second line regimens no longer adequately suppress viral load. There isn’t much point to creating labels beyond the third line regimen.

We encourage writers, educators and physicians to join us in these changes. The new language is less likely to offend and more clearly communicates the concepts involved.

Project Inform plans to continue a wider review of words and phrases. We hope to improve our sensitivity to words that affect women, members of various ethnic groups and people with HIV/AIDS in general. Email us at info@projinf.org with your suggestions.

Third Line Therapy Options

In contrast to the numerous treatment strategy options now available to people who are just starting first or second line anti-HIV therapy, limited choices are available to people exploring “third line” therapy options. Third line therapy refers to any treatment regimen used after two initial rounds of therapy have proven unable to maintain HIV suppression. This could be due either to the failure of the drugs or a person’s inability to tolerate the medications.

So far there have been very few studies of third line therapy. Thus, there is more guesswork and less science guiding third line therapy decision-making.

Many people—patients and physicians alike—have resorted to a “let’s try everything” approach, which some describe as “mega-HAART” (mega Highly Active AntiRetroviral Therapy). Such regimens frequently employ six to nine drugs at once, most of which the patient has previously used. Even though the person is likely to be resistant to many if not all the drugs, the hope is that using so many drugs will somehow produce a significant effect. However, it is not known how long people can tolerate taking so many drugs, let alone how long they will work. Ideally, combinations of new therapies that have new mechanisms of attacking HIV are likely to be most successful.

T-20: A New Therapy for the Third Line

The only new therapy on the immediate horizon that has a new mechanism of slowing HIV replication is called T-20 (pentafuside), the first of a class of drugs known as fusion inhibitors. T-20 inhibits HIV by blocking the virus from fusing with an immune cell.

The drug was studied in a group of 78 people with an average viral load of 100,000 copies HIV RNA and an average CD4+ cell count of 100. Most importantly, study participants had previously used an average of nine different drugs. Most had used three or more currently available protease inhibitors and many had already used up all three classes of anti-HIV drugs. This was truly a difficult population in which to test a new drug—a true examination of third line therapy.

People received one of six different doses of T-20. Participants had been either off all anti-HIV medications for at least two weeks before starting T-20 or they could add T-20 to their existing regimen. Consequently, many people used T-20 as single drug therapy, something

that would rarely if ever be done in people with such advanced disease. In this short-term study, those receiving the highest two doses, 50mg and 100mg twice daily by subcutaneous (subQ, under the skin) injections (total daily doses of 100mg and 200mg respectively) had the best anti-HIV responses. At the end of the 28-day study, people receiving the 50mg subQ twice daily dose had a viral load reduction of 0.6 logs (four-fold change) in HIV RNA while the 100mg subQ twice daily dose group had a 0.7 logs reduction (five-fold change). However, all but the people who received the very lowest dose still achieved some degree of anti-HIV activity.

While on the surface these results may not seem impressive, the majority of study participants had failed all available therapies and were taking T-20 alone. In this context, it is somewhat remarkable that the drug worked at all, since almost any other known therapy would likely have failed altogether. Further, these results showed that people who entered the study with lower HIV levels (below 100,000 copies HIV RNA) had better anti-HIV responses [0.8 and 1.4 log reductions in HIV RNA levels (6 and 25 fold) on the 50mg and 100mg subQ dose respectively]. People with pre-study HIV levels of over 100,000 copies HIV RNA had a 0.3 and 0.4 log reduction in HIV RNA levels (2 and 2.5 fold reduction) on the 50mg subQ dose and 100mg subQ dose respectively.

Most importantly, the drug appears to be active even in people who had developed resistance to all other currently available therapies. This is exactly the kind of response needed if we are to find a successful third line treatment. The results

also suggest that, although T-20 is active against HIV in people who have developed resistance to the currently available drugs, it should be used in combination with other drugs, preferably ones that are new to the individual. As additional new drugs become available, it is likely that the potency of regimens containing T-20 may improve.

A significant drawback to T-20 is that the drug will never exist in pill form. Today, it requires simple, twice daily injections, similar to those that diabetics take. Some people may find this troublesome, but others, such as those who are tired of taking large handfuls of pills every day, may welcome the change in administration methods. Other means of administration are being explored.

At least two other fusion inhibitor drugs are under development. The manufacturer of T-20 is developing a second fusion inhibitor, reported to be many times more potent than T-20.

MegaHAART: Throwing Everything at the Problem

Another third line therapy study employed the megaHAART strategy. Fifty-two people, who were failing a protease inhibitor-containing regimen and had a viral load of over 100,000 copies HIV RNA and a CD4+ cell count of about 100, participated in this study. Almost no participants had previously used the non-nucleoside reverse transcriptase inhibitor (NNRTI) class of drugs. People had extraordinarily high HIV levels at study entry, with a median viral load of 560,000 copies HIV RNA.

Participants received between five and seven anti-HIV drug regimens including efavirenz, hydroxyurea (Hy-drea), ddi (dida-nosine,

Videx), ritonavir (Norvir), indinavir (Crixivan) with or without other nucleoside analogue drugs, AZT (zidovudine, Retrovir), d4T (stavudine, Zerit), 3TC (lamivudine, Epivir) or ddC (zalcitabine, Hivid). After 24 weeks, there was a 1,000-fold reduction in viral load (3 logs) and an average

increase in CD4+ cell count of 125. About 65% of the participants had viral loads below 400 copies of HIV RNA.

These results suggest that treatment can regain control of viral replication if two conditions are met: (1) the patient must be able to tolerate an extraordinary number of drugs (five to seven),

In this context, it is somewhat remarkable that T-20 worked at all, since almost any other known approach to therapy would likely have failed completely.

and (2) the patient must not have previously used or developed resistance to the NNRTI class of drugs. It seems that first time use of an NNRTI drug is critical to achieving success after HIV begins to break through the defense of the protease inhibitors. This may become a problem for many, however, since some sources recommend that people utilize NNRTI drugs as first line therapy. If this is done, the NNRTI class of drugs will not be available to help later in third line therapy.

In another mega-HAART study, 24 of 37 participants had tests performed to determine which drugs they were resistant to before they select a new regimen. Volunteers then received six or more anti-HIV drugs and were followed for about eight months. Of the 24 people who had the resistance tests performed and who used this information to construct a mega-HAART regimen, there was an average viral load decrease of about two logs (100-fold reduction) and about a 100 CD4+ cell count increase. At the end of study, ten people had viral load levels below 500 copies HIV RNA; eight had initial viral load responses below the 500 copies HIV RNA limit but then had increases; and six people were never able to get below 500 copies HIV RNA.

Not surprisingly, this study found that people who were not completely resistant to all of the drugs had better responses compared to people who were completely resistant. However, some people who were completely resistant did mount good anti-HIV responses.

One interesting aspect of this study was that some patients stopped all use of their anti-HIV therapies for two to three months prior to starting this study (called a *washout period*). Apparently these people regained some degree of sensitivity

to drugs to which they had previously shown resistance and all mounted good anti-HIV responses. This apparent ability to regain sensitivity to previously used drugs was probably only partial and unlikely permanent. However, it did seem suf-

ficient to permit at least an initial high level of viral suppression. Thus, it often pushed viral load below the limit of detection on the ultrasensitive tests (less than 50 copies). Once this level was reached, viral replication apparently slowed so much that levels stayed below the limit of detection for several months. This phenomenon needs to be tested further in larger studies. If confirmed, it suggests that using a period of drug *washout* might play a very important role in third line therapy in the future. For now, however, it is hard to draw any absolute conclusions since the study was relatively small.

While the results from these two mega-HAART studies are encouraging, it is not known how long people can or will be willing to take a large number of pills. Additionally, when this many different medications are combined, there is an increasing likelihood of side effects. Certainly in the second study, using the results of resistance testing to guide treatment choices appeared useful. Only larger studies that compare different regimens will provide direction for optimal approaches to developing a third line strategy.

“Second Line” Therapy When Nelfinavir Fails

A small study looked at the activity of ritonavir + saquinavir + d4T + 3TC in people who were failing a nelfinavir-containing regimen. All 26 participants had a good initial anti-HIV response to nelfinavir followed by increases in HIV levels. Participants entering this study had taken nelfinavir for about a year and had a mean viral load of about 45,000 copies HIV RNA and a mean CD4+ cell count of 222. After 48 weeks on the four-drug regimen, 14 of 24 people had HIV levels below 500 copies HIV RNA and an average 120 CD4+ cell count increase. Two people discontinued the study because of diarrhea

associated with nelfinavir. This study observed that people who had pre-study HIV levels below 30,000 copies HIV RNA were significantly more likely to achieve HIV levels below 500 copies HIV RNA.

It's important to note that the study participants were only *assumed* to have failed on or developed resistance to nelfinavir, since no resistance tests were performed. The participants actually may have experienced either nelfinavir failure, or failure of one or two of the nucleoside drugs they were using (most likely 3TC). Whatever the real cause of initial failure, results suggest that the ritonavir/saquinavir combination is a reasonable second line therapy option capable of producing lasting results in about half the people who employ it.

Is It Time to Switch Off 3TC?

Another study examined the wisdom of a common practice: continuing to take 3TC even when resistant to the drug. This study, known as the AIDS Clinical Trials Group (ACTG) Study 370, enrolled 105 people who had previously been on a two nucleoside analogue combination including 3TC. Participants previously on ddi + 3TC or d4T + 3TC received AZT + 3TC + indinavir or AZT + delavirdine + indinavir. At the end of the 24-week study, the results were as follows: Clearly, those stopping 3TC and adding a new drug had superior viral suppression. One interpretation of this study suggests that it *may* not be wise to continue on 3TC, or perhaps any drug after developing resistance to it—hardly a new concept. Most treatment strategies have long recommended switching to two new drugs when adding a third potent drug, like a protease

AIDS Clinical Trials Group Study 370

Treatment Regimen	Percent <200 copies HIV RNA	Percent <50 copies HIV RNA
AZT+3TC+IDV	65%	50%
AZT+DLV+IDV	80%	75%

inhibitor.

Another interpretation is that the superior results of the second regimen is due more to the addition of delavirdine than to dropping 3TC. Adding delavirdine means adding a second, highly potent new drug to the regimen along with indinavir. It seems obvious that this would work better than simply adding a single new drug, indinavir, while retaining two old ones

National HIV/AIDS Treatment Hotline



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

likely to be affected by resistance. The additional potency seen with the delavirdine-containing regimen may also be explained in part by the result delavirdine has on increasing indinavir levels in the blood, perhaps effecting a greater and longer lasting anti-HIV response. Obviously, adding indinavir to a previously used two-drug regimen did not result in the best anti-HIV response.

Does Resistance Testing Help?

Results from a new study show that making treatment decisions based on the use of resistance testing produces significantly better results than decisions made without such test information. These results show that people who acted on resistance information had significantly better anti-HIV responses from therapy choices. Genotypic resistance tests examine samples of virus taken from a person and look for the presence of specific mutations in the virus which are known to be associated with resistance to certain drugs.

This study, also known as the GART (Genotypic Antiretroviral Resistance Test) study, enrolled 153 people who had experienced at least a three-fold increase in their HIV levels while on a three-drug regimen which included a protease inhibitor. At study entry, the participants had a median viral load of 25,000 copies HIV RNA, a CD4+ cell count of about 230. The majority of the participants were on either nelfinavir or indinavir.

After twelve weeks of the study, the group who used genotypic resistance tests had a 1.2 log (16-fold) reduction in HIV RNA levels compared to 0.6 logs (four-fold) reduction in HIV RNA levels among people who did not get the test. Furthermore, people who followed expert recommendations had even larger reductions in HIV levels compared to those who did not follow the recommendations. This study suggests that resistance testing may be useful and may be critical for treatment success, especially when expert advice is followed. While not everyone has access to “expert advice,” this study does confirm the value of seeking a second opinion when making major changes in your treatment regimen.

Commentary

Results of third line therapy studies show some reasons for hope, they do not offer much guid-

Results from a new study prove that making treatment decisions based on the use of resistance testing produces significantly better results than decisions made without such test information.

ance. Unfortunately, for now, third line therapy may require the use of more drugs than many people, in the short-term, are willing or able to tolerate. But it is clear that at least some people can cope with regimens of five to nine drugs, and that those who do generally achieve fairly good results. Still, all third line studies to date have been relatively small and uncontrolled, so it is unclear how well these results will apply to people in general medical practice.

The most hope for third line therapy comes from the addition of several new drugs, ideally from new classes of agents. But it has been difficult to get the different pharmaceutical companies to collaborate on third line therapy studies. An agreement from the Food and Drug

Administration which allows these types of studies to support approval of a specific drug could make it easier to convince companies to work together. Because of the importance of third line therapy studies and the growing number of people running out of anti-HIV therapy options, Project Inform—along with the Forum for Collaborative Research, the Treatment Action Group and the Division of AIDS of the National Institutes of Health—is co-sponsoring a workshop to tackle and hopefully resolve some of these issues.

do generally achieve fairly good results. Still, all third line studies to date have been relatively small and uncontrolled, so it is unclear how well these results will apply to people in general medical practice.

Gender Difference in Nevirapine-Associated Rash E

A study reported at the recent Chicago conference suggest that women are more likely to develop rash, especially severe rash, as a side effect of the anti-HIV drug nevirapine compared to men. Researchers looked at the medical records for 85 women and 176 men receiving nevirapine-containing anti-HIV regimens between 9/93 and 9/98. Overall, 26 people developed rash within the first 90 days of taking nevirapine, of whom twelve were women. Mild rashes were seen in four women and 13 men, whereas severe rashes were seen in eight women and one man.

In this study, rash was more likely seen in people with higher CD4+ cell counts (e.g. greater than 200), but was unaffected by differences in age, race or concurrent use of other medications. In other studies of nevirapine, severe rash was seen in only about 3% of people taking the drug. Overall, however, 85% of participants in studies of nevirapine have been men, so it is not clear how well this figure applies to women.

These recent findings underscore the need for including greater numbers of women in studies of new therapies, so that when gender differences exist they are readily apparent from early study results. Additionally, they suggest that women using nevirapine take special care to watch out for the development of rash and perhaps to use pretreatment, such as Benadryl®, to minimize the risk. It is common when using nevirapine to start therapy at half the standard dose for the first few weeks to minimize the risk of rash. Based on this new data, this practice may be even more important in women than in men.

Pulsed Therapy and Structured Interruptions of Treatment

Research has begun on two new strategies for long-term treatment of HIV disease. Although both theories involve taking people off treatment in some way, they have different goals and expectations. These two strategies are known as *pulsed therapy* and structured interruptions of treatment (sometimes called *drug holidays*).

The first approach, best described as a form of pulsed or intermittent therapy, aims at stimulating a stronger immune response against HIV. Researchers speculate that this will empower the person's own immune system sufficiently to control HIV replication without the continual use of anti-HIV drugs.

The second approach, a type of structured interruption of treatment (or *drug holiday*), can take a number of different forms. On one level, it can be little more than taking people off therapy, after successfully suppressing HIV for a year or more, to simply see what happens. On another level, it assumes that measurable HIV replication will begin again sometime after treatment is stopped but tests whether this is necessarily bad. This kind of therapy interruption compares the benefits and drawbacks of constantly staying on drug therapy against those of periodically taking time off.

While each approach is getting serious attention as a research project, no one suggests that we know enough to recommend these strategies for anyone's personal use. They are experimental strategies whose overall harm or benefits are simply not yet known.

Pulsed Therapy

The *pulsed therapy* approach assumes that people should always maintain viral loads below the limit of detection to be healthy. In this approach, a person who has been treated since the earliest stage of HIV infection is taken off all therapy once viral load remains undetectable for some pre-determined length of time, perhaps six months to a year or longer.

While off therapy, the person would be carefully monitored for the return of measurable virus. If and when viral load becomes detectable again, the person would be put back on aggressive antiviral therapy. Typically, this results in the rapid disappearance of measurable viral load for the second time. After another pre-determined period on therapy, the cycle is repeated—taking the person off therapy while monitoring for

return of measurable viral load.

An interesting phenomenon has been noted in a few cases of pulsed therapy, either as a structured experiment or simply as a matter of patient choice. The first time a person went off therapy, viral breakthrough (return of measurable levels of viral load) occurred after a relatively short period of time, ranging from a few days to a few weeks. After restarting therapy, viral load plummeted again, below the level of detection. Then after staying on therapy for varying periods, they stopped therapy a second time. This time, viral load remained undetectable for considerably longer than the first time, despite the lack of continued treatment.

A few people who cycled on and off therapy twice now have no return of measurable viral load, while off therapy, for periods ranging from 6 to 21 months. Researchers theorize that each cycle of pulsed therapy led to a progressively longer period for the body to fully control viral replication without the help of anti-HIV drugs. In a few cases, people treated with two or more cycles of pulsed therapy have been able to control viral replication with continued therapy for as long as two years (and still counting).

It is hard to draw any clear conclusions from these observations since nearly every patient involved has done something differently from others. For the most part, they were simply choosing to go on and off therapy for personal reasons. They each had varying times on and off therapy, and varied considerably in how quickly they returned to treatment when viral load reappeared. Researchers carefully studied the consequences of their actions, and were understandably surprised by the results.

What is going on here?

Researchers at the Aaron Diamond AIDS Research Institute and the RIGHT group have proposed a theory: the periods in which a person is taken off therapy and viral replication is allowed to resume may be beneficial. They suspect that the returned viral load is acting somewhat like a vaccination. HIV is aggressively presented to the immune system once again, stimulating a more powerful immune response.

This makes some sense because we know when people use antiviral drugs that work for them, HIV is no longer being presented to the immune system. In theory this might allow the normal immune response against HIV to gradually decline. In turn, occasional interruptions in therapy as proposed here may reintroduce HIV into the immune system, thus stimulating a renewed immune response against the virus.

If this is indeed what is happening—and there is promising initial evidence that it is—this approach might be used to help people become less dependent on anti-HIV drugs and more reliant on their immune systems for control of HIV. Such a response might resemble the tiny percentage of HIV-infected people known as “long-term non-progressors.” Such people appear able to control HIV replication without the use of anti-HIV drugs and usually have an abnormally

Some researchers have gone so far as to state that periodic interruptions of therapy may not only be possible, but necessary to help people live out a normal lifetime with HIV disease.

strong immune response against HIV, very similar to that being seen in people who are treated with pulsed therapy.

Still, pulsed therapy is far more theory than reality at this point. The only thing known for sure is that a few people

seem to respond in a way that resembles the theory, including the widely discussed “Berlin patient” reported by Dr. Franco Lori's group. Studies of many more people are necessary and already planned.

Even proponents of pulsed therapy warn that there is no evidence so far that this will work in typical, chronically infected people. The case reports noted have all come from people who began anti-HIV treatment extremely early after initial HIV infection. Such people are known to still be able to mount strong HIV-specific immune responses.

In contrast, many people with more typical chronic HIV infection (where treatment began six months or later after initial infection) frequently show no evidence of this kind of immune response. Some researchers believe that the natu-

ral capacity for this immune response is lost fairly early in the course of HIV infection. Thus, for now, the only realistic target for pulsed therapy research is in people treated from the earliest or *acute* stage of HIV infection, also known as *primary infection*.

Structured Interruptions of Treatment

The second strategy, *structured interruptions of treatment*, responds to a different set of goals and concerns. It assumes that people taken off therapy are likely to see a rebound of measurable viral load. What's not clear is how high the rebound will go and whether it will initially shoot up and then fall back to some lower "set point" level (a viral load level lower than that seen before the person began therapy).

In this approach, people are not automatically put back on antiviral therapy the minute viral load becomes detectable again. Instead, a person stays off drugs for awhile despite the presence of detectable viral load.

So then a question begs to be asked: "Is the harm caused by a return of measurable viral load a greater or lesser danger than constant therapy, and all the attendant side effects and development of resistance to treatment?"

What is the harm of constant therapy? Even if viral load remains undetectable for long periods, there are many possible long-term consequences to constant therapy. The risks of cumulative side effects and tissue damage are perhaps the greatest concerns. This encompasses problems such as fat redistribution (*lipodystrophy*), high cholesterol and triglycerides, diabetes, heart disease and liver problems. These come in addition to the side effects of the older generation of drugs, such as pain in the feet, legs, and/or hands (*peripheral neuropathy*), red and white blood cell suppression (*anemia*), pancreatitis, rash, etc.

Suppression of viral load through anti-HIV drug therapy can produce improvements in overall health and prolonged survival. The challenge is to find the best possible balance—to get the most from therapy without experiencing its down sides which includes the emergence of possible long-term negative effects. For some, this might mean periodically structuring time away from the drugs, for the body to recover

from side effects. Some researchers believe that periodic interruptions of therapy may not only be possible, but necessary to help people live out a normal lifetime with HIV disease.

Since we only have about three years of experience treating people with today's potent three- and four-drug combinations, it remains highly uncertain just how long people will tolerate constant use of the drugs. Few researchers, however, have enough confidence in the drugs to believe that people could use them continually for the 20 to 50 years needed to live a normal life span.

In contrast, we have long known that most people can tolerate long periods of untreated HIV infection without irreparable harm. On the average, people using no treatment at all can usually go for roughly ten years without progression to AIDS. For some, this period is longer, for others it's shorter. Part of the goal of treatment interruptions is to give some of this time back to people, in effect letting them coast along with the virus

for awhile. They then return to medication only when signs of disease progression become apparent. Similar strategies employing periodic interruptions of treatments are routinely used for other chronic illnesses that require long-term therapy.

Another concern caused by constant therapy is simply the

weariness it causes people. The longer many people remain on constant therapy the more likely they begin to miss doses or take short unstructured drug holidays. That can do harm by encouraging development of viral resistance. If structured interruptions of treatment can be offered to people in ways that are unlikely to hasten resistance, with little or no downside, commitment to proper use of therapy may increase during those periods when people use the drugs. This approach offers a compromise, but hopefully one that will provide long-term benefits.

Since we know that short or frequently repeated drug holidays speed the development of viral resistance, the model here focuses not on casual weekend holidays but rather on carefully planned, structured interruptions. An additional benefit already demonstrated in initial studies is that the break from drugs may help a person's virus increase its sensitivity to some previously used drugs. In theory, this might restore their

ability to use drugs to which they had developed resistance. This would greatly enhance their options for future therapy.

Structured Treatment Interruption Research Programs

Treatment interruption programs are just beginning and plan to start with people who have undetectable levels of HIV for six months to a year or more (though this may change after more experience is gained). After that, the approaches vary. Four are outlined below.

1. Some plan to take people off therapy and monitor them to measure the immune and viral responses when therapy is stopped. Here, a person will usually restart anti-HIV therapy as soon as viral load again becomes measurable. The hope is that this may identify the people in whom this approach would be safest and most productive. Such a study is underway at the National Institutes of Health (NIH).

2. Some plan to take people off therapy and monitor them, but not immediately restart therapy if viral load reappears. These seek to determine whether viral load will rise to and maintain a high level peak, perhaps even higher than before the person started therapy. Or they may find that such a peak is followed by a gradual reduction back to a lower and stable level (a *set point*). If viral load comes back down to a modest set point, researchers may choose to withhold therapy as long as viral load remains stable with no major decline in CD4+ cell counts. Such a study is planned at the NIH.

3. Still another approach, perhaps targeted to people with more advanced disease or those who have developed resistance to most available drugs, will keep people off therapy, regardless of viral load, for a period of a few to several months. At some fixed point, anti-HIV therapy will be restarted. The hope of this approach—sometimes called a *washout period*—is to see if the time off allows the virus to return

Expanded Access

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Amprenavir (PI) 800-248-9757

For anyone tolerating or failing current protease inhibitor therapy and needing another new drug for treatment strategy.

Adefovir (NtARTI) 800-445-3235

For anyone failing current therapy and requiring an additional new drug for treatment strategy.

to its natural state (often called *wild-type virus*) and regain sensitivity to previously used drugs. Restarting therapy with a mix of old and new drugs might then kick off another long period of effective viral control.

4. Another approach takes people off therapy for a fixed period, such as two to six months or longer. This is done to let the body heal from drug side effects and rest from the constant rigor of daily therapy. Either at a fixed point in time, or after some permissible level of CD4+ cell count decreases and/or viral load increases occur, the person may be put back on anti-HIV therapy. If successful, this could theoretically be repeated over many years or even throughout a normal lifetime. The hope is that the mix of time on and off therapy might lead to the increased tolerance of therapy and the longest possible life expectancy for HIV-infected people, short of an outright cure.

Commentary

Many important new strategies for the use of anti-HIV therapy must be tested. Until recently, most research focused only on how well individual drugs worked over a period of a few months to a few years. Many people are already coming to the end of the hope offered by such narrowly defined, product-driven strategies.

Today, new strategy research on pulsed therapy or structured interruptions of treatment may well be what's needed. Such research may extend our knowledge of how to best get HIV-infected people through a lifetime, or at least well into the new millennium and not just the next few years. *These strategies should not yet be considered recommendations for medical practice, nor should the fact that they are being tested encourage people to try them on their own.*

We don't have enough information to know whether these procedures will help people live longer or instead cut precious time off what a person has left. If we knew, there would be no need for the research. The right approach is in the context of well-designed studies. Self experimentation seldom leads to knowledge, since there is never a way to know whether what happens to an individual is due to the strategy or drugs used, or whether it is a mere coincidence.

The next several months will see a rash of new strategy studies asking whether and how it might be possible for people to get off therapy, at least temporarily. The more people who volunteer to participate in these studies, the sooner we will know what is and isn't possible.

Lipodystrophy

One of the most common and distressing side effects associated with combination therapy today concerns visible changes in body composition and appearance. Although some aspects of this phenomenon were reported in earlier years of the epidemic, the frequency of reports has greatly increased since the beginning of the *protease inhibitor era* in 1996.

These changes in appearance are brought about by several different forms of redistribution of body fat—fat moving away from the face, arms, butt and legs, and then collecting around the gut (central obesity), at the base of the neck (*buffalo hump*) and/or in the breasts (breast enlargement). Less frequently seen are accumulations of lumpy fat tissue, similar in appearance to cellulite, on the back below the shoulder blades. Associated with these changes, and possibly causally related, are striking increases in a number of blood test markers, such as triglycerides and cholesterol level, and insulin resistance. These blood changes have sometimes been linked to increased risk of heart disease and to the development of diabetes.

The cause of these changes is unknown or at least uncertain. Is it a consequence of HIV disease progression? Is the virus itself interfering with the way the body processes fat and protein? If so, why is it more common today than before?

Are these changes a result of protease inhibitor therapy, as is commonly thought? If so, why have they occurred in some people who haven't used protease inhibitors, or any anti-HIV therapy at all? Are some of the drugs used today more or less likely than others to contribute to these problems? Are there any treatments that can prevent or treat these changes? What is the long-term consequence of these changes, and what percentage of HIV infected people are experiencing them?

Sadly, all these questions currently remain unanswered. Changes in body composition and all laboratory (e.g. blood work results) abnormalities associated with these changes have not been clearly defined, but are currently grouped together and referred to as "lipodystrophy" (pronounced, lip-oh-dis-troh-fee).

Can Lipodystrophy Be Treated?

While lipodystrophy clearly affects an increasing number of people, there have been no controlled

studies investigating how to treat the condition. Reports of individual successes cannot be considered predictive of whether the treatments will work for others.

Three separate reports claim some success in treating lipodystrophy associated with the use of protease inhibitor-containing regimens. Those reports occurred as a result of switching people off protease inhibitors and substituting a non-nucleoside reverse transcriptase inhibitor (NNRTI) (see *Drug Identification Chart* on page 4). Physicians reported some reductions in central obesity (fat around the gut); however, not everyone had a return of peripheral fat (fat in the arms and legs). Reductions were also reported in lipid levels (cholesterol and triglycerides) and a reversal of insulin resistance (which is associated with diabetes).

One potential area of concern from a study showed that 10% of the group who switched to

When lab marker changes reach what appear to be life threatening levels, physicians should act appropriately, just as they would any other time these tests show alarming results.

a NNRTI-class drug had increases in HIV levels. This could be just coincidence. It is possible these people would have had an increase in HIV levels if they stayed on their protease inhibitors. Nevertheless, this observation does cause some concern.

Despite these seemingly positive findings, the number of people involved was very small and some individual physicians have reported contradictory results in their own medical practices.

A physician in New York has observed that growth hormone (Serostim[®]) had some effect in reducing central obesity and buffalo hump in a few patients. But Serostim[®] had no effect on facial and limb wasting or on decreasing lipid levels. One person had to stop growth hormone therapy because of side effects and had a rapid return of central obesity. It was again reduced when the growth hormone was restarted. Considering the extremely high cost of Serostim[®] and the apparent need for continuous therapy, it is hard to consider

this approach particularly hopeful.

A number of people have reported success with using liposuction technology to remove disfiguring *buffalo humps*; however, there is every reason to fear that such humps will slowly grow back over time, since the underlying cause has not changed. Liposuction is not recommended for treatment of central obesity, since the fat is stored deeply behind the abdominal muscles and cannot be easily removed. Some women have resorted to breast reduction surgery when excessive growth lead to pain and difficulty walking. Surgical solutions such as these should only be considered in the most extreme cases, especially since their long-term success is unknown.

Several small studies looked at the use of specific drugs to treat some of the laboratory abnormalities associated mainly with the use of protease inhibitor therapy. One study showed that the combination of gemfibrozil (Lopid[®]) and atorvastatin (Lipitor[®]) lowered lipid levels to the normal range in about 50% of people. Another study showed that metformin (Gluco-phage[®]) reduced central obesity and insulin resistance but also led to an average 2kg weight loss. Finally, one other study showed that troglitazone (Rezulin[®]) reduced glucose levels but had no effect on lipid levels.

Many of these therapies have potential drug interactions with protease inhibitors. Doctors and patients who consider experimenting with these approaches to manage lab abnormalities should talk to a pharmacist about possible drug interactions and any necessary dose adjustments to therapies.

Commentary

It is difficult to conduct studies to treat lipodystrophy because of the need for an agreed upon case definition. An Australian group is likely to have some new results by the middle of this year that may give us a better definition for lipodystrophy. A large US study will start shortly to look at the prevalence of lipodystrophy. That study may also provide us a better working definition to use

in other studies as well as in clinics.

To date, much of the effort to study lipodystrophy has been driven by pressure from AIDS activists. Even though the problem has been evident for nearly three years, it has taken a very long time for pharmaceutical companies and the research community in general to take positive steps toward further understanding it. It appears that community pressure has once again been helpful since several new studies will soon be underway, by both government and industry.

Many groups are studying the cause of lipodystrophy. Glaxo Wellcome scientists have recently reported that they have conducted laboratory studies which seem to have identified two possible causes of fat redistribution. Both mechanisms are similar to, but not exactly the same as, that posed by the Australian group previously. The Glaxo theory suggests that the problem might be caused by one mechanism by ritonavir, saquinavir, and nelfinavir, and/or a somewhat different mechanism related to indinavir. For the moment, they believe that their own protease inhibitor, amprenavir, poses neither problem, but only time will tell if this is accurate or merely self-reporting.

Unfortunately, in the meantime, there is very little information available for people on how to diagnose and treat this syndrome. For most people, fat redistribution does not become physically dangerous. However, triglyceride and cholesterol levels can become so severely elevated that many physicians worry about increased risks of heart disease and other serious conditions. Careful and frequent monitoring of lab tests, along with regular physical examinations, should become part of the medical routine for people on combination therapies. When lab marker changes reach what appear to be life threatening levels, physicians should act appropriately, just as they would any other time these tests show alarming results.

It is unclear just how widespread these problems are, with various groups reporting incidence levels ranging from roughly 15% to as high as 75%. This widespread difference probably reflects variations in the underlying definition used for lipodystrophy. There is as yet no reason to suspect that these problems will affect everyone, but there is certainly enough evidence to suggest that a serious problem exists which demands greater attention than it has been given.

What Is "Lipodystrophy"?

Currently there is not an official definition for lipodystrophy, which makes it difficult to study in any systematic way. The following "working" definition lumps together the thinking of a number of groups. Much of this information may prove useful for doctors and their patients in monitoring for possible early signs of lipodystrophy.

Noted changes in body composition (self-reported by a patient, diagnosed or confirmed by a physician with the aid of tests such as magnetic resonance imaging (MRI), comparative photographs and measurements, or made apparent review of medical records). *These changes include at least one of the following:*

- **Peripheral fat wasting** (a significant decrease in fat from the face, arms, butt and legs), resulting in a thin or *drawn* look.
- **Central obesity** (truncal obesity or *protease paunch*). This build-up of fat behind the stomach muscle is generally not "mushy" but rather fairly firm/hard; this fat is different than the normal increases in fat associated with aging.
- Development of a **dorsal fat pad** (*buffalo hump*), a build-up of fat at the base of the back of the neck between the shoulders.
- **Breast enlargement**. This is a build up of fat in the breasts and has been observed in both women and men.

The changes in body composition are commonly accompanied by *abnormal lab results including at least two of the following:*

- Elevated triglyceride levels, >2mmol/l
- Elevated cholesterol, >5.5mmol/l
- Elevated C-peptide, >2.5mmol/l
- Glucose intolerance
- Impaired fasting glucose, 6.0-7.0mmol/l
- Impaired glucose intolerance, 7.8-11.1mmol/l
- Diabetes mellitus, >7.0mmol/l fasting or >11.1mmol/l non-fasting

Because other HIV-related conditions might effect body composition, if an individual has had a serious HIV-related condition (e.g. an AIDS-defining condition) within the past three months, it can't be certain that changes in body composition are a result of lipodystrophy. They might be due to other infections.

We know that certain therapies (*anabolic steroids*) also affect body composition. If changes in body composition occur while someone is taking these therapies, it is unclear if the changes are HIV-related, related to anti-HIV therapies and/or related to the anabolic steroids.

Project Inform Website



If you have an internet connection to the world wide web and are looking for HIV/AIDS treatment information, log onto Project Inform's HIV/AIDS Treatment Website at:

www.projinf.org

Lipodystrophy Studies in Women E

Several studies on body composition changes and abnormal changes in laboratory values (i.e. blood work results) associated with the use of anti-HIV therapy were presented at the recent conference in Chicago (For a definition of “lipodystrophy,” see *Lipodystrophy* on page 14).

The first examined the relationship between body composition (fat distribution) and two laboratory measures being associated with lipodystrophy, insulin levels and cholesterol levels, in 33 women treated with protease inhibitor-containing anti-HIV regimens. It found that women treated with protease inhibitors were more likely to have elevated waist-to-hip ratios (WHR) compared to HIV negative women and that this increase was independent of any overall change in weight (i.e. weight gain). This means that women with HIV receiving protease inhibitors were more likely to have larger waste sizes, relative to their hip size compared to HIV-negative women.

Whether women living with HIV not receiving protease inhibitors also have higher WHR compared to HIV-negative women will be important in understanding the contribution of protease inhibitor therapy to this observation. Another interesting finding was that the elevated WHR was significantly correlated with higher levels of triglycerides, glucose levels and apoB. While this study was relatively small, it suggests important clues about the relationship between physical and chemical changes some women on protease inhibitors appear to be experiencing.

A second study compared changes in body shape between women receiving protease inhibitors (PI) and women not using protease inhibitor-containing anti-HIV regimens. Ninety-five women on protease inhibitors and 35 women not receiving protease inhibitor regimens were examined. While increases in breast and waist size were reported among both groups, women on protease inhibitors tended to have a more

dramatic size increase in both measurements (3 or more size increase for bras and 4 or more size increase for pants). The difference among the two groups, however, was not dramatic enough to be able to equate increases in breast or waist size, overall, strictly to the use of protease inhibitor-containing regimen. Despite the increase in breast and waist size, changes in overall body weight for both groups was minimal (a median gain of 7.8 pounds for women on PI versus 3.8 pounds). Finally, 7% of women participating in the study discontinued PI therapy because of changes in body shape.

Further confirming these findings was a study showing similar patterns of body shape changes in women taking anti-HIV regimens that did *not* include protease inhibitors. Among 306 women

participating in the study, enlargement of the breasts and waist (abdomen), and wasting of the butt, thighs and calves were reported in 32 women (10.5%). All of the women reporting fat redistribution were receiving a regimen containing 3TC (lamivudine, Epivir[®]), a nucleoside analog reverse transcriptase inhibitors (NARTI). Twelve of the 32 women reporting body shape changes were taking double combination therapy (including 3TC) that did not include a protease inhibitor. Additionally, among women taking 3TC, the risk of developing changes in body shape was significantly lower in those also taking AZT (zidovudine, Retrovir[®]) and higher in women taking D4T (stavudine, Zerit[®]). Thus, the study suggests a strong association between body shapes changes and the use of 3TC, including women who had never taken a protease inhibitor. While far from confirmed, these data suggest that the mechanism causing changes in body shape in women on anti-HIV therapy may not necessarily be related to protease inhibitors.

Menstrual Irregularity Co-Factors Chart

(accompanies *Women and AIDS*, page 17)

FACTOR	COMMENTS
Age	Younger and older age are both associated with menstrual irregularities. Young women often have irregularities when first beginning to menstruate, sometimes lasting through puberty. Older women, especially those going through menopause, also commonly have irregularities. On either end of this age spectrum, hormone therapy (e.g. progesterone/estrogen) may help to regulate menstrual cycles. However, it is not known if trying to regulate these natural changes is helpful.
Body Mass Index	Women who are very thin, malnourished, or who generally have extremely low levels of body fat often have menstrual irregularities, particularly increased time between menstruation and/or very light bleeding during periods. For women who are thin because of malnutrition and unwanted weight loss issues, attention to the treatment of unwanted weight loss can help to regulate the cycle.
Drug Use (substance use/abuse)	Injection drug and other substance use are associated with changes in menstrual cycles.
Illnesses and Infections	Some illnesses, and side effects from drugs used to treat them, can influence menstrual cycles. Inflammatory and infectious conditions (e.g. vaginitis and pelvic inflammatory disease) can also affect regularity.
Dysplasia	Dysplasia (e.g. vulvar, vaginal, cervical and ovarian) is associated with changes in menstrual cycles.
Race	While this particular study only looked at whites, Latinas and African Americans, there did appear to be more menstrual irregularities among African Americans compared to the other groups. It may be, in this particular study, that other factors confounded the ability to truly isolate any differences caused by race difference. However, even this hint of a racial differential warrants further study.

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Women and AIDS Update E

The following are selected treatment briefs from the 6th Conference on Retroviruses and Opportunistic Infections. While these studies are of special interest to women, they do not exhaustively cover all the gender-specific information presented at the conference or reviewed in this issue.

Menstrual Irregularity

Women have long reported menstrual irregularities associated with HIV infection, including shortened or lengthened time between menstruation, heavier or lighter flow of menstrual blood and other irregularities. Research findings, however, have been yielding conflicting results regarding the association between menstrual irregularity and HIV status. A new study confirms an association and observes that irregularities appear more frequently as HIV disease progresses.

Included in this report were 802 HIV-positive and 273 HIV-negative women from two large studies (HIV Epidemiology Study or HERS and Women's Interagency HIV Study or WIHS). Women self-reported information about their menstrual cycle over the course of six months.

Overall, the study found that HIV-positive women, who were otherwise healthy, had high CD4+ cell counts, were not experiencing unwanted weight loss (wasting syndrome) and not using/abusing drugs were unlikely to have menstrual irregularities. As HIV disease progresses, however, there does appear to be some effect of HIV on hormones, as measured by increased incidence of menstrual irregularities. Women with lower CD4+ cell counts (below 200) were 50% more likely to have longer menstrual cycles (over 40 days) than women with counts above 200. Women with high HIV levels (above 150,000 copies/ml) had the most variability in their menstrual cycle, shorter and longer times between cycles with a large amount of unpredictability.

This study confirms a relationship between HIV infection and changes in the menstrual cycle, which becomes more pronounced as HIV disease progresses, CD4+ cell counts fall below 200 and HIV levels increase. The study confirms that other factors are important determinants of menstrual irregularity and should be considered when and if they occur. These include drug use, poor nutrition, severe medical illness and weight loss associated with chronic illness. A number of other factors have also been identified in other studies (see *Menstrual Irregularities Co-Factors Chart* on page 16).

Comments

It is not surprising that there is a relationship

between HIV infection and menstrual irregularities. Male hormone irregularities (testosterone deficiencies) are associated with HIV disease progression, fatigue and wasting syndrome. Similarly, female hormone changes, as measured by increases in menstrual irregularities, are associated with advanced HIV-disease and wasting syndrome. The question now is what to do about these changes. Will hormone replacement therapy (e.g. estrogen/progesterone) help regulate menstrual cycles and/or improve symptoms associated with hormone imbalances such as fatigue and decreased sexual drive? Should women receive anabolic steroids (like testosterone) when they experience signs of unwanted weight loss and/or decrease in sexual energy? Now that menstrual irregularities have been documented, and the group of women likeliest to experience them have been defined, studies looking at therapies to intervene and correct these irregularities should proceed quickly. Activist attention is needed to make it happen.

Human Papilloma Virus

Human Papilloma Virus (HPV) is a sexually transmitted disease that causes anal and genital warts and is associated with anal and cervical dysplasia. It is a common infection, particularly among women with HIV. Several studies confirm previous findings that women with HIV, particularly those with low CD4+ cell counts, have increased frequency and severity of HPV-associated cervical dysplasia.

One study examined the incidence of HPV-associated lesions in women without HPV who were enrolled in a study from 1991-98. Every six months, 369 HIV-positive and 334 HIV-negative volunteers had gynecological (GYN) exams and colposcopies. Thirty-one (8%) of HIV-infected and two (1%) of HIV-negative women developed

HPV-related lesions throughout follow-up (3.3 years, 3.7 years, respectively). Not only were HIV-positive women more likely to develop HPV-related lesions, but the average time to lesion development was shorter (24 months, 44 months, respectively). Also, the majority (61%) who developed a lesion had a history of cervical intraepithelial neoplasia or CIN. (CIN—or cervical dysplasia—is a form of abnormal cell growth of which, at its most severe, is cervical cancer.) The study found that risk factors for lesion development included CD4+ cell counts below 500 and detection of HPV in cervico-vaginal lavage (CVL, a screening procedure).

Another study examined the relationship between incidence of HPV and immune suppression in 268 female intravenous drug users. In it, 814 HIV-positive and 84 HIV-negative women underwent an average of six HPV measurements. Among 187 women with follow-up visits subsequent to the first measurement, the probability of testing HPV-positive increased dramatically for HIV-positive (78.7%) compared to HIV-negative women (47.5%). It was high among HIV-positive

HIV-related immune suppression is a co-factor for the development of HPV and HPV-associated cervical dysplasia. These studies underline the importance of careful and regular GYN screenings for women with HIV, particularly those with CD4+ cell counts below 500.

women with CD4+ cell counts below 200 (92.9%). Also, of 107 women evaluated by colposcopies, eleven had biopsies confirming CIN. These results suggest that HIV-infection and its associated immunodeficiency is strongly related to the persistence of HPV which in turn is associated with CIN.

Another study characterized the incidence and progression of HPV in HIV-infected women with varying levels of immune suppression. Between 3/96 and 7/98, 112 women were evaluated by twice-yearly GYN exams, CVL and STD screenings. In the study, 112 women (63%) had detectable HPV at the initial exam, with another 77 (69%) testing HPV-positive during the course of the study. In addition, 23 (20.5%) were infected with two or more HPV types, and three were infected with a unique or previously unidentified type. These results demonstrate that HPV is highly prevalent and persistent among women with HIV. They demonstrate that HPV types may be distinct in women with HIV.

Comments on HPV

These studies confirm that HIV-related immune suppression is a co-factor for the development of HPV and HPV-associated cervical dysplasia. Other co-factors include smoking, age of first sexual

intercourse and, possibly, hormonal issues. These studies underline the importance of careful and regular GYN screenings for women, particularly those with CD4+ cell counts below 500 (e.g. at least every six months).

Treatment of Recurrent Cervical Dysplasia (CIN)

Previous studies confirm that abnormal cell growth in the cervix (cervical dysplasia), associated with cervical cancer, is more common and potentially more aggressive among women living with HIV compared to uninfected women. Women with HIV have extremely high recurrence rates of cervical dysplasia after standard treatment (39–87% among HIV-positive women vs. 0–18% among HIV-negative women). A study of the AIDS Clinical Trials Group (*ACTG 200*) examined the safety and effectiveness of a therapy called 5-Fluorouracil (5-FU) for preventing recurrent cervical dysplasia (CIN). 5-FU has been successful in treating skin lesions in HIV-negative people as well as vaginal dysplasia in women with immune suppression not associated with HIV.

One hundred and one women who had received standard treatments for cervical dysplasia (CIN grades 2 or 3) received either 5% 5-FU or no therapy and were followed for a year and a half (18 months). Those receiving 5-FU received one 2 gram application intra-vaginally at bedtime every two weeks for six months. The medication was not administered during menstruation. Pap smears and colposcopies were scheduled at regular intervals during the 18 months of follow-up.

Of the 50 women who received 5-FU, 14 (28%) developed cervical dysplasia recurrence, compared to 24 (47%) of the 51 women in the observation arm. Most significantly, 5-FU therapy was significantly correlated to prolonged time to recurrence of CIN and decreased probability of developing high grade CIN, which requires more aggressive treatment. Additionally, 5-FU therapy reduced recurrent cervical dysplasia with minimal side effects (vaginal discharge was the most common, occurring in six women). These results suggest that this treatment should be offered to HIV-positive women after therapy for high-grade CIN.

For more information on GYN conditions associated with HIV infection, call the Project Inform Hotline and ask for the new *GYN Conditions Discussion Paper*.

Gender Difference in Viral Load E

In current medical practice, HIV levels and CD4+ cell counts are measured and interpreted and help guide anti-HIV therapy decision-making without regard to gender. Two recently reported studies are giving pause to this standard of practice. They suggest that women have progression of HIV disease at lower viral levels than men.

A Federal Guidelines Panel, which provides guidance on the use of anti-HIV therapy in adults, recently held a meeting to review new information on gender differences in viral load. It concluded that presently these new data are not different enough to warrant recommendations for a different standard of care for women with HIV, nor should they be cause for alarm for women living with HIV. Nevertheless, women and their doctors should be aware of these data which may support initiating and switching therapy at a lower HIV levels than what is currently recommended in the Federal Guidelines document.

The A.L.I.V.E. Study Results

The first of two studies was presented at the 1998 World AIDS Conference in Geneva, Switzerland and was recently summarized in the scientific journal, *The Lancet*. Based on a large group of HIV-positive men and women with a history of injection drug use, involved in the A.L.I.V.E. study. It compared blood samples collected and stored from 527 participants since the late 1980s with 285 blood samples collected at least three years later.

HIV levels, CD4+ cell counts and information about the general health of the study participants at both time points were examined to see if there were unique differences according to gender and/or race. Differences based on gender did come forward. Women in the study had HIV levels 38 to 65% lower than what was observed in men. In general, women's HIV levels were half that of men in the study.

Viral load was consistently lower in women than men even after adjustments for CD4+ cell count differences were made. This difference persisted after accounting for other factors that the researchers felt could possibly influence the lower viral levels seen in women, such as race, current and previous use of anti-HIV therapy and use of street drugs. None of these factors explained the

gender difference in HIV viral levels.

Researchers also looked at the association of viral load, CD4+ cell count and time to AIDS between men and women. They found that women and men with similar CD4+ cell counts had a similar progression time to AIDS. In addition, the differences in viral levels among men and women suggest that women appear to progress to AIDS with about half the viral load as men. In other words, women with half the viral load as men had a similar time to AIDS. Respectively, women with the same viral load as men had a higher risk of AIDS. What this probably means in is that for women with low CD4+ cell counts (e.g. below 200), CD4+ cell count is a more reliable indicator of general health and overall risk of HIV disease progression than is HIV levels. It also suggests that in-

creases in HIV levels that are sustained, even modest ones, might be slightly more of concern to women than their male counterparts.

CD4+ cell counts provide useful measures of the risk of disease progression and their meaning is not influenced by gender.

The WIHS Study Results

Similar findings were presented at the recent Conference on Retroviruses and Opportunistic Infections from a second study. Stored blood samples in 1984-85 from 1,511 HIV-positive men enrolled in the Multi-center AIDS Cohort Study (MACS) were compared with blood samples obtained in 1994-95 from 1,262 HIV-positive women enrolled in the Women's Interagency HIV Study (WIHS). When the original blood samples were collected, no one from either group was using anti-HIV therapies.

Like the ALIVE study, differences in viral load emerged. The degree of difference, however, was less dramatic. Also, differences were associated with specific CD4+ cell count levels. HIV levels were not different among men and women with CD4+ cell counts below 200. However, women whose CD4+ cell counts were 200–500 had a 40% lower viral level compared to men

with the same CD4+ cell count. For CD4+ cell counts above 500, viral levels were 24% lower for women than for men. Thus, according to the WIHS/MACS comparison, women's overall viral load was approximately 20% lower than men's, with significant differences in the two CD4+ cell groupings shown below.

Researchers from the WIHS/MACS cohort conclude that HIV load is lower in women than men, but only at CD4+ cell counts above 200. They suggest that the use of the viral load tests, particularly when used as a starting point for beginning anti-

Differences in Viral Load According to CD4+ Cell Count (WIHS/MACS)

CD4+ Cell Count	Percent Lower Viral Level in Women
Less than 200	Insignificant
200–500	40%
Above 500	24%

HIV therapy, may need to be adjusted for gender to account for this difference. The largest impact of these findings is probably on how they affect women with CD4+ cell counts in the 200 to 500 range who are making decisions about therapy changes based on viral load.

Commentary on These Findings

While these findings are far from confirmed, they do raise important questions with regard to viral load in women and related risks of disease progression. These studies also remind us of two other points. CD4+ cell counts provide useful measures of the risk of disease progression and their meaning is not influenced by gender. Moreover, the decision to start, add or change therapy should never be decided solely on the basis of one laboratory measure (e.g. just viral load, just CD4+ cell counts, etc.).

Treatment decisions should factor in trends in viral load, trends in CD4+ cell counts, the number of available future options, side effects, ease of adherence, how one feels about anti-HIV therapy and measures of overall general health. Whether or not viral load differences according to gender should be considered a treatment decision point demands further study.

For more information on gender differences in viral load, call Project Inform's toll-free National HIV/AIDS Treatment Hotline at 1-800-822-7422 and request *WISE Words*, Issue #3.

Opportunistic Infections Update

Until recently, the incidence of opportunistic infections (OIs) had been steadily decreasing. This is partially a result of the use of effective anti-HIV combination therapies containing a protease inhibitor (sometimes called Highly Active AntiRetroviral Therapy or HAART) and partially a result of a general decline in the number of people infected several years ago. Although hard figures have not been presented, many researchers at the recent Conference on Retroviruses and Opportunistic Infections noted that they have recently seen increases in the number of new cases of OIs.

This seems to suggest that some people have already worked their way through all or most of the available therapies and can no longer keep their viral loads low enough or their CD4+ counts high enough to ward off the risk of opportunistic infections. At least in theory, there is no magic to this observation. If anti-HIV regimens are working well enough, and some people are seeing their immune health begin to decline, it is natural to expect an increased risk of opportunistic infections. This re-emphasizes the need to start or restart preventative medications for opportunistic infections. Listed below are summaries of several studies presented at the conference.

Mycobacterium Avium Complex

Mycobacterium avium complex (MAC) is a serious bacterial infection and is one of the most common OIs in people with advanced HIV disease. A recently completed study for the treatment of MAC shows that the three-drug combination of clarithromycin (Biaxin[®]) + ethambutol (Myambutol[®]) + rifabutin (Mycobutin[®]) is more effective than two-drug regimens of either clarithromycin + ethambutol, or clarithromycin + rifabutin. Compared to people on either regimen, those who received the three-drug regimen had more improvements in symptoms and decreases in the number of MAC organisms (called MAC colony forming units) found in their blood. Additionally, people on the three-drug combination had a survival advantage compared to those receiving either of the two-drug regimens.

Further, participants who received clarithromycin + rifabutin were more likely to relapse (develop MAC disease again) and develop resistance to clarithromycin. This is important to know as clarithromycin is widely considered to be the most active drug against MAC. Once resistance sets in a person's ability to combat MAC is greatly diminished. The results from this study suggest that the triple combination of clarithromycin+ethambutol+rifabutin should now be considered the standard

of treatment for people with MAC disease.

Two hundred and three people with MAC were enrolled in this study, also known as AIDS Clinical Trials Group Study 223. The doses used in the various combinations were 500mg twice a day of clarithromycin, 15mg/kg/day of ethambutol and 450mg once a day of rifabutin.

Cytomegalovirus

Cytomegalovirus (CMV) is a potentially life-threatening virus and is the leading cause of blindness in people with HIV disease. Recent evidence suggests that the incidence of CMV is down. A number of studies are looking at the feasibility of stopping therapy aimed at preventing recurrence of CMV disease (or *maintenance therapy*). Results so far suggest the need for caution when one thinks about stopping maintenance therapy. They underline the continued importance of CD4+ cell counts as the primary measure for determining one's immediate risk of developing CMV.

One study reported on 17 people who stopped their CMV maintenance therapy after getting an increase in CD4+ cell counts from HAART. All of the participants had CD4+ cell counts over 70 and had healed CMV retinitis, an inflammation of the eye that can cause blindness if left untreated. Despite continuing their HAART regimen, five of the seventeen participants had their CMV retinitis reactivated after being off maintenance therapy for 6–28 months. All volunteers who had CMV reactivation had seen their CD4+ cell counts return to below 50 and typically had higher HIV levels compared to people who did not have reactivation. Also, five of the six people with CMV reactivation had very low levels of the immune system marker that has the ability to combat CMV (called CMV-specific lymphoproliferative responses). No participant who maintained CD4+ cell counts above 100 had CMV reactivation.

This study suggests it may be wise to wait until CD4+ cell counts go above 100 for several months

before discontinuing CMV maintenance therapy. Also, people who have a subsequent decline in CD4+ cell counts to below 75 may want to reconsider starting CMV maintenance therapy before CMV reactivation recurs. In many ways, these findings reflect the general guidelines employed for CMV before the use of highly potent antiviral regimens. Earlier guidelines typically suggested taking CMV prevent medications when the CD4+ count fell below 75.

***Pneumocystis carinii* Pneumonia**

Preventative treatment against *Pneumocystis carinii* Pneumonia (PCP) is typically recommended for HIV-positive persons with CD4+ cell counts below 200 or for those below 300 while persistent fungal infections (thrush) occur.

Preliminary results from a study indicate that it may be safe for people who have improvements from HAART resulting in sustained CD4+ cell counts above 200 and no persistent infections, such as recurrent oral or vaginal thrush to discontinue PCP preventative therapy. All partici-

pants had sustained improvements in health due to HAART, including a CD4+ count over 200 cells and HIV levels below 500 copies HIV RNA for at least three months. Participants were assigned to either continue or discontinue their PCP preventative therapies. After a median follow-up of almost seven months, there have been no cases of PCP recurrences. This suggests that it may be a safe strategy for people with continued improvements due to HAART to consider discontinuing their PCP preventative therapies.

Three hundred and thirty-two people participated in this study, all of whom had previous CD4+ cell counts below 200 or had been previously diagnosed with PCP.

Hepatitis

Results from a new study suggest that almost all people with HIV who are given the hepatitis A vaccine (VAQTA) achieve levels of antibody that should be protective against hepatitis A virus. Everybody with CD4+ cell counts above 300 showed antibody titer levels that should be protective against hepatitis A compared to 88% of people with CD4+ cell counts below 300. This study suggests that hepatitis A vaccines can be safely administered to people with HIV.

Other studies have reported that people co-infected with HIV and hepatitis C virus (HCV) experience a more rapid decline and generally worse course of liver disease than people infected only with HCV. People with both HIV and HCV have higher viral loads of both viruses. They have more severe fibrosis (abnormal formation of fibrous liver tissue); are more likely to develop cirrhosis (more severe liver damage resulting in the loss of functioning cells); and have higher rates of mortality compared to people only infected with HCV (and not HIV) or people only infected with HIV (and not HCV). Available therapies to treat HCV are limited to the various brands of interferon-alpha (Intron A[®], Roferon A[®]), consensus interferon (Infergen[®]) or a combination of Intron A and ribavirin sold in a bundle called Rebetron[®].

The strongest and longest lasting results generally come from combination therapy with Intron A interferon with ribavirin. Other brands of interferon combined with ribavirin may work as well or perhaps even better, but the forced bundling of ribavirin with Intron A by the sponsor, Schering-Plough, makes it all but impossible for physicians, patients, or even researchers to explore the possible benefits of other such combinations. Other brands of interferon that could be combined with ribavirin may offer different or lesser side effects, or may offer potential advantages in potency. The marketing practice of Schering-Plough which currently block such

research and uses can only be described as self-serving and not in the patients best interests.

A number of other drugs are also understudy for the treatment of HCV. Eventually other combinations are likely to become available, perhaps even following in the footsteps of HIV research which found that three drug combinations were usually the most effective.

One disturbing observation reported in some HCV studies involving people who were HCV- but not HIV-infected. It showed that African Americans appear less likely to respond to interferon-alpha therapy compared to Caucasians. Preliminary results suggest that about 30% of Caucasians respond to interferon-alpha therapy compared to only about 5% of African Americans. Conversely, women and Asians seem to have better responses. Whether this is also true of the more potent combination of interferon and ribavirin is unclear. Even across ethnic lines, the maximum success rate of interferon used alone, about 30%, is not very encouraging. Today, it is more important to determine whether African Americans respond as well to approved therapies for treating hypertension. More research needs to be focused in this area so that effective therapy against HCV can be given to everyone.

Commentary

Some of these studies suggest that it is possible for people to stop their preventative or maintenance therapies after getting improved immune response (usually defined by an increase in CD4+ cell count) from HAART. However, it appears that there is increasing risk for people to develop or have relapses to opportunistic infections after HAART fails and CD4+ cell counts start to decline. The availability of better measures of immune response to specific opportunistic infections would help in predicting who can safely stop preventative or maintenance therapies or who needs to restart them.

Ultrasensitive PCR Approved

The Food and Drug Administration recently approved the ultrasensitive PCR (polymerase chain reaction) test, which measures the amount of HIV found in blood. This new test is an improvement over the existing test because it can measure the amount of HIV found in blood down to 50 copies of HIV RNA per milliliter of plasma (the liquid part of blood). The older test is only able to measure down to 400 copies per milliliter of plasma.

Several studies have shown that people who are able to suppress HIV levels below 50 copies HIV RNA are more likely to have longer-lasting anti-HIV activity. The ultrasensitive test is considered to give accurate results in people with HIV levels between 50 and 75,000 copies HIV RNA whereas the older test is considered accurate between 400 and 750,000 copies HIV RNA.

Roche Diagnostics, the developers of these two tests, has established a Patient Assistance Program to ensure access to the test for those not covered by insurance or other third-party payers. The program can be reached at 1-888-TEST-PCR.

Interleukin-2 (IL-2, Proleukin®)

Several studies of IL-2 were reported at the recent conference. Together, they confirm the ability of IL-2, when added to anti-HIV therapy, to produce dramatic CD4+ cell count increases above what is observed when anti-HIV therapy is used alone. Moreover, study results confirm the safety of IL-2 with regard to its impact on HIV replication.

In laboratory experiments, in which IL-2 acts alone independent of other processes of the immune system, IL-2 can dramatically increase HIV replication. It does this by activating T-cells, including those which are infected with HIV, causing them to produce more HIV and to replicate themselves, leading to even more HIV production. In human studies, however, the use of IL-2 has been shown to only temporarily increase HIV replication. Overtime, people receiving IL-2 in addition to standard anti-HIV therapy appear to have control of HIV replication comparable to those receiving only anti-HIV therapy. An important new finding from one study is that people receiving IL-2 with anti-HIV therapy may have even greater suppression of HIV replication compared to what is observed in people receiving anti-HIV therapy alone.

What is the Optimal Starting Dose of IL-2?

An IL-2 study in Argentina included 73 volunteers with CD4+ cell counts greater than 350 who received one of three doses of IL-2 in combination with anti-HIV therapy or anti-HIV therapy alone. Thirty-six volunteers received 1.5, 4.5 or 7.5 million international units (MIU) of IL-2, twice daily, delivered through injection under the skin (subcutaneous injection) for five consecutive days every eight weeks. The remaining 37 volunteers received only anti-HIV therapy.

At the end of 6 months, the 4.5 and 7.5 MIU, twice daily IL-2 doses produced the most dramatic CD4+ cell increases. Those receiving the 1.5 MIU twice daily dose experienced a mean CD4+ cell count increase of 81 cells, whereas those receiving the 4.5 and 7.5 MIU twice daily doses had increases of 359 and 520 cells over their pre-therapy counts, respectively. Those receiving only anti-HIV therapy experienced an increase of about 100 after 6 months.

These results are similar to those of other dose ranging studies of IL-2. When looked at together, studies seem to suggest that the most immediate and pronounced CD4+ cell increases are seen among people who start IL-2 at the higher (4.5 or 7.5 MIU twice daily) doses. However, even

in these studies, most people who start at this highest dose (7.5 MIU, twice daily) experience side effects that necessitate IL-2 dose reductions. A number of different studies appear to show, in general, that after 1 year of IL-2 therapy the 4.5 MIU twice daily dose is the most commonly used dose to maintain CD4+ cell increases.

What is the Effect of IL-2 Therapy on HIV?

Another recent study (known as CS-L2002), examined the impact of IL-2 with anti-HIV therapy on CD4+ cell counts and HIV replication. This study concluded that IL-2 might also lead to enhanced control of HIV replication.

CS-L2002 included people with pre-study CD4+ cell counts ranging from 200 to 500. Forty-one volunteers received anti-HIV therapy alone and 37 received IL-2 with anti-HIV therapy. Most studies of IL-2 reported to date were initiated in the pre-protease inhibitor era. This study is among the first initiated after 3-drug regimens had become the standard of care. Therefore, most of the people in the study were on at least a 3-drug combination, typically including a protease inhibitor. Note that a significant percentage of people in all groups started the study with viral load already under control due to their on-going use of anti-HIV therapy. The primary interest of the study was to measure the effect on CD4+ cell counts and to see whether adding IL-2 had any

further positive or negative impact on viral load. The following are the results after 1 year: Clearly those receiving anti-HIV therapy and IL-2 experienced more dramatic CD4+ cell increases than those receiving only anti-HIV therapy. Perhaps even more interesting is the obvious trends toward better anti-HIV responses among those receiving IL-2. At study entry, the percentage of volunteers with viral load below the limit of detection on the most sensitive test was 31 in the anti-HIV therapy alone group and 39 in the group receiving IL-2. At the end of one year, the number of people with viral load below the limit of detection of the most sensitive test grew only slightly (5%) among those receiving anti-HIV therapy, to 36%. This suggests that simply continuing on potent anti-HIV therapy had little overall effect compared to that seen at the start of the study. In contrast, the group which added IL-2 on top of anti-HIV therapy saw a large increase in the percentage of people with viral level suppression to below the limit of detection after a year, from 39% to 65%. This suggests that IL-2 might be enhancing control of HIV replication.

Commentary

Two large studies of IL-2 are currently enrolling. IL-2 has serious side effects and can be very difficult to use. Fortunately, the side effects usually affect people on the days they use the drug and IL-2 is typically used only for a few days every other month. Knowledge of, preparation for and management of side effects is key to incorporating IL-2 into a treatment regimen. For more information about IL-2 and IL-2 side effects, call the Project Inform hotline.

Results of IL-2 Therapy in Combination with Anti-HIV Therapy

Viral Load Count	At Study Entry	Results @ 1 Year
Mean CD4+ cell count (AT alone)	341	405 (18% increase)
Mean CD4+ cell Count (AT + IL-2)	355	739 (112% increase)
% with viral load below 500 (AT alone)	44%	46%
% with viral load below 500 (AT + IL-2)	59%	68%
% with viral load below 50 (AT alone)	31%	36%
% with viral load below 50 (AT + IL-2)	39%	65%

AT = Anti-HIV therapy

IL-2: Flushing the Reservoir?

The previous issue *PI Perspective* reported preliminary results of a study conducted at the National Institutes of Health (NIH). The initial findings suggested that IL-2 therapy, used in conjunction with potent anti-HIV therapy, might enhance control and elimination of HIV from certain reservoirs where the virus is known to be preserved in the body (See *IL-2: A Path Toward Functional Eradication? PI Perspective 26*). At the Chicago meeting, the researchers reported that two of the volunteers have now stopped their use of anti-HIV medications with no rebound in HIV levels after being off therapy for the first three weeks. Researchers will continue to follow these patients to see when and whether HIV replication again becomes detectable. A few other studies presented at the conference did not support the findings observed in the NIH study. Since all of these studies are using somewhat different methods, it is difficult to compare their results. Larger studies are underway which may shed further light on this subject.

One study included people with a mean CD4+ count of 487 at study entry, who received a four-drug anti-HIV therapy regimen (including two protease inhibitors) with or without IL-2 therapy. The goal of the study was to see if adding IL-2 to aggressive anti-HIV therapy will further decrease evidence of HIV infection in deep tissue reservoirs, such as the lymph nodes. Four women and 52 men were included. Lymph node biopsies were performed before initiation of anti-HIV therapy, and again after patients had sustained HIV levels below the limit of detection on the most sensitive test (Roche Ultrasensitive) for greater than six months. Levels of HIV detected in the lymph nodes were similar in both those receiving anti-HIV therapy alone and those receiving anti-HIV therapy and IL-2. After a mean of 150 days after starting anti-HIV therapy, this study showed similar rates of decline of cell-bound HIV in the lymph nodes between the two groups. This suggests that, in this combination, IL-2 did *not* have an impact on accelerating HIV clearance from reservoirs of HIV infection. However, this study used a somewhat different method of measuring the effect of IL-2 on reservoirs of infection. While based on results from only a small number of people, there was information suggesting that fewer people receiving IL-2 showed evidence of persistent virus production, however.

Another study included only three people, and included a more aggressive eradication approach, combining anti-HIV therapy with IL-2 and a potent but highly toxic immune activator, OKT3. The rationale behind this approach is to see if using IL-2 and OKT3 to activate immune cells, HIV hidden quietly in cells will be forced into view of both anti-HIV drugs as well as anti-HIV responses of the immune system. While there was clearly evidence that IL-2 and OKT3 were activating the immune system, the combined toxic effects of the therapies, particularly the side effects of OKT3, overwhelm any potential benefits of this therapeutic approach. Side effects include severe fevers and rigors. One volunteer experienced temporary kidney (renal) failure.

HIV/AIDS 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.

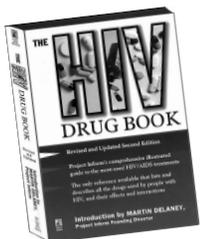
National AIDS Hotline. This Hotline operates 24 hours a day and provides referrals to local services throughout the U.S. and information about a wide variety of non-treatment related topics. Call 1-800-342-AIDS (2437). Spanish-speaking operators are available 8AM – 2AM EST at 1-800-344-SIDA (7432). For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

STEP Perspective is a newsletter produced by the Seattle Treatment Education Project. Call 1-800-869-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 1-510-986-0340.

AIDS Treatment News
San Francisco
1-800-873-2812

Treatment Issues
Gay Men's Health Crisis
New York
1-212-337-1950



The HIV Drug Book, 2nd Edition!

Revised and completely updated by the staff and volunteers of Project Inform and published by Pocket Books, the *second edition* is now available in bookstores, or it can be ordered through www.amazon.com. Look for the new cover, new look and all the new information. Over 30 new individual drug profiles . . . Updated information and new articles . . . A summary of the new guidelines on using anti-HIV drugs . . . A discussion of adherence to HAART . . . and more.

Children & HIV: Treatment Briefs E

Presentations on pediatric AIDS at the recent Retrovirus Conference focused on broadening treatment options. Highlighted were studies of anti-HIV therapies, particularly protease inhibitor (PI) containing regimens. While encouraging, studies elicited concerns of adherence and long-term side effects. Few studies dealt with these concerns, but one addressed the use of a surgically inserted feeding tube to improve adherence. Another indicated that children on PI regimens experience changes in cholesterol and other lab markers associated with body composition changes in adults.

Anti-HIV Therapy and Children

Preliminary data from studies using indinavir (Crixivan[®]), nelfinavir (Viracept[®]) or amprenavir (Agenerase[®]) with two nucleoside analogue reverse transcriptase inhibitors (NRTIs) all showed positive effects on viral load suppression and CD4⁺ cell count improvements, even among extensively treated children. The durability of the response, however, remains to be seen.

A study evaluating the dual PI regimen approach using saquinavir soft gel capsules (Fortovase[®]), nelfinavir and NRTIs also showed encouraging results. Seventeen children (median age of five) with a median CD4⁺ cell count of 600 and viral load of 10,000 HIV RNA copies/mL enrolled. Starting doses of saquinavir and nelfinavir were 33mg per kg of body weight given three times daily. While the short-term anti-HIV activity of the combination looked good, it wasn't much different from what has been seen with single PI regimens. After 24 weeks, 65% of the children had a viral load of less than 400 copies/mL, 47% had HIV levels below 50 copies/mL and CD4⁺ cell counts increased by about 159. While the regimen was generally well tolerated, the overall benefits compared to single PI regimens have not been demonstrated.

Hydroxyurea (HU, Hydrea[®]) has been shown to be a useful adjunct therapy to some nucleoside analogue drugs in the treatment of HIV infection. Studies in adults confirm that adding HU to some regimens, especially those containing ddI (didanosine, Videx[®]), enhances their anti-HIV activity. However, HU suppresses white blood cells in general and then sometimes blunts CD4⁺ cell increases usually observed with anti-HIV therapy. Therefore, in general it is probably unwise to use HU in people with very low CD4⁺ cell counts unless other alternatives are lacking. The negative effect HU may have on CD4⁺ cell counts is likely to be temporary and should stop once it is withdrawn.

A study evaluating HU in combination

with ddI and/or d4T suggests that it has similar anti-HIV effects in children as in adults. Sixteen children (median age of 6.7) participated in the 48 week HU dose-escalating study. The initial dose was between 10-20 mg/kg daily, and the final dose was 30 mg/kg once daily. While results were only available through week 16, they suggest that short-term HU therapy is safe and generally well tolerated, with moderate anti-HIV activity and minimal effect on CD4⁺ cell percentages.

Compared to adults, children appear to have more rapid clearance of HU from their blood, which may mean that children will require higher doses relative to body weight. HU remains of interest to researchers because it offers another mechanism of action against HIV, one unaffected by the development of resistance to other classes of drugs. Another possible benefit shows HU readily penetrates a wide range of cell types, some not easily reached by other drugs.

While these studies point to expanding anti-HIV therapies, more information is needed to determine how to dose these new drugs, particularly in infants and pubescent children. More data are needed to determine the most appropriate time to start or change therapy in the pediatric population.

Children and Adherence

Adherence issues are important to consider when evaluating the effectiveness of anti-HIV therapy. Dosing schedules, dietary requirements, the amount and taste of medications and children's dependence on adults may influence adherence and present obstacles to effective viral suppression.

One study described a controversial approach to dealing with adherence in kids. Seventeen children (median age of 2.9) receiving anti-HIV therapy had feeding tubes inserted. They were generally well tolerated, with 23% of children experiencing tenderness at the site within the first two months and one case of

infection requiring antibiotics. In addition to improved adherence and viral load reductions, there was a reduction in drug administration time and associated behavioral problems, such as resisting efforts to administer the medication.

Feeding tubes have been used in adults and children for nutritional support, but are not widely used because of risks associated with infections, like sepsis. This study suggests that they might be considered for some children to overcome adherence challenges. They may be very useful in situations where the parent or guardian is ill or unavailable, when the child is in school or daycare for long periods of time or in the overall absence of day-to-day stability. However, the increased risk for bacterial infections that can lead to serious, life-threatening complications remains a primary concern.

Metabolic Complications

Changes in the way fat (lipids) is processed (i.e.

Anti-HIV Drugs Used to Treat Children

Protease Inhibitors

ritonavir, indinavir, nelfinavir, saquinavir soft gel

Nucleoside Analogue Reverse Transcriptase Inhibitors

zidovudine, didanosine, stavudine, lamivudine, abacavir

Non-Nucleoside Reverse Transcriptase Inhibitors

nevirapine, efavirenz

metabolized) in adults have been noted with the use of PIs. A study examining the effect of PIs on cholesterol metabolism in children showed changes similar to those observed in adults. Pre- and post-treatment cholesterol levels from 82 HIV-infected pre-pubescent children showed a mean increase of 34mg after PI-containing therapy. Cholesterol levels were highest in those children on a combination of ritonavir and saquinavir. The study concluded that PI therapy is associated with significant increases in cholesterol levels.

As with adults, it is unknown if PI-induced increases in cholesterol levels are associated with complications related to cholesterol increases in the general population (e.g. heart disease). These changes in adults are believed to be associated with changes in overall body composition and fat distribution in the body—a *syndrome* known as lipodystrophy. Little is known or reported on the incidence of lipodystrophy in children. For more on lipodystrophy, see pages 14–16.

Treatment Information Assessment Project

Project Inform recently published the final report summarizing the conclusions of the Treatment Information Assessment Project (TIAP). The project was developed with the Kaiser Family Foundation to investigate the range of treatment concerns of callers to Project Inform's National HIV/AIDS Treatment Hotline.

This report is a first step to ensure that Project Inform's National HIV/AIDS Treatment Hotline is responsive to all callers. In particular, Project Inform wanted to know if women calling the hotline had significantly different concerns than men. How had they been referred to us? Were African American callers more or less likely to ask about antiretroviral treatment than Caucasians? If someone lived in a rural part of Nebraska, were they likely to ask about complementary therapies as someone in an urban setting? The answers to all of these questions are key not only to improving Project Inform's Hotline, but also its information, outreach and advocacy services.

Callers to the Project Inform Hotline were surveyed during the first half of 1998 to determine the range of treatment concerns facing them and to ascertain the roles that gender, ethnicity, age or geographic location of the callers might play in their concerns. Also, if demographic characteristics of callers were related to their treatment questions, then Project Inform wanted to know if outreach, education and advocacy efforts could address the concerns.

One of the most interesting conclusions discussed in the final TIAP report was that—aside from some expected gender differences regard-

ing pregnancy and pediatric issues—gender, ethnicity, age and geographic location did not determine treatment questions and concerns of callers to the Hotline. The primary drives for discussion were length of time a person was infected with HIV and HIV treatment experience.

The report also recommends avenues that healthcare providers, treatment educators, treatment advocates and other organizations involved in HIV-related service might consider as they look to serve more fully those affected by HIV. It is hoped the information contained in the report will influence programs within AIDS service organizations and healthcare systems serving people with HIV.

Anyone who is interested in receiving a copy of the full report of the *Treatment Information Assessment Project* should call David Evans at 415-558-8669 or email him at devans@projinf.org with their name, title, organization name, address and phone number.

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