PROJECT inform

PERSPECTIVE

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

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Millennial Heresy

Beginning in 1996, protease inhibitors and three-drug combination therapy revolutionized HIV treatment. At least in the developed world, a new highly aggressive treatment standard emerged almost overnight. Not surprisingly, four years of experience with the new therapies have shown a few cracks in that standard and it may be time to reconsider some of the common beliefs about therapy.

Raising such questions is not a condemnation of past practices or a sudden declaration that everyone should abruptly change strategies. It is instead a statement that our knowledge is advancing—a sign of progress not retreat. Many of these concerns have been raised all along—what's different now is that more people are speaking out. These concerns should not be misunderstood to suggest that people are suddenly worse off than before. By any measure, most people with HIV and AIDS continue to do far better than they did just a few short years ago.

The Questions

Seemingly heretical answers are being proposed for a variety of questions, including:

- When should people start therapy? Is there such a thing as too early?
- Must people stay on treatment permanently?
- Must every combination include a minimum of three drugs, two of them from the class of drugs known as nucleoside analogues? Have we overlooked other options?
- Are some of our most popular drugs as good as we have been led to believe?
- Is the pursuit of *undetectable* viral load—at any cost—a necessary medical goal or a growing part of what threatens people with HIV?

What's at stake in getting the answers to these and similar questions is whether advances in therapy will provide an entire lifetime of benefit, or just a few years respite from HIV.

When to Start?

When talk of the eradication of HIV accompanied the new therapies, the slogan "*Hit it hard and hit it early*" was incorrectly translated into meaning that everyone who was HIV-positive, regardless of stage of disease, should be permanently put on an intensive, three-drug regimen ***now***. Accepting this was easier at the time since some of the long-term toxicities of aggressive treatment were not yet apparent. *Lipodystrophy* was not yet a household word, nor were reports being received about possible dangers of heart, kidney and liver disease, the high rate of HIV/hepatitis co-infections, or the previously overlooked problems of *mitochondrial damage* and *lactic acidosis*. Although the incidence of such problems is unclear and frequently overstated, they have clearly become more common in this era of aggressive treatment.

We quickly learned that aggressive treatment also set HIV-positive people on paths that risked developing resistance to the drugs. After only a few rounds of treatment failure, people sometimes acquired resistance to almost every available drug.

There's no doubt the new drugs can make a profound, life-or-death difference, especially

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In This Issue

E - *May be of special interest to women*

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for people with advanced disease. However, people in much earlier stages of disease were now being put on treatment. Many who were healthy and may have remained healthy for many years before developing AIDS suddenly found themselves coping with drug side effects, along with adherence and resistance problems.

The present debate is not about whether to use treatment, but when. No one disputes that people with CD4+ cell counts below 200 should be on treatment. Getting people into care and starting therapy before the onset of opportunistic infections remains one of the great challenges of the public health system in the US. At the other extreme, there's no clear evidence that starting treatment in people with very high CD4+ counts—above 500—provides any proven benefit, though it exposes them to the risk of side effects and resistance—possibly long before necessary.

In between these extremes, the picture is muddy. Some studies have shown benefits from treatment in people who started with CD4+ cell counts of 350 or below. There is less clear evidence for people with counts between 350 and 500. Ironically, the success of the new drugs in restoring the immune system has complicated this debate. Before, it was easier to recommend early treatment because there was evidence of significant early damage to the immune system. Today's treatment strategies are remarkably effective in repairing much of the apparent damage—making it easier, in theory, to delay treatment.

The present debate is not about whether to use treatment, but when.

But early treatment, at almost any stage of progression, may still be proven beneficial in future studies. There may be advantages to starting therapy early, but the effects may not be readily apparent because we don't yet know how to measure them. We simply don't know which is best today, and there isn't much hope of getting a clear answer anytime soon. Even if needed studies begin tomorrow, they will take several years to complete. Unfortunately, the constantly changing standards of treatment have caused many researchers to despair about ever being able to design proper trials to answer these questions.

People with HIV and their doctors must recognize that there's no one right answer to this question. For now, what counts most is making sure everyone is given the knowledge and opportunity to make this choice for him or herself.

Must Treatment be Permanent?

Until recently, treatment was assumed to be permanent once begun, a factor that weighed heavily in the decision to start treatment. While many researchers assume that a lifetime of uninterrupted therapy is necessary, others are experimenting with intermittent therapy options, known as Structured Treatment Interruption (STI). This research has produced a handful of people who, after a few repeated cycles of therapy interruption, have apparently strengthened their natural immune response against HIV so much that they no longer need drugs to keep their viral load below the limit of detection. If this could be routinely achieved, it would make many of the other dilemmas of treatment disappear, like long-term side effects or treatment fatigue.

Other recent research has begun to confirm earlier findings that treatment interruptions can sometimes reverse drug resistance. While the reversal may not be complete or permanent, it often seems sufficient to permit a new regimen to work long enough to get viral load under control and keep it there for long periods of time.

Perhaps the most important but elusive question is whether or not people can safely take time off from therapy at various stages of HIV infection. Researchers have historically looked only at the harm it might do: increased viral load, reduced CD4+ cell counts, possible loss of some of the gains achieved by therapy. But we must also ask how much good STI might do (and how much harm constant therapy might be doing to some). Can people live longer, more comfortable lives with an occasional STI? No one yet knows, but there is growing evidence that people won't be able to sustain constant therapy for the rest of their lives. Side effects, organ and tissue damage, viral resistance, treatment fatigue and obstacles to adherence accumulate over time and will take their toll. (For more information about STI research, call Project Inform's Hotline).

In Memory Of . . .

We dedicate this issue of the *PI Perspective* to:

Rick Bell
Dick Pabich
Juan Rodriguez
Terry Williams
Hank Tavera
Maurice Call

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

The Three-drug, Two-"nuke" Minimum

One of today's most sacred rules is that every regimen must include at least three drugs, typically a combination of a protease inhibitor or non-nucleoside ("non-nuke") plus two of the nucleoside analogue ("nuke") drugs. While using two nucleosides may have been the best choice in 1995, it may not be the best we can do today. In light of recent findings of previously unrecognized toxicity associated with the nucleoside analogue drugs, it seems critically important to know whether or not people always need two of them, or need them at all.

Why were two nucleoside analogues always recommended instead of one? Primarily because they are weak drugs and it took two to make a substantial contribution to therapy. Of the available nucleosides, 3TC was probably the most potent, so it quickly became a standard element in most combinations (even though later data showed that resistance to 3TC quickly developed and was the most common cause of failure of three-drug regimens). A new generation of this class of drugs, represented by abacavir (Ziagen®), offer potency far exceeding that of previous nucleosides.

Unfortunately, most people had already used the older nucleoside drugs for years, often to the point of resistance. Thus, the benefits seen in studies of people starting treatment for the first time overstated the results people would get if they had used the older drugs before, while perhaps understating the long-term toxicity.

A number of other alternatives to the dual nucleoside standard have yet to be considered or tested, and some that have proven them-

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selves have had a very difficult time being accepted. The most obvious overlooked combination was two protease inhibitors. This option was studied from the beginning, but only to save saquinavir from the dump heap. Studies using a ritonavir/saquinavir combination without nucleosides show it is at least, if not more, potent and durable than standard three-drug combinations. The advantages include eliminating the side effects of nucleoside analogue drugs and simplifying the regimen.

Once non-nucleoside analogue drugs and higher potency, second generation nucleosides were available (see *Drug ID Chart*, page 10), other combinations became possible. The list of possible combinations has grown each year, yet little effort has been made to challenge the old standard of care. Its time is overdue.

A European Perspective

Perhaps the most heretical view of all is that of some European and American researchers argue that aggressive therapy—a three-drug combination—isn't necessary for everyone. They believe that for at least some people, notably those with very low viral loads, simpler two-drug combinations may be sufficient, even if they don't always result in sustained, undetectable viral load. They also argue that three-drug regimens are seldom feasible in developing nations and that in these situations a two-drug regimen is better than nothing.

Most US researchers scoff at this, saying studies have proven three-drug therapy is superior. However, the studies that "proved" this point included people with widely varying CD4+ cell counts and viral loads, who took either two or three drugs. In these settings, three-drug therapy always looks better, but only because people with the most advanced disease typically decline on two-drug combinations. This conclusion overlooks the fact that many do very well for long periods on the two-drug regimens. People with high CD4+ counts and low viral load often maintain undetectable viral load status for long periods—on just two drugs. It's unclear whether more aggressive therapy is warranted for such people.

If two-drug therapy were proven sufficient for at least some people, it would save a great deal of money and a lot of anguish, side effects, and effort. Nonetheless, dogma perseveres and in the US, almost any doctor who puts a patient on a two-drug therapy for any reason runs the risk of being accused of medical mismanagement. The three-drug standard is "locked in" because any study that proposes to use two drugs is branded as "unethical."

Perhaps the most heretical view of all is that of some European and American researchers who argue that aggressive therapy—a three-drug combination—isn't necessary for everyone.

How Good are the Most Popular Drugs?

Our perceptions of the value of drugs are based on many perspectives, not all of them balanced and unbiased. The results of independent studies get blended with those conducted by a drug's sponsor. Drug company analyses are sometimes massaged by their marketing departments and almost never find fault with the sponsor's drug. Doctors also develop their own favorites, which may be influenced by the hard sell tactics of manufacturers. People hear the preferences and beliefs of their friends, along with the views of community newsletters, magazines, the press and treatment educators.

The only real way to sort out the net value of a drug is to follow the results of studies over time. Good drugs stand the test of time, while mediocre ones may not. Although people often need to make decisions based on short-term studies, they need to keep an open mind and be prepared to change their beliefs as the long-term picture emerges.

This long term view has begun to raise doubts about the most widely used protease inhibitor, nelfinavir (Viracept®), a drug often chosen for its relatively limited side effects, ease of use, and some debatable beliefs about its role in viral resistance. Despite this, three recent studies have raised serious concerns about whether it meets the standards of potency established by some other protease inhibitors. (For more information, see page 5.)

Over time, we may see similar concerns raised about other drugs; but conversely, we may also see the reputations of some drugs improve. Two non-nucleoside analogue drugs,

nevirapine (Viramune®) and delavirdine (Rescriptor®), were initially viewed as having only modest activity, but this was largely a remnant from when they were only tested in two-drug combinations while being compared to other drugs in three-drug combinations. More recent studies using three-drug combinations have raised the perceived value of nevirapine, and a similar process is now taking place with delavirdine.

Undetectable Viral Load

While the hope of eradication thrived, keeping viral load as low as possible for as long as possible made sense as a step toward that goal. Even though eradication is not currently considered feasible, most researchers still seem wedded to the pursuit of *undetectable viral load* at any cost. It is not clear that this is always in the patient's best interest.

Perhaps the most compelling argument for undetectable viral load is that it may present the greatest obstacle to developing drug resistance. At least in theory, once viral load becomes detectable and a person continues using an anti-HIV drug, it will cause the development of ever more mutations and thus resistance, crippling the potential for future drugs to work. But it doesn't always seem to work that way in the real world. Many people, including some researchers, report that viral load often becomes detectable despite continued anti-HIV therapy, but it stays at a stable level while people thrive and their immune systems continue to improve.

Others believe that if eradication isn't possible, the best balance between the immune system and the virus may be one that permits enough HIV replication to keep stimulating a natural immune response, but not enough to do much harm. At the very least the perceived value of keeping viral load undetectable must be measured against the price paid to achieve it. When the price is too high in terms of toxicity and treatment fatigue, it's important to remember that people can live long and well despite measurable viral load.

Where Does the Road Lead?

These and other concerns are causing the first serious rethinking of the goals and tactics of "HAART" (Highly Active AntiRetroviral Therapy). HAART may still be the preferred approach for people with serious immune deficiency, or even for those with modest degrees of immune dysfunction, but that doesn't mean it's right for everyone. As long as drugs can cause serious side effects in some people, there will be room for debate over just when and how to use them.

For many, HIV disease is a long slow process, not the titanic daily battle between massive amounts of virus and the valiant drugs envisioned in 1996. On the contrary, for some, the rate of viral reproduction is relatively low and stable, at least compared to truly aggressive viruses. Keeping it sufficiently, if not completely suppressed, may be easier than previously thought, and it may be possible to do it at a lower cost and with fewer side effects and adherence demands. The coming period of rethinking and change should be welcomed, and we can only hope that the researchers who promoted HAART will not view it defensively. ▪

ddI, d4T and Hydroxyurea Side Effect Warning!

The FDA recently issued a warning that when using ddI (didanosine, Videx®), some people may develop pancreatitis (a potentially life-threatening inflammation of the pancreas). An early symptom includes severe abdominal pain, which should be carefully diagnosed. Adding d4T (stavudine, Zerit®) and/or hydroxyurea (Hydrea®, Droxia®) to ddI may further increase the risk of pancreatitis.

Results from ACTG A5025 suggest that people taking ddI, d4T and hydroxyurea together are more likely to develop this side effect than those taking AZT (zidovudine, Retrovir®) and 3TC (lamivudine, Epivir®). All people had been on stable treatment with AZT+3TC+indinavir, and after six months, either stayed on AZT+3TC+indinavir or switched to d4T+ddI+indinavir with or without hydroxyurea.

After 24 weeks there were no differences in viral load changes among the groups, but people taking ddI+d4T+hydroxyurea+indinavir were more likely to have side effects. These included pancreatitis, neuropathy and increased liver enzymes. Further, the group taking hydroxyurea had about a hundred CD4+ cell loss compared to a slight increase in the other two groups.

There are several possible reasons why those taking hydroxyurea had more side effects. The most obvious is that they took four drugs while the others used three. Another is that the dose of hydroxyurea used was higher than the standard dose (1,200mg vs 1,000mg) and it was not adjusted for weight. Also, hydroxyurea causes more ddI to get into cells, increasing the risk of ddI-related side effects, like pancreatitis. Additionally, regular monitoring was not done by the researchers but by their primary physicians, who may have been less familiar with the procedures for monitoring and responding to early signs of pancreatitis.

These findings suggest that people should be cautious if they're taking ddI and hydroxyurea together. If they experience any type of pain in the stomach, they should immediately notify their healthcare provider. ▪

Nelfinavir Potency Concerns

Results from several recent studies may help clarify how to best use anti-HIV drugs as part of first line therapy. These results seem to suggest that nelfinavir (Viracept®), the most widely used protease inhibitor, may not be as potent as other drugs in its class or some of the non-nucleoside RT inhibitors (NNRTIs). This article provides an overview of the studies.

EuroSIDA Study

EuroSIDA, an observational study that has enrolled over 8,500 people in over twenty European countries, recently reported several findings. Of note is one that suggests nelfinavir is a less potent first line protease inhibitor in a typical three-drug combination (along with two nucleoside analogue drugs) than indinavir (Crixivan®), ritonavir (Norvir®) or two protease inhibitors together.

An analysis of about 1,500 people showed that those starting therapy with either hard gel saquinavir (Invirase®) or nelfinavir were less likely to achieve viral loads below 500 copies within 24 weeks of therapy. They were also more likely to have their viral loads rebound above 500 copies compared to people who started with indinavir, ritonavir or two protease inhibitors.

Eighty-five percent of the participants used three drugs; the rest used four or more. People who started with high viral loads and low CD4+ cell counts and those who started with one or two new drugs were least likely to have sustained responses.

Although this was expected in the case of hard gel saquinavir, known to have serious absorption problems, it was a surprise for nelfinavir. No obvious reason was given as to why nelfinavir fared so poorly. While there are limitations to observational studies, two other recent studies raised similar questions about nelfinavir, including ACTG 364 and the European COMBINE study.

ACTG 364

ACTG 364 compared nelfinavir alone, efavirenz (Sustiva®) alone, and both drugs together. All groups also received two nucleoside analogue drugs (NARTIs). Those receiving nelfinavir used the standard dose, given three times per day. ACTG 364 showed that people taking nelfinavir fared less well than those taking efavirenz, though people who used both did the best of all. In addition to nelfinavir, efavirenz or both drugs, all 189 participants took ddI+d4T, d4T+3TC or ddI+3TC depending on which NARTIs they had used before. After 48 weeks, the results showed the following.

Those taking combinations including efavirenz or efavirenz + nelfinavir were more likely to maintain good HIV control than those taking only nelfinavir. There was no difference in the suppression of HIV between these two groups. No difference in the rate of side effects was seen among the three groups.

Regimen	% with viral load <500 copies HIV RNA
NFV+2 NARTIs	35%
EFV+2 NARTIs	60%
NFV+EFV+2 NARTIs	74%

NFV=nelfinavir EFV=efavirenz
NARTIs=nucleoside analogue reverse transcriptase inhibitors

Another surprising finding was that all study groups looked equivalent at the end of 16 weeks, originally planned as the end of the study. However, longer-term follow-up showed a real difference developed between the regimens. This should remind us that short-term studies can be misleading.

The COMBINE Study

The COMBINE study compared nelfinavir (1,250mg twice daily) + AZT/3TC (Combivir®) against nevirapine (200mg twice daily) + AZT/3TC. The study followed 142 people taking HIV treatment for the first time. Results seen in the two groups after 24 weeks were as follows. The outcome, favoring nevirapine, was equally true in people who began with either high (over 100,000 copies) viral load or low viral load (below 100,000 copies).

Commentary

These are troubling findings given that nelfinavir is the most widely used protease inhibitor. Agouron Pharmaceuticals, its manufacturer, has tried to explain these results. It claims that a disproportionate number of people with mutations related to nucleoside analogue resistance were in the nelfinavir arm. Other scientists dispute the role this may have played. Agouron has not commented on the EuroSIDA or COMBINE studies.

Regimen	A	B
NFV+AZT/3TC	33%	22%
NVP+AZT/3TC	58%	57%

NFV=nelfinavir NVP=nevirapine

A=All patients, % with viral load <20 copies HIV RNA.

B=Subgroup, % of patients starting with viral load above 100,000 copies who reached viral load <20 copies HIV RNA.

What complicates this further is that the current federal *Guidelines* lists nelfinavir-based combinations as *preferred* and the nevirapine-based ones as *less desirable*—the opposite of these new findings. Since the approval of nelfinavir, Project Inform has publicly questioned whether it offers the same potency as indinavir and ritonavir. Now that studies have raised the same question, the burden is on federal authorities to decide what to do. One study suggesting inferiority may not be enough to question the value of a drug, but aren't three studies enough?

For people already using nelfinavir and having a good response, these findings may not warrant changing regimens. But it suggests more frequent checking of viral load. For those making their first treatment decisions, the new data should become one more fact in deciding which therapy to begin. There are now so many options for first-time treatment that learning about the reduced potency for one of them doesn't necessarily create a crisis. ▪

Anti-HIV Drug Update

Slow but steady progress continues on a number of new anti-HIV drugs in the three drug classes. If approved, some of these represent true second-generation therapies that will offer some degree of advance over current drugs. Others are not that much different from today's drugs. The article below combines information from the most recently announced studies, including those presented at the 7th Conference on Retroviruses and Opportunistic Infections.

First Line: Indinavir/Ritonavir Combination Shows Promise

One combination getting wide attention lately is ritonavir + indinavir. Ritonavir greatly stabilizes indinavir blood levels and, as a result, both can be taken two instead of three times a day, while using less indinavir overall. Perhaps more importantly, this combination eliminates the food restrictions that otherwise make indinavir difficult for some people. In theory because higher sustained drug levels are achieved, the combination may also make it more difficult for HIV to develop resistance to either or both drugs. The lower total daily doses of indinavir may also decrease the risk of kidney side effects associated with indinavir. However, this point is not yet proven.

Results from a recent study show that this is indeed a potent combination. Ninety-two people with CD4+ cell counts around 200 and viral load around 220,000 copies HIV RNA participated. None had been on anti-HIV therapy before. Volunteers received ritonavir + indinavir (both 400mg twice a day) plus any two nucleoside analogue drugs. Most took either AZT+3TC or d4T+3TC.

After one year, 67% had less than 500 copies HIV RNA, and 64% had less than 80 copies. Participants also had about a 200 CD4+ cell increase.

One potential confounder in this study was that midway, people switched from ritonavir capsules to the liquid formula due to manufacturing problems. The most common side effects were nausea, diarrhea and numbing around the mouth (oral parasthesia). People also had increases in their triglyceride and cholesterol levels.

Other studies of this combination experiment with different doses of ritonavir and indinavir. Some have used as little as 100mg ritonavir along with up to 800 or 1,200mg indinavir twice daily. Researchers, and especially the manufacturer of ritonavir, Abbott Laboratories, debate about ritonavir's proper dose. Abbott and some researchers prefer to use 400mg ritonavir daily, arguing that this higher dose allows it to contribute its own anti-HIV activity. At lower daily doses, typically 100 or 200mg daily, there is probably little or no anti-HIV activity from ritonavir. The drug instead serves only to boost the potency of indinavir. Those who favor the lower doses cite concerns about ritonavir's toxicity, which can be troubling even at the 400mg dose. One interesting point to note is when Abbott combines ritonavir with its own new drug, lopinavir (ABT-378), it uses only 100mg of ritonavir.

Lopinavir Shows Good Activity

The new protease inhibitor from Abbott Laboratories, lopinavir (formally known as ABT-378), continues to look extremely promising. In a study using the drug as part of a three-drug combination in people who had not taken anti-HIV therapy before (see *PI Perspective 27*), about 80% continue to have viral loads below 50 copies HIV RNA after 72 weeks. Similarly, among people who failed a single protease inhibitor regimen but had not used a non-nucleoside reverse transcriptase inhibitor (see *PI Perspective 28*), 70% of the participants had viral loads below 400 copies after 48 weeks. Although this is still early data and not a direct comparison, the response rate for people failing a previous protease inhibitor seems to be better than any previously seen.

Early results from a study of people who failed numerous protease inhibitors also show good activity. Volunteers took lopinavir + efavirenz (Sustiva®) + nucleoside analogue drugs. After twelve weeks, about 70% had viral loads below 400 copies HIV RNA. The main limitation of this data, however, is that people had to be using NNRTIs for the first time, even though they had considerable prior experience with protease inhibitors. It is thus unclear how much of the benefit is due to the lopinavir and how much is due to efavirenz.

Lopinavir is currently distribruted free under a broad expanded access program. The drug is available to any individual who needs it to construct a viable anti-HIV treatment regimen.

The Future: Once a Day Therapy?

Early results from several studies suggest that simpler dosing of anti-HIV drugs may be possible. New formulas of existing drugs will eventually lead to easier to take regimens, such as the use of ritonavir to boost the activity of other protease inhibitors.

Early results from a small study of ritonavir (RTV) and indinavir (IDV) suggest that it may be possible to take this combination only once a day. Three different doses were studied: 1) 800mg IDV+ 100mg RTV, 2) 800mg IDV+200mg RTV, and 3) 1,200mg IDV+100mg RTV. Indinavir blood levels achieved 24 hours after taking dose #2 or ~~#3 were similar to the levels seen with t~~he standard 800mg dose taken three times daily. Planned studies will look at this dosing scheme to determine if it's as effective as the standard dose.

The criteria for the lopinavir compassionate use program has been broadened. It is now open to any individual who needs the drug to construct a viable anti-HIV treatment regimen.

Another once-a-day regimen being studied is 100mg ritonavir + 1,600mg saquinavir (Fortovase®). Saquinavir blood levels 24 hours after taking both drugs were higher than those with the standard 1,200mg three times daily dose. It's still early to suggest that these regimens are as effective as the standard ones.

A small Italian study suggests that it is possible to put together a potent once-a-day regimen. Volunteers who were reluctant to

start one of the standard two or three times daily dosing regimens because of adherence problems received 300mg ddI + 300mg 3TC + 600mg efavirenz, all dosed once a day.

All participants had either never taken anti-HIV therapy or had been minimally treated. About a quarter of them were under observed therapy through a methadone clinic. The average viral load at study entry was about 90,000 copies HIV RNA and CD4+ cell counts were about 275.

After four months, about 60% had viral load levels below 400 copies HIV RNA (about 50% below 50) and had a mean increase of over 125 CD4+ cells. How this outcome compares to other possible dosing regimens is unclear. One observation was that people on methadone had to increase their dose presumably because efavirenz lowers methadone levels. ▪

Manufacturer Ends Adefovir Development

Gilead Sciences has stopped development of its drug, adefovir, for use against HIV infection. This news came after the Food and Drug Administration (FDA) informed Gilead that adefovir would not be approved based on existing data and that additional studies would be necessary if it wants the FDA to reconsider the matter. The Antiviral Drugs Advisory Committee to the FDA had earlier recommended that the drug not be approved on the grounds that its potential serious side effects outweighed its potential benefits.

Contrary to the company's claims, the FDA analysis of the adefovir studies concluded that in three studies the drug did not provide any significant anti-HIV activity, while evidence of marginal activity was seen in two other studies. The FDA, like the advisory committee, was troubled by the side effect problems, most notably kidney toxicity. In addition, the FDA analysis concluded that the company had not made a convincing case that the drug would be useful in people who had developed resistance to multiple nucleoside analogue drugs such as AZT, ddI and 3TC.

Participants in studies with adefovir will be rolled over into the existing expanded access program, but the expanded access program will otherwise not accept new requests to supply the drug. For those already receiving the drug, the program will continue for as along as the individuals and their healthcare providers feel they are benefiting from it.

Gilead officials have now concluded that they can better use their resources in developing another drug, tenofovir (PMPA), which is in the final stages of studies. Project Inform and some other AIDS advocacy groups made a similar recommendation to the company almost three years ago. Results to date suggest that tenofovir may be more potent and have fewer side effects than adefovir. Gilead will continue its development program for adefovir as a potential treatment for hepatitis B virus.

The rejection of adefovir by the FDA represents something of a milestone in AIDS research. It is the first time in recent years that the FDA has rejected a request for the approval of an AIDS drug, and it is the first time that most AIDS advocacy groups did not rally to the drug's defense. While adefovir might have been approved had it appeared on the scene in earlier years, today's environment already offers a wide spectrum of AIDS drugs, many of which are clearly more potent and less troublesome than adefovir. But whether this means that the overall standard for approval of AIDS drugs has been raised is unclear. ▪

NIH Study Cautions Use of St. Johns Wort with Anti-HIV Drugs

A study conducted by the National Institutes of Health (NIH) found a significant interaction between the popular herbal therapy, St John's Wort (*Hypericum perforatum*), and the protease inhibitor, indinavir (Crixivan®). Indinavir blood levels were substantially decreased when the two drugs were used together, greatly reducing indinavir's anti-HIV activity. This can quickly lead to the development of resistance to indinavir. Individuals commonly use St. Johns Wort as a mild anti-depressant.

St. John's Wort is also likely to significantly decrease blood levels of some other protease inhibitors as well as non-nucleoside reverse transcriptase inhibitors. People who take these drugs are advised not to use St. Johns Wort. Similar problems with drug interactions may occur between St. John's Wort and medications used to treat other life-threatening illnesses, such as heart disease.

One possible limitation of the current finding is that it is not clear how it applies to the various forms of St. John's Wort on the market. Because they are completely unregulated, there is no way of knowing how much St. John's Wort is actually present, or the quality of the product. Other preparations may have a stronger or weaker effect. Also, the methodology of the study has not been fully described yet.

As this study illustrates, there's a definite potential for some herbal and nutritional supplements to lower the effectiveness of anti-HIV drugs or other medications. Individuals who use complementary therapies should always discuss possible interactions with their doctors and pharmacists. ▪

New Drugs in Development

In the last issue of *PI Perspective* (#28), we reviewed some new anti-HIV drugs in development. Since then, setbacks have occurred that will delay, and in some cases stop, the development of some of these therapies. However, other therapies show promising activity and continue through the development process quickly.

Protease Inhibitors

Tipranavir

Tipranavir represents the first of a new class of protease inhibitors (PIs). What's different about this one, at least in lab studies, is that the drug is active against viruses that are resistant to the other protease inhibitors. Whether this will actually be the case in human studies is not yet fully known.

The earliest human studies showed the drug suppressed viral load and seemed to work best when combined with a small dose of ritonavir (Norvir®), as do many other PIs.

A report from a small, incomplete tipranavir study in people resistant to other PIs was submitted but not accepted for presentation at the recent Human Retrovirus Conference. The drug's sponsor at the time, Pharmacia & Upjohn, claimed the drug was doing well in the study. Shortly before the Conference, the rights to develop and market tipranavir were sold to Boehringer Ingelheim. It is unclear whether the sale will affect the pace of the drug's development.

Once-a-Day Protease Inhibitor Looks Encouraging

Early results report that a new once-a-day protease inhibitor, BMS 232632, shows encouraging activity. Participants took 200mg, 400mg or 500mg of BMS 232632 once a day or the standard three times a day dose of nelfinavir. After two weeks, d4T and ddI were added to their regimens.

Volunteers had not taken anti-HIV therapy before. They had viral loads around 60,000 copies HIV RNA and 400 CD4+ cells at the start of the study. There were no real differences in anti-HIV responses among the three doses of BMS 232632 and nelfinavir. About 60% of the participants achieved viral loads below 400 copies HIV RNA and 40% were below 50 copies after 16 weeks.

The most common side effects of BMS 232632 were mild to moderate diarrhea and elevated bilirubin levels (a measure of liver function), especially among those using the highest dose. Bilirubin levels normalized after stopping the drug or reducing it to the lowest dose studied.

A once-a-day protease may be a significant advance in aiding adherence. It may also lessen treatment fatigue. It remains to be seen how well this drug will perform in people with resistance to the other protease inhibitors and lab studies are somewhat conflicting in this regard. Also, it is quite unusual that no difference was seen among the three doses used in the current study, raising questions about how much of the current response rates is due to chance and the small number of people studied. This has the potential to slow the drug's development because of the difficulty in picking the proper dose.

NNRTI's

Emivirine Interacts with Nelfinavir

A recent study revealed significant interactions between nelfinavir (Viracept®) and the experimental NNRTI, emivirine (Coactinon®, formerly MKC-442). An earlier study suggested that emivirine decreased nelfinavir blood levels by about 30%. A new study suggests the interaction is far greater.

This study evaluated emivirine added to d4T + 3TC + nelfinavir to see if the four drugs might result in better and longer control of HIV. The exact degree of the interaction between emivirine and nelfinavir is still unknown, but it's thought that it reduced nelfinavir levels by over half. As a result, nelfinavir probably contributed little if any anti-HIV activity to this combination.

Triangle Pharmaceuticals, the developer of emivirine, had hoped to file for new drug approval by the end of 1999, but that has been delayed while the company reconsiders the role of emivirine in multi-drug regimens. It is unlikely that emivirine will be combined with a single protease inhibitor as it probably decreases the levels of all protease inhibitors to some degree. However, it may be possible to use emivirine with two protease inhibitors if one is ritonavir (Norvir®), since it would counteract the problem created by emivirine. The company is now exploring this possibility, though it is unclear whether this will provide a practical solution.

NARTI's

Lodenosine (FddA) and Liver Side Effects

One of the most serious setbacks has been the emergence of severe liver side effects related to the new NARTI, lodenosine (FddA). Early results from a study comparing three different doses of lodenosine showed potent anti-HIV activity. The study compared lodenosine (100mg, 200mg, and 300mg all taken twice a day) + d4T (stavudine, Zerit®) + indinavir (Crixivan®) to a standard regimen of 3TC (lamivudine, Epivir®) + d4T + indinavir.

After twelve weeks, some participants taking lodenosine developed life-threatening liver problems. Four died from liver failure and others were hospitalized. The study was put on hold as the company studies the cause of the side effects. Considering the severity of the problem, it's likely development will be stopped.

Early Results for dOTC

Early results of a small study of Biochem Pharma's new nucleoside analogue drug, dOTC, show promise. The study compared six different doses: 200mg, 300mg, and 400mg taken twice a day and 400mg, 600mg, and 800mg taken once a day.

Volunteers had not taken anti-HIV therapy before and had an average viral load around 40,000 copies HIV RNA and CD4+ cell counts around 400. After eight days of dOTC alone, 53–100%, depending on dose, had either a lowered viral load of at least one log (10 times) or had viral loads below 400 copies. This suggests that dOTC may be unusually potent for this drug class.

However, the development of dOTC was recently delayed because of deaths in monkeys that were given the drug for over three months. Some developed severe swelling and died soon

after. It's possible that this is unique to monkeys since rats were given the drug for six months with no side effects. On the other hand, monkey data may be more predictive of what will happen in humans. Biochem Pharma is starting studies with a slightly different version which is less likely to cause this side effect.

Early Results of DAPD

Early results from a small study of a new nucleoside analogue drug, DAPD, from Triangle Pharmaceuticals show promising antiviral activity. The ongoing study compared four different doses each taken twice a day: 25mg, 100mg, 200mg and 300mg.

Volunteers had not taken anti-HIV therapy before. They had an average viral load around 10,000 copies HIV RNA and CD4+ cell counts of 300–400 when they entered the study. After two weeks of DAPD alone, people taking the highest dose had the best response (about a 1.5 log or 32 times reduction in viral load). Higher doses will be studied including taking the drug once a day.

NtARTI's

Tenofovir

Another drug showing anti-HIV activity is tenofovir (PMPA), an NtARTI. Results were recently presented of a study using tenofovir as part of a "treatment intensification" effort. This refers to the effect of adding an additional anti-HIV therapy to a regimen when the viral load starts to rise again after an initial period of suppression.

The study included 189 people with an average viral load around 5,000 copies HIV RNA and CD4+ cell counts around 370. They received 75mg, 150mg, 300mg or placebo all dosed once a day in addition to their current therapy. (After 24 weeks, volunteers receiving placebo had access to tenofovir.)

After 24 weeks, about 25% of those who took tenofovir reached viral loads below 400 copies HIV RNA (15% below 50). No differences occurred among the dose groups.

The results are somewhat disappointing since viral load at study entry was very low. An earlier study showed better activity. It's possible that tenofovir was not used optimally in this study since participants had increased viral loads on their current therapies. It's likely that some drug resistance had already occurred and tenofovir was simply added to a failing regimen. On a positive note, no volunteers showed kidney dysfunction, a common side effect of the chemically related adefovir (PMEA).

Fusion Inhibitors

Early Results of T-20

Results from a study of pentafuside (T-20), a drug in a new class known as fusion inhibitors, confirm that it is active against protease inhibitor resistant virus. Seventy-one people who had previously taken protease inhibitors were enrolled in the study. Volunteers had an average viral load around 80,000 copies HIV RNA and CD4+ cell counts around 70. Participants could add pentafuside (50mg injected under the skin twice a day) to any combination therapy.

After 16 weeks, about 33% had viral loads below 400 copies HIV RNA (about 20% below 50). Volunteers had been on most available therapies. As such, pentafuside was probably the only active drug in their therapy. It's likely that if pentafuside were combined with another new drug, a greater anti-HIV response could be achieved.

Commentary

Hopefully, safety issues with some of the new drugs can be resolved so people can use them in the future. People who have exhausted their treatment options need new potent drugs, especially against drug-resistant virus.

Unfortunately, these setbacks illustrate some of the difficulties in developing drugs, as animal studies sometimes do not predict what will happen in humans. What is urgently needed are combination studies of new therapies still in development for people who need third line regimens. Project Inform has been working with the Coalition for Salvage Therapy in advocating for just such studies. ▪

Drug Identification Chart

INITIALS	GENERIC NAME	TRADE NAME	MANUFACTURER
Protease Inhibitors (PIs)			
APV	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
Ribonucleotide Reductase Inhibitor (RRI)			
HU	hydroxyurea	Hydrea®	Bristol-Myers Squibb

Mitochondrial Toxicity and Lactic Acidosis

Mitochondrial toxicity and one of its symptoms called *lactic acidosis* have been highlighted recently as a previously undiagnosed side effect of anti-HIV drugs. Some researchers believe that *mitochondrial toxicity* contributes to the fat redistribution (lipodystrophy) associated with anti-HIV therapy. Although much more research is needed to fully understand this issue, this article explores the current thoughts about the connections among *mitochondrial toxicity*, *lactic acidosis* and lipodystrophy.

What Are Mitochondria?

Mitochondria are tiny rods found inside all human cells. Essentially, they are the cell's "power plants" and are also involved in the formation of protein and the processing of fat in cells.

Several things can affect how well mitochondria work. As people age, get an infection or take certain anti-HIV drugs, changes can occur in mitochondria. These changes, or mutations, may damage the mitochondria and either disrupt the normal function of the cells or cause them to stop working altogether.

Mitochondrial toxicity is a general term that refers to these changes. Perhaps more accurately, it is mitochondrial *damage*. It can cause different symptoms in the heart, nerves, muscles, pancreas, kidney, and liver (or perhaps anywhere it occurs), and it can also cause changes in lab tests.

How Anti-HIV Drugs Affect Mitochondria

Mitochondria need an enzyme called *polymerase gamma* to reproduce. Almost all nucleoside analogue drugs (NARTIs) such as 3TC (lamivudine, Epivir®), AZT (zidovudine, Retrovir®), abacavir (Ziagen®), d4T (stavudine, Zerit®), ddC (zalcitibine, HIVID®), and ddI (didanosine, Videx®) interfere with polymerase gamma to some degree. As a result, the NARTI class of drugs can block the production of new mitochondria, which then results in lower numbers of mitochondria and interference with their ability to function normally.

Among the nucleoside analogues, lab studies suggest ddC and ddI interfere the most with *polymerase gamma* followed by d4T. Lab studies also suggest that ddC and d4T are the strongest blockers of making new mitochondria (ddI wasn't studied). However, lab studies may not accurately predict what happens in the body. The other three nucleoside analogues are rather weak in this regard. It's not known whether using nucleoside analogues together interferes with this enzyme synergistically (where 1+1 = more than 2). At least one group of researchers claims d4T is most commonly related to mitochondrial damage in people, though others do not accept this finding.

What Are Common Results of Mitochondrial Toxicity?

Anti-HIV drug side effects linked to mitochondrial toxicity have been around for years. It has been brought into the limelight recently because of its growing incidence and its possible role in lipodystrophy. The reason for the higher rate may be due to people taking anti-HIV drugs longer. As a result, some once rare side effects are now more common. It is also possible that mitochondrial toxicity has always been present but was poorly diagnosed. Previous analysis, for example, may have focused only on the symptoms or conditions which resulted from mitochondrial toxicity.

Other more common conditions related to mitochondrial toxicity include myopathy (muscle cell destruction and weakness), peripheral neuropathy (numbness and tingling in fingers and toes) and pancreatitis (inflammation of the pancreas). Many common blood abnormalities are also thought to be related to this condition. These include thrombocytopenia (low levels of platelets), anemia (low levels of red blood cells) and neutropenia (low levels of neutrophils). All these problems have been seen since the earliest use of nucleoside analogue drugs for HIV.

All these conditions are reversible if diagnosed early and the offending therapy is stopped or the dose is reduced when appropriate. However, in some cases, especially when the condition is improperly diagnosed and not managed well, the condition might become irreversible.

Mitochondrial Toxicity and Lactic Acidosis

Healthy cells normally produce *lactate*, a natural by-product when mitochondria process glucose and fat. The body routinely clears itself of lactate through normal body functions. However, mitochondrial toxicity can create abnormally high levels of lactate in the cells. This, in turn, can lead to *lactic acidosis*, a life-threatening condition caused by too much lactate.

In early stages of lactic acidosis, people experience shortness of breath, nausea, vomiting and pain in the gut. At later stages (lactate levels over 5mmol/liter), it can lead to widespread loss of energy in the cells and cause organ failure and a high risk of death. In the past, such conditions may have simply been attributed to AIDS.

In early stages of lactic acidosis, people experience shortness of breath, nausea, vomiting and pain in the gut.

What Is Fatty Liver?

One of the more serious conditions linked to mitochondrial damage is "fatty liver," or *hepatic steatosis*. This build-up of fat around the liver can affect the way it processes fats. *Hepatic steatosis* often also leads to *lactic acidosis*, as described earlier.

People who weigh over 70kgs or about 150 pounds—especially women—may be more at risk for developing *hepatic steatosis* and, as a result, *lactic acidosis*. It is currently not a part of standard of care to measure lactate levels so this condition may go unnoticed. To further complicate matters, lactate breaks down rapidly when not stored properly, and only certain

labs can accurately measure these levels.

Mitochondrial Toxicity and Lipodystrophy

Contrary to early reports that only protease inhibitors were associated with changes in body composition, there are now many reports showing that people taking only nucleoside analogue drugs develop lipodystrophy (read Project Inform's *Lipodystrophy Discussion Paper*). Until recently, research may have overlooked the fact that protease inhibitor use almost always includes use of nucleoside analogue drugs.

Moreover, different patterns of fat redistribution consistent with symptoms of mitochondrial damage have been seen among people only on nucleoside analogue drugs compared to people on protease inhibitors along with nucleoside analogue drugs. There are very little data available about people who use protease inhibitors without nucleoside analogue drugs. These theories and questions are being actively investigated and more information should be available soon.

Reducing the Risk of Mitochondrial Toxicity?

The best thing you can do is to recognize the potential of the drugs you take to contribute to this condition. Also, pay attention to your body for these side effects. Talk to your doctor about getting accurate lab tests to check changes in your lactate levels. Again, since these tests are not part of standard of care, they may be difficult to get or have covered by health insurance.

Beyond that, the only tested approach is to reduce the dose or stop using nucleoside analogue therapy. However, this is usually done after mitochondrial toxicity occurs and symptoms develop. Research needs to be quickly started to test combination drug regimens that don't include using nucleoside analogue drugs or use versions that cause less mitochondrial toxicity. To date, the only such combination tested to a significant degree is ritonavir + saquinavir.

Other approaches need to be tested to correct mitochondrial toxicity. At least one researcher has suggested testing the supplements coenzyme Q10, L-carnitine and riboflavin. Furthermore, lab studies suggest that some nucleoside analogue drugs in development, like Fd4C, may be less likely to cause mitochondrial toxicity. They may actually prevent it from developing when used with other nucleoside analogue drugs. ▪

If you are looking for HIV/AIDS treatment information, log onto Project Inform's HIV/AIDS Treatment Website at:

www.projectinform.org

Resistance Testing Comes of Age

The Antiviral Drugs Advisory Committee (ADAC) to the Food and Drug Administration (FDA) recently held a two-day meeting to discuss HIV drug resistance testing. The discussion centered on currently available results from drug resistance tests and not on any one specific test or drug. For more information on HIV drug resistance and resistance testing, call Project Inform's Hotline and ask for the *Geno- & Phenotypic Resistance Tests Quick Sheet*.

ADAC Pushes for Study Testing

The ADAC recommended that companies submitting anti-HIV drug approval applications should include resistance data as part of their package to the FDA. More data will be required if companies want to claim their drug is effective against virus that is resistant to other drugs.

All ADAC members agreed that resistance testing had a role in drug development and that both genotyping and phenotyping are important tools for making treatment decisions. The ADAC suggested that, when appropriate, resistance testing should be performed on all participants at study entry and at the time of viral load rebound (when viral load becomes detectable or starts increasing again). This would help to better understand how a drug combination performs in the presence of drug-resistant virus and also the effect of new or added drug resistance on other anti-HIV drug regimens.

Ideally, the resistance testing should be performed in real time—that is, people should get the results within three to four weeks so they may act quickly on the information. Unfortunately, many studies prefer to batch all their resistance testing together at fixed time points. This approach may be easier for the researchers and might even slightly increase the accuracy of the results, but the outcome is far less useful to the study volunteers. A growing number of people get these tests done on their own outside of a study as a way to select an optimal regimen and to know when to switch regimens without waiting for the end of the study. If real time resistance testing is not routinely included in studies, then people may simply choose to get it independently. Researchers, however, fear that people who get their own results in real time may be more likely to drop out of studies when their regimens fail or show signs of resistance.

Defining Drug Resistance

One area of contention between drug developers and resistance test developers is the level of drug resistance that should be considered significant. Currently, most people consider a four-times decrease in sensitivity to the drug

to mean low-level resistance and anything above a ten-times decrease to mean high-level resistance.

This has generally been considered acceptable because the amount (level) of drug measured in a person's blood is usually four to eight times higher than what is needed to simply block HIV replication. It is usually not possible to increase the dose of a drug much beyond this because this will also increase the number and severity of side effects.

The developers of these tests need to make them more affordable and guarantee a rapid turnaround for results.

However, as we move towards using combination protease inhibitor therapies—especially using ritonavir (Norvir®) to boost the amount of drug found in blood (see *First Line: Indinavir/Ritonavir*, page **6**)—these standard four times and ten times changes may become irrelevant. With some drugs and combinations, it is possible to safely achieve much higher drug levels (15 or more times higher than needed to block HIV replication) and potentially overcome some viruses with low-level resistance, even though test results indicate you may be resistant to one or more of these drugs. The ADAC recommended that the amount of resistance to a drug that renders it ineffective should be determined for each individual drug, rather than having a single standard apply to all drugs.

Virco Phenotypic Study Report Early Results

Several studies show that resistance testing can determine which drugs in a regimen no longer work. But few studies show that resistance testing can predict the success of a new regimen. Currently, resistance testing provides little-to-no information on the durability of a new regimen.

New preliminary results presented at the ADAC meeting show that resistance testing can predict short-term response to a new drug. Virco, developers of Antivirogram® phenotypic and VircoGen® genotypic tests, conducted this study. The phenotypic test was used on 274 people with a viral load of at least 2,000 copies HIV RNA who were taking at least two nucleoside analogue drugs and one protease inhibitor.

Half the participants received immediate phenotypic testing and could change therapies based on all available information (treatment history, viral load and CD4+ cell counts) *plus the* results of the phenotypic testing. The other half had delayed phenotypic testing results and could change therapies based only on the other available information.

After 16 weeks, the group with immediate testing had much better anti-HIV therapy responses. Their average viral load decreased by 20 times (about 1.3 logs) while the delayed testing group's average viral load only decreased by four times (about 0.6 logs). This ongoing study should provide information on the durability of response to a regimen selected on the basis of resistance test information.

Resistance Testing in Standard of Care

In the near future, resistance testing is likely to become part of standard of care in managing HIV. Currently many third party payers are not reimbursing for these tests. Consumer and community pressure for payment warrants action.

Commentary

Resistance testing can help people living with HIV and their healthcare providers make better treatment decisions. Other needed tools are tests for monitoring anti-HIV drug levels in blood, commonly called therapeutic drug monitoring. Increasingly, studies show that people who achieve higher sustained drug levels in their blood have better and more sustained anti-HIV responses.

Considering that many factors dictate why people break down drugs differently, drug blood levels can be vastly different among individuals taking the same doses. Therapeutic drug monitoring may make it possible to ensure a good and lasting anti-HIV response. Achieving the ideal dose makes it more difficult for the virus to develop resistance. However, the feasibility of adding blood level monitoring to the already complex and costly practice of AIDS medicine is in doubt.

The developers of genotypic and phenotypic tests need to make them more affordable and guarantee a rapid turnaround for results. Genotypic test developers also have to ensure that the results they produce and send back to healthcare providers include quality interpretation and guidance for using them. ▪

What Are Genotypic and Phenotypic Tests?

Genotypic testing looks for the presence of changes in HIV's genetic structure that are commonly associated with the development of drug resistance. When present, these changes, called mutations, alter the way the virus makes key proteins (like reverse transcriptase and protease) and often cause resistance to specific drugs. *Phenotypic* testing is a more direct measure of resistance. It examines the amount of drug needed to inhibit the growth of a person's HIV in a laboratory setting.

In its natural or *wild type* state, HIV is not resistant to any particular drug and known drug levels are needed to suppress HIV replication. Drug-resistant HIV requires higher levels of the same drug to remain suppressed. However, because few if any direct comparisons have been made between the two types of tests, at this time no single test was determined better than any other. Both genotyping and phenotyping are useful and may be used differently in various settings (treatment management vs. drug development, etc.). ▪

New Information on Opportunistic Infections and Co-Infections

Many reports have shown fewer opportunistic infections (OIs) and deaths since the wide-scale availability and use of potent anti-HIV therapy. Also, there have been many reports of people stopping preventive therapies for OIs. Now several studies further confirm that it may be safe for some people to stop preventive therapies when their CD4+ cell count increases are sustained over time. In addition, ongoing research into hepatitis co-infection (with HIV) is beginning to show progress.

Despite success in these areas, there also appear to be increases in the rate of certain AIDS-related cancers. Moreover, a major hospital is beginning to document new increases in the rates of OIs.

Stopping MAC Prevention

An AIDS Clinical Trial Group (ACTG) study examined the safety of stopping MAC (*Mycobacterium avium* complex) preventive therapy in people who had significant increases in their CD4+ cell count from highly active antiretroviral therapy (HAART). The study enrolled 643 people on MAC preventive therapy who at one time had CD4+ cell counts below 50 but had over 100 cells at the start of the study.

Volunteers were either continued their current MAC preventive therapy, azithromycin (Zithromax®, 1,200mg once a week) or switched to a placebo. About 60% of them had good control of HIV with HIV RNA below 500 copies.

After over a year, only two people got MAC, both of whom took the placebo. These results imply that it's safe to stop MAC preventive drugs for people whose CD4+ cell counts increase to and remain over 100. If you wish to consider stopping your MAC preventive therapy, discuss it with your doctor.

Stopping PCP Prevention

A Spanish study evaluated the safety of stopping PCP (*Pneumocystis carinii* pneumonia) preventive therapy. Almost 500 people with a history of CD4+ cell counts around 100 participated.

At the start, all volunteers had CD4+ cell counts over 200, HIV RNA below 5,000 copies and were using HAART for at least three months. About 20% had been previously diagnosed with PCP.

Volunteers either continued PCP preventive therapy or received no preventive drugs. After almost a year, not a single case of PCP was diagnosed.

These results suggest that it's possible for people to stop PCP preventive therapy if they have sustained CD4+ cell count increases over 200 and stay on potent anti-HIV drugs that optimally control HIV.

An early report from a similar study, ACTG 888, appears to confirm these results. No cases of PCP have yet been reported in the 252 participants to date.

The federal guidelines for the treating opportunistic infections suggest that it's possible for people to stop primary PCP preventive therapy (to prevent first PCP infection) if they have sustained CD4+ cell counts over 200. However, the guidelines do not recommend that people stop secondary preventive or maintenance therapy (to prevent PCP from coming back). If you consider changing your PCP preventive therapy, talk to your doctor.

Advances in Hepatitis C Virus Therapy

There is possible good news for people with hepatitis C virus (HCV). Results from a small study of peg-interferon (Pegasys®, a new formulation of interferon-alfa) suggest that it's far more effective in treating HCV than the current formula of interferon-alfa. The new formulation was compared to standard interferon-alfa in 271 people with cirrhosis of the liver due to HCV. Cirrhosis is a permanent scarring of the liver and indicates a decrease in the amount of functioning liver tissue. Furthermore, the scarring interferes with the normal flow of blood through the liver and results in poor liver function.

The new version of interferon-alfa is bound to polyethylene glycol, which helps the interferon to remain stable and active in the blood for longer periods than standard interferon.

In the study, people received 48 weeks of anti-HCV therapy with a follow-up period of 24 weeks when they did not take any therapy. They received either 90 micrograms (mcg) or 180mcg of peg-interferon once a week or three million international units of interferon-alfa three times a week. Both formulas required injections under the skin.

Results showed that at 72 weeks, 29% of the participants receiving peg-interferon had undetectable blood levels of HCV compared to only 6% using standard interferon-alfa. Side effects were similar between the two formulas and included headaches, fatigue, flu-like symptoms, nausea, vomiting, depression, fever and chills.

In truth, neither of these success rates are overly impressive. Optimally, even the peg version of interferon may need to be used in combination therapy approach. Another study is ongoing in people who have both HIV and HCV to determine the effectiveness of peg-interferon combined with ribavirin (Rebetol®). Ribavirin combined with a standard form of interferon is called Rebetron® and is generally considered the current standard for treating HCV. Also, HCV advocacy groups including Project Inform are working with Hoffman-La Roche, the developers of peg-interferon, in designing studies that include complementary therapies. The new studies would determine if these therapies (such as milk thistle, coenzyme Q10 and vitamin B12) really benefit people

. . . it's possible for people to stop PCP preventive therapy if they have sustained CD4+ cell count increases over 200 and stay on potent anti-HIV drugs that optimally control HIV.

with HCV infection.

AIDS-Related Cancer on the Rise?

Recently, the large EuroSIDA study highlighted the increasing rate of non-Hodgkins lymphoma (NHL), an AIDS-related cancer. The study enrolled over 7,000 people in Europe since 1994. While the overall rate of opportunistic infections has declined dramatically, the incidence of NHL has increased substantially.

It's not entirely clear why this is occurring. But one theory explains this may be a result of people living longer or that NHL was seen less frequently in the time before protease inhibitors because people died of other conditions before developing NHL. Immune restoration (increases in CD4+ cell counts) among people on HAART seemingly has little or no impact on NHL. Some researchers wonder if the extensive use of anti-HIV drugs might be contributing to the increase, but there is no clear evidence that this is the case.

The increase in the number of OIs clearly indicates the need for newer and more potent anti-HIV therapies, as well as more effective efforts to get people into testing and treatment programs in earlier stages of HIV infection.

Are OI Rates on the Rise?

One alarming trend observed over the past 18 months at the San Francisco General Hospital (SFGH) is the rising numbers of OIs. In 1997 cases of PCP, MAC, cytomegalovirus, and cryptococcal disease (a fungal infection primarily of the brain) fell to an all-time low. However, by 1998 the number of these infections diagnosed at SFGH grew above 1997 levels. The 1999 numbers are expected to be even higher.

Earlier HIV testing and better access to treatment and care may have prevented many of these infections. It's been noted that what happens in San Francisco usually happens in the rest of the country a year or two later. So, returns in rates of new AIDS-related infections may be expected over the coming years.

Conclusion

We now have some clear data on the safety of stopping preventive therapy. However, the more worrying issue is the apparent increase in the number of OIs. This clearly indicates the need for newer and more potent anti-HIV therapies, as well as more effective efforts to get people into testing and treatment programs in earlier stages of HIV infection. It also indicates the need for better third line therapies so that we do not return to the situation in which we were in 1996. ▪

Treating and Preventing Fungal Infections Naturally

There is a strong connection between what you eat and the health of your immune system. Nevertheless, nutritional approaches to prevent and treat conditions like candidiasis (fungal, yeast infections) are complicated and controversial. While there isn't a magic recipe that prevents or treats yeast infections in everyone, following some basic guidelines may lower the risk of yeast becoming a problem.

Most nutritionists agree that sugar, yeast, dairy, wheat, caffeine, nicotine and alcohol are the main culprits because they help yeast to grow. In people with healthy immune systems, the body is usually able to fight off the excess yeast made by these products. But for people with weakened immune systems, yeast can grow out of control, leading to certain kinds of fungal infections, like oral or vaginal candidiasis, or more seriously, esophageal (in the throat/esophagus) candidiasis. To prevent this, nutritionists recommend eating as little as possible of these foods that contribute to the excess production of yeast.

Another approach is to eat larger amounts of foods that may suppress the growth of yeast. For example, garlic is believed by some nutritionists to have natural anti-fungal properties and may help to prevent candidiasis. Fresh garlic is considered best, although commercial garlic "pills" offer the advantage of reduced odors. Fresh garlic can be mixed into other foods, eaten raw after removing the dry outer skin, or minced and put into empty gelatin capsules, up to six cloves a day.

Another factor that can contribute to uncontrolled yeast growth is the use of antibiotics. "Friendly" bacteria are found naturally in the body and establish a healthy balance while eliminating unfriendly yeasts. These bacteria are similar to *Lactobacilli,* the bacteria that turn milk into yogurt. Many common antibiotics (like tetracycline and penicillin) kill these bacteria which then allows yeast to grow, especially in the vagina. It is not unusual, even in people with healthy immune systems, to experience some form of candidiasis after a prolonged use of antibiotics, so it is important to use antibiotics only when truly necessary.

In order to lessen this effect from antibiotics and promote healthy bacteria in general, many nutritionists recommend adding *Lactobacilli acidophilus* bacteria to your diet. It can be found in yogurts and certain milks (look for *Lactobacilli acidophilus* on the label). You can also take it in pill form, available at many health food stores.

Oral candidiasis or *thrush* can change how you taste and enjoy foods. It can also make eating and swallowing difficult. Avoiding acidic, spicy or hot foods as well as cigarettes, alcohol and carbonated drinks may lessen this

effect. All of these can irritate the insides of your mouth. Soft, cool and bland foods (like oatmeal, mashed beans, apple sauce) are recommended.

Many people use liquid food supplements to ease painful mouth infections and to keep or add on weight. Unfortunately, many of these supplements are high in sugars, which can promote yeast growth. If you use liquid supplements, make sure they contain mainly complex carbohydrates, are high in protein and have low-to-moderate sugar levels. It's important to remember that these products are intended to be *supplements* and should not replace solid food.

. . . garlic is believed by many nutritionists to have natural anti-fungal properties and may help to prevent candidiasis.

There are some reports that gargling with Tea Tree oil diluted with water can help treat oral candidiasis. Generally these gargles (two drops of oil in a tablespoon of water) are used in the morning, night and after meals. They are sometimes swabbed directly on mouth sores (one drop of oil to one drop of water). Grapefruit seed extract and 1% hydrogen peroxide may also be used in a similar way, but must be more heavily diluted and should NEVER be swallowed. However, these approaches (especially grapefruit seed extract) may irritate the mouth and promote infection. Moreover, they only address the local symptoms of yeast growth and not the underlying causes.

Overall, the best way to naturally treat and prevent fungal infections is to eat healthfully and regularly, avoid excessive sugar intake and avoid or decreasing alcohol and cigarettes. ▪

Candidiasis Update E

Sustained CD4+ cell count increases as a result of potent anti-HIV therapy have been credited with a steep drop in many HIV-related conditions. Indeed, the most recent guidelines for preventing opportunistic infections (OIs) reflect the growing practice of stopping preventive and maintenance therapies. While the risk of developing OIs or having them reappear still exists after therapy fails, the possibility of stopping OI therapy after achieving an improved immune response is promising for many. Unfortunately, despite success with many OIs, declines in the rate of the fungal infection candidiasis have not been observed.

What is Candidiasis?

Candidiasis is caused by the fungus *Candida* and while it is a relatively common condition in general, it remains the most common HIV-associated disease. Some lab studies show that protease inhibitors have a direct anti-candida effect. Other studies suggest that the chance of developing candidiasis does not significantly decrease when using combination anti-HIV therapy. Thus, at one point or another, candidiasis continues to affect the majority of people with HIV disease who suffer from clinical declines in immune function. In people with damaged or weakened immune systems, candida can recur and be difficult to treat.

Candidiasis can occur in the mouth, esophagus (throat), digestive tract, vagina or on the skin. The most common site of infection is in the mouth (thrush) and/or vagina (yeast infections, vaginitis). Among women, vaginal candidiasis appears as the most common symptom. Although vaginal candidiasis is slightly more common among HIV-positive women than negative women, there is no clear relationship between its occurrence and CD4+ cell count. Thus, the relationship between vaginal candidiasis and HIV infection remains unclear. Finally, esophageal candidiasis has been reported as the most common AIDS-defining OI, probably due to the decreased incidence of other OIs.

Candidiasis Prevention Tips E

- Maintain good oral health: brush teeth daily, gargle with antiseptic mouthwash (like Listerine®) and floss.
- Decrease or avoid sugars (corn and maple syrup, glucose, fructose and sucrose). Sugars are food for candida and help it to grow.
- Decrease or avoid alcohol. Alcohol converts to sugar and promotes the growth of candida.
- Ingest large amounts of garlic (fresh is considered best—mince and put into empty gelatin capsules, up to six cloves a day). Garlic is believed to have some natural anti-fungal properties and may help to prevent candidiasis.
- Drink milk or eat yogurt that contains acidophilus bacteria. Acidophilus is "friendly" bacteria which helps keep our body in balance and able to fight of "unfriendly" bacteria and fungus, like candida.
- Apply yogurt containing "friendly" bacteria directly into the vagina (such as *Lactobacillus bifidus* or *Lactobacillus acidophilus*).
- Wear loose fitting clothes to help prevent vaginal candidiasis, since these allow areas of the body ventilate better and dry out. ▪

Symptoms of Candidiasis

Thrush can sometimes occur without symptoms. However, the most common symptoms or oral candidiasis include burning pain, altered taste, difficulty swallowing and/or whitish coatings or spots on the gums and tongue. Thrush is rare when CD4+ cell counts are above 500 and more common as CD4+ cell counts decrease and near 100.

Symptoms of vaginal candidiasis include itching, vaginal swelling and thick and odorous discharge. Vaginal candidiasis is often associated with pregnancy, high estrogen oral contraceptives, diabetes, antibiotics use, tight fitting clothes, dietary factors and sexually transmitted disease.

Esophageal candidiasis tends to occur more frequently when CD4+ cell counts are below 100. It is usually accompanied by thrush and esophageal/throat pain.

Treatment Considerations

The range of treatments for candidiasis boil down to two kinds: local (treating at the site of the disease) or systemic (treating the disease throughout the body). Local therapies include topical creams to treat candida infections in the skin, vaginal creams to treat vaginal candidiasis and lozenges or mouth washes to treat candida in the mouth. Systemic therapy include pills (taken by mouth) and intravenous (in the vein) therapies. Generally speaking, local therapy will be the first choice for treating candidiasis. If the infection is aggressive, not responsive to therapy and/or shows signs of spreading throughout the body, then systemic therapy will be employed.

Systemic therapies can be used for any type of candidiasis. They must be used for esophageal candidiasis or candidiasis that has spread throughout the body. Intravenous treatment is generally the least desired option because it can have many side effects. It is left as a last resort in rare but serious, life-threatening cases that have not responded to other treatments.

The Problem of Anti-fungal Resistance

Candidiasis that fails to respond to treatment has been increasingly reported, especially among people who have not experienced benefit from fluconazole (Diflucan®) and other *azole* anti-fungal drugs. This is partly due to the widespread, long-term use of *azole* drugs for treating and preventing candidiasis. Other factors associated with azole-resistance include tuberculosis (TB) exposure, treatment with anti-TB drugs, treatment with the antibiotic ciprofloxacin (Cipro®) and CD4+ cell counts below 50.

Resistance to *azole* drugs has often required treatment with amphotericin B (Fungizone®). While potent and effective, amphotericin B—both intravenous and oral formulas—is toxic, especially to the kidney. Newer liposomal versions of the drug, such as amphotericin B lipid complex or ABLC, have proven less toxic to the kidneys than its earlier formula.

A recent study compared the original form of the drug to the newer form in people who could not tolerate conventional amphotericin B and/or who did not respond to the drug. The study found that people were more likely to tolerate ABLC and were thus more likely to be able to take the drug until their fungal infection successfully cleared. Even among people with some underlying kidney disease, ABLC was better tolerated, resulting in only very small changes in kidney function tests.

More recently studies have shown that exposure to *azole* treatment (including fluconazole, ketoconazole and itraconazole) results in the decreased anti-fungal activity of amphotericin B. This will likely be the case for newer, less toxic forms of the drug; but more studies are needed to confirm this. Like the quandary created by anti-HIV drug resistance, the development of anti-fungal resistance underlines the importance of developing new classes of drugs that can effectively treat candidiasis. ▪

Organ Transplant Study Moves Forward

As HIV-positive people live longer, fewer are dying from infections usually associated with AIDS. Instead, a rise in a variety of other complications, including organ failure, are beginning to threaten the lives of people with HIV. For example, liver disease may be a complication of hepatitis C virus, a common infection among people with HIV but it may also be a result of HIV disease itself. Either way, liver disease may be worsened by some therapies commonly used to treat HIV. HIV infection and some HIV therapies may likewise cause or worsen other health problems such as poor kidney function. In advanced stages of liver and kidney disease, organ transplants may be the only hope. A recently funded organ transplantation study offers new hope for people facing these dilemmas.

For information about the UCSF study, contact the receptionist at the UCSF Kidney Transplant Unit at 415-353-1551. Physicians or patients should let the receptionist know they are inquiring about Dr. Stock's HIV transplant study. Dr. Stock notes that it's best to call 9am–4pm PST to avoid getting the answering service and increasing the likelihood that the call will be directed appropriately. (Note: you *do not* have to be a California resident to participate in the UCSF study). ▪

WISE Words is the publication of **Project WISE**, Project Inform's program focused on HIV/AIDS treatment information and advocacy for women. Each issue provides women with important tools for making HIV treatment decisions, covering topics such as anti-HIV therapy, prevention and treatment of infections, management of side effects and more.

Recent issues include:

- Sex and Transmission, a Continued Concern for Positive Women
- Gender Difference in Viral Load?
- Highlights from the 1999 National Conference on Women and HIV/AIDS.

If you would like to be added to the mailing list for *WISE Words*, call Project Inform's National HIV/AIDS Treatment Hotline at 800-822-7422 or email SUPPORT@projectinform.org.

1999 National Conference on Women and HIV/AIDS

The 1999 National Conference on Women and HIV/AIDS, held last October in Los Angeles, convened its largest number of participants. Over 2,000 researchers, clinicians, policymakers, AIDS activists and HIV-positive women came to discuss new treatment, behavioral and political issues affecting women. The strong and diverse turnout provided a lively and sometimes conflicting forum that reflected the growing visibility of women's issues. Following are selected highlights from the conference. *For more on the 1999 Conference, call Project Inform's Hotline and ask for WISE Words #5, which fully covers the conference.*

Disease Progression and Survival

Studies that have shown worse outcomes for women have attributed poorer survival and disease progression to differences in access to healthcare. The Community Program for Clinical Research on AIDS (CPCRA), a community based research network, studied this issue. It reviewed the outcomes of men and women receiving similar medical care. The CPCRA divided them into three groups according to the anti-HIV therapy used: one-, two- or three-drug therapy. Across all groups, no gender differences were noted in rates of disease progression or death. Factors that seemed to influence survival and rates of disease progression included CD4+ cell count and type of treatment, with those on three-drug therapy doing better than those on one or two drugs.

Disease progression and survival rates do not appear to vary between genders in populations who have similar access to healthcare and therapy. However, studies with larger numbers of women are needed to determine whether gender influences disease progression or response to therapy when using potent combination therapy. Also, two important studies point to the fact that women of color and women with past or present drug use—who make up most of the women in the epidemic—still lack access to regular healthcare and are less likely to use combination therapy.

Side Effects

There were several presentations on women and side effects related to anti-HIV therapy. Recent studies reported on women's experiences of side effects compared to those of men. They found that women are less likely to tolerate a full dose of ritonavir (Norvir®) than men. Women also seem more prone to rashes from using nevirapine (Viramune®) and nelfinavir (Viracept®). In addition, women might be more likely to develop lactic acidosis, a rare but life-threatening condition reported in some people taking anti-HIV therapy. *For more on lactic acidosis, see page 10.*

Studies are currently exploring the possible causes of gender-specific side effects. Biological factors like body composition and weight, metabolic and hormonal differences, and presence of other complicating factors (concurrent auto-immune diseases, anemia, etc.) were discussed. Further analysis of these factors is sorely needed to determine if or how they contribute to these gender differences. This is particularly true given the many personal examples shared by women at the conference struggling with drug side effects.

Anemia

Anemia is a low amount of red blood cells, the cells that carry oxygen throughout the body. Early signs include feeling fatigued and low cell counts on lab reports. Anemia has long been shown to negatively affect quality of life and survival among men living with HIV. A study examining the rate of anemia in women who participated in the WIHS support these findings among women.

The study found that HIV-positive women were more likely to be anemic than their HIV-negative counterparts, regardless of age, ethnicity and past or present drug use. Among women living with HIV, risk of anemia was related to: history of an AIDS-defining condition, low CD4+ cell count (below 200), high viral load (above 50,000 copies/mL) and the use of AZT (zidovudine, Retrovir®). African American race and red blood cell counts below 80 are also associated with anemia.

Women of color and women with past or present drug use still lack access to regular healthcare and are less likely to use combination therapy.

Epoetin (Epogen®, Procrit®) is used to treat mild-to-moderate anemia. One study examined epoetin given once a week by injection for eight weeks in HIV-positive women with anemia. Major increases in red blood cells were seen in most of the women, as well as improved quality of life. Overall, the drug was well toler-

ated with only minor side effects, like nausea, body aches and fever. However, people with severe anemia should not count on epoetin to solve their problem; in these cases blood transfusions may be still be required.

Hormone Contraceptives and Hormone Replacement Therapy

This is an area of obvious interest and concern, particularly among older HIV-positive women using or considering hormone replacement therapy (HRT). Unfortunately, it was barely dealt with at the conference. One study compared HIV levels in women using hormonal contraceptives (oral contraceptives, injectable DepoProvera®, Norplant®). It found that the contraceptives did not affect viral load, but more research is needed to examine the interaction of contraceptives with specific anti-HIV therapies and HIV disease itself.

Another study looked at testosterone replacement therapy in women with AIDS-related weight loss and a related condition, *amenorrhea* (loss or absence of periods). It found that women who took a replacement dose of testosterone (a dose bringing the hormone to normal levels in the blood) experienced weight gain, return of menstruation and improved quality of life.

Depression

Finally, depression is a common condition among older and HIV-positive women. While depression among older women may be influenced by psychological and social factors, it may be physical. In short, after menopause women produce less *serotonin*. Low levels of serotonin have been linked to depression. The use of HRT to ease depression in HIV-negative women is being explored and should also be looked at for women living with HIV. However, like testosterone replacement therapy, studies examining HRT must also consider the possible interactions with anti-HIV drugs and HIV disease itself. ▪

Summary of the Eighth Immune Restoration Think Tank

Project Inform hosted the eighth meeting of the *Immune Restoration Think Tank: The Dobson Project (IRTT)*, October 8–10, 1999 in Chicago. Researchers from around the world, in partnership with community activists, convened to review data from ongoing projects, previously inspired through the Think Tank effort, and discuss new strategies and areas of focus for immune reconstitution research in people with advanced stage AIDS.

Participants spent the weekend discussing and planning actions around a variety of topics, ranging from cell therapy to bolster immune responses against HIV to strategic therapy interruptions as a way to achieve several possible goals of therapy. The following are four highlights from the discussions:

1 There is a need for the Food and Drug Administration to convene a meeting to determine what types of studies should be required to prove the usefulness of immune-based therapies for HIV infection. The most important question is whether there is any alternative to large, clinical endpoint studies. In such studies, participants must be followed until they decline to disease or death while being treated with a particular therapy compared to a placebo or a standard therapy. If there is a concensus that certain lab markers or blood tests might predict the outcome without waiting for people to suffer serious consequences, then development and approval of such lab tests are critical. Think tank participants identified one potential laboratory measure, being developed by Beckton Dickinson Laboratories, which may prove useful in assessing immune function. Using a technology commonly used to measure CD4+ cell counts, called flow cytometry, it may also be possible to look for the loss and/or return of specific immune responses.

2 Increases in measures of immune activation have long been noted as HIV disease progresses. This activation may interfere with immune function as well as increase HIV replication. Studying therapies that slow this immune activation are needed. A few studies are already ongoing, including a study of cyclosporine-A at VirX, and a study of radiation therapy at the Gladstone Institute, both in San Francisco. Moreover, it was recommended that studies of the potential anti-HIV drug, mycophenolate (CellCept®) evaluate how the immune suppressive effect of this drug might be adding to its anti-HIV effect. (For more information on mycophenolate, see *PI Perspective 28*).

3 While most people with HIV are familiar with CD4+ and CD8+ cells, other cells also play key roles in initiating effective immune responses. These include antigen presenting cells (APC), which carry or present HIV and other infectious agents to CD4+ cells so that they may act to eliminate or contain an infection. A number of studies suggest that there is a defect in APC activity in people with HIV and there are some therapies that, at least in test tube studies, might enhance the function of APCs. These include CD40 ligand and flt3 ligand. Neither is currently available for use in human studies in HIV and activist pressure is needed to accelerate the sponsor's interest in

testing these strategies against HIV disease. **4** A number of other strategies which have not been studied in the setting of HIV need to be evaluated, including:

- Interleukin-2 (IL-2) has been studied in people with early and middle-stage HIV, but not adequately studied in people with advanced stage HIV disease.
- Interleukin-7 (IL-7), which might enhance the function of the thymus, an important organ for new T cell development (including CD4+ and CD8+ cells).
- Interleukin-15 (IL-15) may increase CD4+ cell counts, similar to what has been seen with IL-2 therapy, but perhaps without the serious side effects seen with IL-2 therapy.
- Destruction of macrophages: This may lead to reconstitution of new and more functional macrophages. Macrophages are APCs which can become infected by HIV. Destruction of infected macrophages was the goal sought in early years of the epidemic with the drug trichosanthin, more popularly known as "compound Q." While the drug itself is no longer under study, the strategy behind it remains valid.
- Alloimmunization includes injecting someone with another person's cells to trigger an immune response. A number of researchers propose, and preliminary observations suggest, that this approach may enhance immune responses against HIV.

For more information about these approaches, others aspects of Project Immune Restoration and a full report from the recent IRTT, read Project Inform's *Project Immune Restoration Discussion Paper.* ▪

Thinking About Immune-Based Therapy . . . ?

In HIV disease, even though the immune system generally weakens over time, it is also in some ways over-boosted. When it comes to the immune system, "more" is not always better. For example, a whole range of diseases are called "autoimmune" illnesses in which the immune system is overactive and attacks the body itself. In some ways, HIV causes the immune system to overreact and damage cells and tissues. Still other illnesses, like the opportunistic infections associated with AIDS, result from diminished immune function. In HIV disease, it is more accurate to think of the immune response as abnormal or disrupted, rather than just in need of a "boost."

Creating drugs or strategies that suppress the reproduction of HIV is a very complex task by itself, which is why such drugs are far from perfect. The same, or worse, may be true for immune based therapy, however "natural" the idea sounds. The immune system is perhaps the most complex product of human evolution. The immune system carries on a daily war against invading enemies, both known and unknown. It does this through an almost unthinkably complex interaction of dozens of different cells and tissue sites, which communicate with each other and invading agents through hundreds or even thousands of chemical messages made by cells.

The goal of immune based therapy in HIV disease is to first understand how the immune system reacts against HIV, why it fails to "cure" the infection the way it does with most diseases, and finally, to figure out how to change or manipulate the immune response to improve its activity against HIV. This task is inherently more complex than merely building chemical toxins that slow the production of new virus.

Despite this complexity, many researchers have dedicated their lives to the study of the immune system because they believe it ultimately holds the keys for conquering all human illness. ▪

Immune-Based Therapies In Brief

Immune-based therapy is considered by many to be the "holy grail" of AIDS research. Most successful therapies to date have been anti-HIV drugs that suppress reproduction of HIV, the virus that causes AIDS. Success, however, usually comes at the price of many side effects. Researchers and patients alike have longed for therapy that doesn't so much try to wage war against the virus, but rather strengthens the weakening immune response associated with AIDS. The hope is that such an approach might be more natural or less toxic. Although health food stores offer an abundance of products that claim to "boost" or "strengthen" immunity, these are mostly just advertising claims. Helping the immune system in its battle against HIV is far more complex than simply "boosting" anything.

IL-2 (Proleukin®) and HIV-1 Immunogen (Remune®)

IL-2 or interleuken 2 is a chemical messenger of the immune system which, among other things, causes T-cells to quickly divide and reproduce, thus increasing their numbers. The body naturally produces IL-2 to help in its battles against a variety of infections by quickly growing an army of T-cells to fight the invader. IL-2 was one of the first products ever tested against AIDS because it was clear from the earliest years of AIDS research that

the body was not producing its normal level of T-cells. The decline in the number of one type of T-cell, called CD4+ T-cells, is one of the easily measured characteristics of HIV disease. Most studies of IL-2 in HIV disease have used IL-2 alone or in combination with standard antiviral drugs.

One new study compared the use of IL-2 against a therapeutic vaccine known as Remune®. IL-2 was administered in five-day cycles, every four weeks for the first three cycles then every six weeks for subsequent cycles. Remune was administered once every three months.

After four months, those receiving only anti-HIV therapy or anti-HIV therapy with HIV-1 Immunogen experienced an increase in CD4+ cell counts of about 100 cells. Those receiving anti-HIV therapy combined with IL-2 showed more pronounced CD4+ cell count increases, of about 750. People in all three groups showed better immune responses to HIV, though the highest percentage of people with these increased responses received Remune. Whether this corresponds to better immune control of HIV remains unknown.

The vast majority, in all three groups, had viral load decreases to below the limit of detection of the test. As time went on, the number of people with optimal viral suppression increased steadily through week 48. However, after week 48, additional increases in CD4+ cell counts among the three groups were not noted.

IL-2 and Strategic Therapy Interruption

A very small study of low dose IL-2 given daily, was presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy and follow-up information was presented at the recent Human Retrovirus conference. The study produced puzzling results while the conference presentation created quite a buzz among the participants.

Volunteers who started anti-HIV therapy and experienced optimal viral suppression added IL-2 to their treatment regimen. They then stopped anti-HIV therapy but continued taking IL-2. After stopping anti-HIV therapy, HIV RNA levels initially rose, but then fell to levels lower than what had been observed prior to starting anti-HIV therapy.

What's important to note is that IL-2 without anti-HIV therapy didn't control HIV replication. Furthermore, in this study, CD4+ cell counts did not increase but CD8+ cell counts increased dramatically. Also, it's unclear if IL-2 added anything to this picture, as studies of strategic therapy interruption without IL-2 have sometimes shown similar results. For more information on *Strategic Therapy Interruptions*, call Project Inform's National HIV/AIDS Treatment Hotline.

French Compassionate Use Approval of IL-2

On the basis of a 72-person study conducted in Europe, the French government approved IL-2 for Compassionate Use in people with CD4+ cell counts below 200 with controlled viral replication (HIV RNA below 1,000 copies/ml). The French Compassionate Use system is similar to an accelerated approval in the United States, with restrictions on who has access to the therapy.

This approval is based on results from a study of people with CD4+ cell counts between 50 and 200 and HIV RNA levels below 1,000 copies/ml who received anti-HIV therapy alone or in combination with IL-2. IL-2 was administered through injection directly under the skin (subcutaneously), twice daily for five days, every six weeks. The dose was 4.5 million international units (MIU), for a total daily dose of nine MIU. At the end of six months, people receiving IL-2 experienced a CD4+ cell count increase of 65, whereas those who only received anti-HIV therapy realized a small cell count increase of 18. Viral load was similar in the two groups. French authorities apparently concluded that the greater increase in CD4+ counts seen in the people treated with IL-2 warranted making the drug available to people with very low CD4+ levels. The study, however, did not follow the patients long enough to know whether those with increased CD4+ counts actually lived longer or had greater freedom from opportunistic infections. A much larger international study, described below, attempts to answer this question.

IL-2 Study Enrollments

A 4,000-person study of IL-2, called ESPRIT, officially launched in January 2000. Volunteers receive either IL-2 by injection directly under the skin, twice daily, for five consecutive days every eight weeks, or no IL-2 therapy. The study will last for five years. Volunteers must have CD4+ cell counts above 300 to be eligible.

A second study, called SILCAAT, is open to people with CD4+ cell counts below 300 and HIV RNA levels below 10,000 copies/ml. A third study, evaluating the use of very low doses of IL-2, given daily in people with low CD4+ cell counts, is fully enrolled and expected to report data shortly. Rumor has it, however, that the low dose approach did not result in substantial increases in CD4+ cell counts.

For more information about IL-2, read Project Inform's *Interleukin-2 Fact Sheet*. For more information about these studies, call 1-800-TRIALS-A. ▪

Researchers and patients alike have longed for a type of therapy that doesn't so much try to wage war against the virus, but rather strengthens the weakening immune response associated with AIDS.

Post Exposure Prevention

There has been growing interest in the use of Post Exposure Prevention (PEP) as a means of preventing HIV infection. PEP involves a person beginning anti-HIV therapy within hours of suspected HIV exposure, with a goal of blocking the establishment of HIV infection.

Certainly the use of anti-HIV therapy by HIV-positive pregnant women and their newborns has been extremely effective in lowering the rate of mother-to-child HIV transmission. The use of anti-HIV therapy among HIV-negative healthcare workers, within hours of a possible HIV exposure (e.g. needlestick accident with a needle exposed to HIV-infected blood), is standard of care in hospital and clinic settings and has been shown to reduce the risk of developing HIV infection. There is a great deal of controversy, however, about the risks, benefits and public health impact of using PEP among HIV-negative people who have had a recent possible sexual or injection drug use-related HIV exposure. Three posters presented at the recent Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) provided additional insight into the use of PEP for sexual and other non-occupational exposures.

France, Switzerland and Australia are the only countries in the world with recommendations and guidelines for the use of PEP for suspected sexual HIV exposure. A small observational study in Lyon, France evaluated PEP use and follow up in sexual assault victims. To be eligible for PEP, a person must arrive at the clinic and start anti-HIV therapy within 48 hours of the possible HIV exposure incident. Anti-HIV therapy is continued for four weeks with intensive monitoring.

While no data were available regarding HIV transmission rates, interesting information was provided regarding the use of PEP in this setting. Of the 65 people seen at the Lyon clinic, nine were ineligible for PEP because they arrived more than 48 hours after the potential HIV exposure. Thirty five people, slightly more than half, chose to start PEP, but of those, only 19 returned to the clinic for follow-up visits. Findings from the French study suggest that programs to enhance follow-up for PEP recipients are critical, not only to document the effectiveness of PEP but also to monitor for side effects of anti-HIV therapies.

In Brazil, a study of PEP nested within a larger study looking at new infection rates among gay men evaluated the impact of PEP usage on subsequent HIV risk-taking behaviors. While the primary study is quite large (202 gay men), the PEP study included only 29 men who presented within 48 hours of a suspected HIV exposure and elected to use anti-HIV therapy. In the overall study, after 18 months of follow up, three people have become HIV-positive, none of whom received PEP. None of the 29 men who received PEP has become HIV-positive.

The individuals who chose PEP had documented repeated high-risk behavior (e.g. unprotected sex) which persisted over time. The decision to use PEP neither increased nor decreased their risk-taking activities. Of the 29 people who chose PEP, a few individuals repeated the use of PEP because of subsequent suspected HIV exposures. Three people initiated PEP twice and one person initiated four courses of PEP over the 18 months follow up of the study.

The largest study of PEP was reported by Dr. Michelle Roland of UCSF. This study enrolled 436 people who initiated PEP within 72 hours of a suspected non-occupational HIV exposure. In this study PEP included HIV testing, ongoing risk reduction and adherence counseling, the option to use one month of anti-HIV therapy and intensive monitoring. Not all individuals chose to use anti-HIV therapy, but all individuals, regardless of their decision about anti-HIV therapy, were encouraged to remain in the PEP program for counseling and monitoring. The majority of individuals who chose to receive anti-HIV therapy received dual nucleoside analog reverse transcriptase inhibitor (NARTI) therapy.

Six month follow up data are available on 293 people and twelve-month follow up information is available on 145 people. Thus far, four people in the study have become HIV-positive. This includes one person who did not choose to take anti-HIV therapy and three people who initiated anti-HIV therapy. None of the four infections are believed to be associated with the suspected HIV exposure incident that first brought the individual to

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, 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 clinic. All four people reported repeated high-risk activities after their initial intake into the PEP program.

Of note, one of the women in the study who became HIV-positive engaged only in protected sex with her HIV-positive partner after presenting to the study as a result of a broken condom. Six months after her course of anti-HIV PEP therapy, she and her partner began having unprotected sex when his HIV levels fell below the limit of detection, believing he was not infectious. Shortly thereafter she developed symptoms of an acute infection syndrome and later documented HIV infection. This particular case underscores the need for continued safe sex practices among people living with HIV who have optimally suppressed HIV levels to below the limit of detection of current tests. Having undetectable HIV levels in the blood does not mean that HIV is absent in either semen or vaginal secretions, nor does it mean a person cannot transmit HIV. Some existing data also suggests that it takes longer to reach "undetectable" levels of HIV in semen or genital secretions than it does in the blood. Thus, reaching undetectable levels in the blood—the only thing that most patients can easily measure—should never be considered a sign that a person has suddenly become incapable of transmitting virus to others.

There is a great deal of controversy, however, about the risks, benefits and public health impact of using PEP among HIV-negative people who have had a recent possible sexual or injection drug use-related HIV exposure.

Commentary

None of the above studies either confirms or denies the value of anti-HIV therapy in preventing HIV infection in the non-occupational HIV exposure setting. The use of PEP for sexual, injection drug use or other non-occupational exposures is extremely controversial. While in the setting of occupational (healthcare worker) HIV exposure, the use of anti-HIV therapy within a few hours of suspected HIV exposure has been shown to decrease HIV transmission/infection rates, it is not clear that this finding applies in any other setting. It is unknown if starting therapy after 24–36 hours will have any impact on blocking an HIV infection when exposure to HIV has occurred. Moreover, the majority of people with a suspected exposure to HIV, regardless of the use of therapy, will not go on to develop an established HIV infection.

For people who repeatedly engage in high-risk activities that may result in an exposure to HIV, the repeated use of anti-HIV therapy could theoretically weaken the immune system and leave them more susceptible to HIV infection. This is not to say that anti-HIV therapy weakens the immune system, per se, but rather that the drugs do have side effects and they can be hard on the body, as any person taking the drugs to treat HIV can well testify. In general, the use of PEP is not recommended for people who document repeated high-risk HIV exposure activities.

The most effective way to prevent HIV infection is to reduce risk-taking behavior, practice safer sex, use clean works and don't share needles or works. Project Inform is developing a discussion paper on PEP that should be completed by the end of this year. For a full discussion of issues regarding PEP for non-occupational HIV exposure, call Project Inform's hotline or check the website to see if the paper is available. For more information on preventing mother-to-child HIV transmission, ask for the new discussion paper on this topic. However, as a general rule, the Project Inform hotline is not a prevention counseling hotline. If you have specific questions about HIV prevention, risk behavior or risk reduction counseling call the Centers for Disease Control's National HIV/AIDS Prevention Hotline at 1-800-458-5231. ▪

The Basic Message

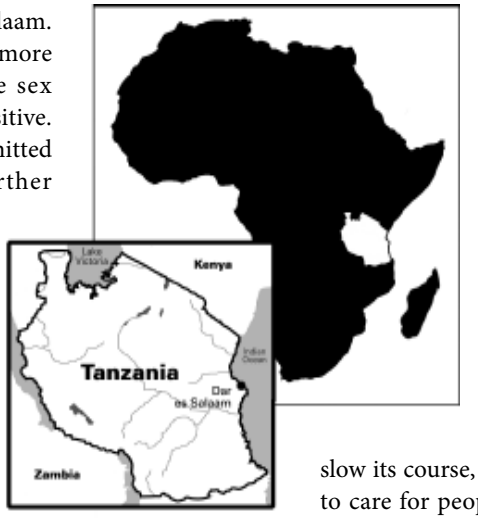
- **Get tested**, *anonymously*.
- **Learn your options** and line up your support.
- If positive: **maximize your health, get a complete physical, a full immune health workup** and **get *informed*!** (See Project Inform's discussion paper *"Day One"*).
- **Get baseline CD4+ and HIV RNA tests, repeat quarterly**. Chart the trends. Women should get "GYN" exams and "Pap" tests every six months.
- If the CD4+ trend is downward or already below 500, and HIV RNA above 5,000, **or** if HIV RNA is above 30,000-50,000, regardless of other factors, **optimize nutrition and consider combination anti-HIV treatment**.
- If viral measures do not decline below the limit of detection, **consider a more aggressive anti-HIV regimen.**
- If the CD4+ trend stays below 300, **consider preventive treatment against PCP** (oral drugs if possible). If the count continues to fall below 200, **consider a more aggressive anti-HIV regimen** if not already on one and **learn about preventive treatments** against other opportunistic infections. **Learn about drug interactions.**
- If you have begun preventive therapies and your CD4+ cell count rises as a result of anti-HIV therapy, **remain on any preventive treatments you have started for at least six months.**
- If CD4+ cell count stays below 75, **intensify monitoring,** con-sider prevention against MAC/MAI and CMV infections. **Learn about preventive therapies.**

The Global Crisis: E AIDS in Tanzania

More than 90% of people living with HIV/AIDS are in the developing world, most of whom live in Africa, followed by Asia and Latin America. In an effort to increase awareness of the HIV epidemic in these regions, *PI Perspective* will feature short profiles of the epidemic in some of these countries. In this issue, *PI Perspective* looks at the United Republic of Tanzania.

In recent years, the nations of sub-Saharan Africa have experienced rapid and alarming increases in HIV infection rates. In Tanzania, the AIDS epidemic has primarily affected urban areas, where nearly 10% of the adult population is HIV-positive. Unlike many other African countries, the current spread of HIV/AIDS in rural communities is relatively low (almost 3%), though that number is also growing.

Heterosexual sex accounts for the majority of HIV infections in Tanzania. The highest rates have occurred among female sex workers, with prevalence rising to 50% in 1993 in the capital, Dar es Salaam. In other urban areas, more than 60% of female sex workers are HIV- positive. Other sexually transmitted diseases (STDs) further fuel the epidemic among sex workers and their clients by making it easier to spread HIV. HIV prevalence among men with STDs is above 20% in urban areas.



Mother-to-child transmission is also an increasing problem. In many areas, upwards of 15% of pregnant women aged 15–49 are HIV-positive. The advances in anti-HIV therapy that have allowed for the dramatic reduction in mother-to-child transmission in the US and Western Europe are not yet available in resource-poor Tanzania. Moreover, it is estimated that HIV transmission through breast feeding accounts for approximately one quarter to a third of infections in infants. The lack of alternatives to breast-feeding increases HIV transmission rates among infants and children.

The spread of HIV has also contributed greatly to the re-emergence of tuberculosis in Tanzania. *Tuberculosis* is one of the most common opportunistic infections, as well as the leading cause of death among people with AIDS in Tanzania.

There are several factors that influence the shape of the HIV epidemic in Tanzania. Poverty, migration, and stigma are a few of the factors that hinder the people of Tanzania from protecting themselves and others from HIV infection. Poor families and communities struggle to purchase drugs, medical services, and funeral services. Yet, in spite of the epidemic's magnitude and the limited resources available to slow its course, there is a growing effort to care for people with HIV/AIDS and prevent the spread of the disease.

WAMATA, a Swahili acronym for "people in the fight against AIDS", is one important example of Tanzania's grassroots response to HIV. Building on the country's strong sense of community, WAMATA provides psychosocial and material support for entire families affected by HIV/AIDS. Last year, Project Inform's staff was fortunate to meet WAMATA's Founding Director, Theresa Kaijage. "My role is to give hope rather than despair," Kaijage said. The hope WAMATA provides comes in many forms—from a place to safely obtain information on HIV, to counseling, home care, financial, legal and material support. WAMATA also provides a forum to engage in advocacy for the rights and needs of people living with HIV and their loved ones.

There are many worthy organizations like WAMATA who need financial support, equipment, medications and other materials. We urge our readers to consider contributing to such organizations. Project Inform is working in partnership with WAMATA to raise funds that will help ensure that they remain in touch with a vital network of activists and educators world wide. If you are interested in making a contribution, please indicate the amount of your donation that you would like to designate for WAMATA on the donor form on page 24. Project Inform will deliver donations to WAMATA.

For further information about making a donation on behalf of WAMATA, please call or email David Evans at 415-558-8669 x215 or devans@projectinform.org.

For further information about WAMATA in particular, readers may contact Theresa Kaijage at the following email address: WAMATA@ud.co.tz. ▪

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

Global Strategies for Mother-to-Child HIV Transmission Prevention

Women and children account for over half of those living with HIV throughout the world. Despite the growing list of HIV prevention methods (condoms, needle exchange, treatment of sexually transmitted diseases, use of maternal anti-HIV therapy, elective C-section, etc.), the number of HIV-infected women and children continues to rise dramatically. The second International Conference on Global Strategies for the Prevention of HIV Transmission from Mother to Infants, held September 1999 in Montreal, Canada, asked why—given the many advances in HIV prevention and treatment—women and children suffer from the greatest disparities in this epidemic.

The Conference emphasized scientific, social, ethical, political and economic issues affecting HIV transmission and treatment. It highlighted areas where HIV knowledge is adequate or growing, but its benefits are unevenly felt. Perhaps nothing encapsulates this quandary more than the growing number of HIV-positive children that comprise the mounting "orphan crisis."

In addition to the focus on simpler, more cost-effective treatments for preventing mother-to-child HIV transmission, considerable attention focused on the risks and benefits of breast-feeding. While it's discouraged in the United States due to risk of transmitting HIV, breast-feeding provides nutritional, economical and cultural advantages in developing nations.

The nutritional and immune benefits breast-feeding provides infants are well-known and persist in the presence of HIV infection. Breast-feeding is also an inexpensive source of infant food and is socially and culturally expected in many settings. Given these issues, new approaches that prevent transmission *during* breast-feeding are needed.

Proposals for HIV prevention during breast-feeding were discussed at length, including the need to:

- better understand the timing of HIV infection through breast-feeding and related risk factors;
- bolster the nutritional health of the mother;
- optimize use of anti-HIV therapy during breast-feeding;
- treat breast lesions and other maternal illnesses; and
- monitor and treat oral lesions in the infant.

Advances in these areas would help HIV-positive women make more informed decisions around breast-feeding infants, particularly where alternatives to breast-feeding are sparse. ▪