PROJECT inform

# PERSPECTIVE

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

35

## Times, They are a-Changing

The outcome of the US elections in the fall of 2002 serve as symbol of the high degree of change currently affecting the fate of people with HIV. The political and economic environment raises serious concerns about the future of treatment access, support for medical care and the overall priority given the fight against HIV within the federal government. HIV programs, with the exception of research at the National Institutes of Health, have not seen increases in the President's budget since the current administration took office, despite obvious increases in demand. The recent election gives little reason to think that will change. Not only are different attitudes affecting every aspect of HIV funding, but different people, with different agendas, have significant influence over federal HIV policy.

The core body of experts that served as advisors in the previous administration has largely been sent home. They have been replaced in many cases by people who support ideas that have not shown to be effective in fighting HIV, such as abstinence-based prevention programs. On another front, the number of people available to address HIV at various places in the federal bureaucracy is dropping as career incentives are being offered to people to switch to positions in fighting potential bio-terrorism. All of this occurs against a striking picture of the effects of AIDS internationally, described in the article *The Challenge of Barcelona* on page 22of this issue. Truly, the times are changing in the war against HIV, and it seems unlikely that the change will be for the better.

### Positive Change in the Treatment of HIV

Fortunately, not all is bleak. This year and next will almost certainly be seen as periods of positive change in the treatment of HIV. Before the end of 2003, at least three more new drugs will likely be approved by the FDA, while at least another will become available on expanded access. These new drugs were the subject of much attention at the International AIDS Conference at Barcelona and in subsequent scientific meetings. A number of these new options are described in detail in the article entitled *New Hope from New Classes of Therapy*, page 8 of this issue. Still others that are rapidly moving through the approval process are described in detail in *Three Drugs on the Near Horizon* on page 4. The first fusion inhibitor, now called enfuvirtide (Fuzeon, previously known as T-20), offers a genuine advance for people who have failed other forms of treatment. The drug will likely be approved by the FDA no later than mid-March of 2003. It remains unclear, however, whether approval will mean universal availability, as drug supply problems may not be fully resolved by the same date. Moreover, the price of the drug is expected to be so high as to make it difficult or impossible for many state AIDS Drug Assistance Programs (ADAP) to offer it.

Another advance comes in the form of the first protease inhibitor that doesn't seem to affect cholesterol levels to a significant degree. Atazanavir has been shown to be a reasonably powerful protease inhibitor that works without increasing cholesterol levels in people just starting therapy. It also allows people who are experiencing cholesterol increases from another protease inhibitor to normalize their cholesterol levels by switching to atazanavir. Another feature is that it is the first protease inhibitor designed for

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## In This Issue





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once daily dosing. One other new drug, FTC (Coviracil), will be evaluated for approval by the FDA in 2003, but it is less clear just what it brings to the toolbox of treatments for HIV. The drug is widely considered to be a clone of 3TC, though the manufacturer, Triangle Pharmaceuticals, insists otherwise. The burden will be on Triangle to prove to the FDA, patients, and doctors that the drug offers something new or different.

### New Ways to Use the Current Drugs

Perhaps as important as new drugs is new information about the drugs we already have. On this front, the news is both good and bad. The recently approved drug tenofovir (Viread) has now been shown to be a highly effective therapy for first time users, in addition to its previous use as a drug for people who have failed other regimens. So far, its initial record of high potency and low side effects is unchallenged, though truly long-term effects have yet to be defined. The expanding story of tenofovir is described in the article *New Uses for Tenofovir, New Problems for d4T* on page 15. A more disturbing picture has arisen, however, of the older, widely used combination of d4T (Zerit) plus ddI (Videx). As a result of recent studies, this combination has moved from being considered a preferred option for initial therapy to a combination that is now actively discouraged because of potency issues and side effects. See the article *New Questions about an Old Combination*, page 13. Above and beyond this, there are growing concerns about the use of d4T (Zerit) in general and its role in producing certain side effects.

*A consequence of these findings is that many of the "3-drug combinations" commonly used really don't provide three active drugs all the time.*

Also on the front of new ways to use old drugs is a newly developed theory of drug activity that, if correct, has profound implications for how drugs should be combined. In the simplest terms, the new research studied how the activity of various drugs is affected by the status or activity state of the cells that are targeted by the drugs. The data show that several widely used drugs only work on cells when they are in an "active" (replicating) state, and that the anti-HIV activity is greatly diminished when the cells are in their resting state. In contrast, other drugs work without regard for the state of the cells. A consequence of these findings is that many of the "3-drug combinations" commonly used really don't provide three active drugs all the time. Instead, depending on the state of the cells, only one or two (or perhaps none) of the drugs are working at certain times. The implications of this are striking and may help explain why resistance develops so easily in some cases, or why some people fail treatment despite high levels of adherence to their regimens. To overcome this problem, the data suggests that combinations must be chosen in ways that make sure a person is always on three active drugs, regardless of the state of the cells. This will rule out the use of some combinations altogether. For more information, and a listing of how the various drugs fare in this regard, see the article entitled *Cell Cycles, HIV Drugs and Tretment* on page 18.

### In Memory Of . . .

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

**Linda Grinberg**
**Keenan O'Brien**
**Sal Rinauro**

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

### New Developments

This year's conference in Barcelona brought helpful new attention to the subject of complimentary therapies. No matter what one's personal beliefs may be about complimentary therapies, science needs to study such treatments simply because people use them. We need to know what they do and don't add to treatment and how they may interact with other prescription medications. This area of research needs to answer literally hundreds of questions. A few were answered at the conference this summer. See the article *Complementary Corner* on page 10.

A step further behind are drugs in the

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new classes known as receptor blockers (a subset of entry inhibitors) and integrase inhibitors. These are in the earlier stages of human trials so it is difficult to predict their fate. Still, the mere presence of actively studied drug candidates working against two more targets on HIV is encouraging.

Finally, as people live longer and longer lives with HIV as a result of improved treatment, a number of additional issues are being raised. In particular, as people age with the combined effects of HIV, co-infection (like hepatitis) and various drug side effects, organ transplantation sometimes become necessary. Just like the general public, and perhaps to an even greater degree, some percentage of people with HIV will require various organ transplants over time, including heart, kidney, lung and liver transplants. Previously, this issue was ignored because few people were living long enough to experience the need. Now that this has changed, many obstacles have stood in the way of performing organ transplants for people with HIV. As a result of the hard work of a small team of concerned physicians and activists, however, the first report of a relatively large scale organ transplant program in HIV is now available. The bottom line is simple: organ transplants are just as feasible, and just as effective, in HIV-positive people as in the general population. See *Progress Report: Organ Transplantation in HIV* on page 20.

### Looking to the Future

Given the changed political outlook, it's hard to predict what the next two to six years have in store. On the scientific level, major change is unlikely as the processes leading to further advances are already underway. It would take a dramatic drop in federal funding for research to derail the current momentum. There is some concern, however, that a continued decline in the economy could further damage industry's commitment to HIV. The HIV drug pipeline has a limited number of serious candidates for the years after 2004. Though many potential new drugs show up on the promotional publications of the pharmaceutical industry, we know from past experience that many of these candidates are likely to go nowhere. For the most part, what counts are the products that have serious financial backing from major companies.

How do we weather the purely political winds of the future? Perhaps by accepting that there is ultimately not much we can do about some of them and, where community involvement can make a difference, by making our voices heard. We are all going to have to struggle for at least the next two years, while finding new ways to support care, services and treatment for those in greatest need. We have done this successfully before, through much of the 1980s and even in the early 90s during the "first" Gulf War. Perhaps the toughest question is whether this period of reduced resources and concern will be able to continue to support the large infrastructure of organizations working in the field of HIV. ■

*No matter what one's personal beliefs may be about complimentary therapies, science needs to study such treatments simply because people use them.*

# Anti-HIV Drug Updates – Three Drugs on the Near Horizon

The most significant new information about anti-HIV drugs offered in Barcelona concerned those drugs that are either already available or which will soon be available. This includes new information about T-20 (now called enfuvirtide or Fuzeon) and atazanavir—two drugs which will likely be approved within the next six months. Another new drug likely to be approved soon is FTC (Coviracil), a close relative of 3TC (lamivudine, Epivir), though its importance is less certain than that of enfuvirtide and atazanavir. Important new information was also released about tenofovir (Viread), a drug approved by the FDA late in 2001 (see article on page 15). Equally important were new observations about some older drugs, particularly the combination of ddI and d4T (see article on page 13). Many comparative studies of different drug combinations were also reported, offering new information about the relative value of a number of treatment strategies.

***T-20 (enfuvirtide / Fuzeon)***

Since enfuvirtide represents the first of an entirely new class of drugs, it is of great interest to people who have developed resistance to all or most other classes of drugs. It will, of course, work best when combined with two or more drugs that are still active, but it has shown that it can help even when people are already resistant to most other anti-HIV therapies. Enfuvirtide's main limitation is that it cannot be made into a pill and therefore must be taken by injection twice daily. Using the drug properly is complex, as it comes in a powder that must be mixed with sterile water and then injected. The principle side effect of the drug is injection site reactions, which are seen in virtually all people taking it (though not to a degree that prevents them from using the drug). As the drug becomes more widely available, the manufacturer is providing training sessions for doctors throughout the country. The current expanded access program for the drug requires that doctors be trained before the drug is shipped. It is likely that some form of training will be required when the drug is approved by the Food and Drug Administration (FDA).

In the main studies submitted to the FDA, enfuvirtide was used in people who had previously developed resistance to all three classes of drugs and were in need of "salvage" treatment. At Barcelona, researchers reported on two such studies, called Toro 1 and Toro 2. All volunteers were given an "optimized" regimen composed of five to eight anti-HIV drugs and half were also given enfuvirtide. The "optimized regimen" was chosen individually for each person based on expert evaluation of resistance tests and prior anti-HIV drug history. Patient advocates applauded the study design because it closely approximated the real-world choices that people with advanced disease must face.

The main side effect reported in both studies was injection site reactions, which to some degree affected nearly 98% of the study volunteers. Not all such reactions, however, were serious. These reactions, while very unpleasant, caused only a small number people to drop out of the study. The study underlined the importance of careful training for both doctors and users in order to minimize such reactions and to maximize benefits.

While the results of Toro 1 and Toro 2 differ slightly, the basic picture is the same. In both, volunteers who received enfuvirtide on top of an optimized regimen fared much better than those receiving only the optimized regimen. In many if not most people, the drug was very likely the only fully active anti-HIV therapy in the mix. Still, the results are impressive, considering the challenge such "salvage" situations present. It is fair to say that enfuvirtide represents an important advance in the treatment of advanced HIV

**Toro 1: Results @ 24 weeks**

| | % <400 copies HIV RNA | % <50 copies HIV RNA | HIV RNA change | CD4+ cell count change |
|---|---|---|---|---|
| O.R. Alone | 16 | 7 | -0.76 logs | +32 |
| O.R. + T-20 | 37 | 20 | -1.7 logs | +76 |

490 people (**O.R.** = Optimized Regimen)
Volunteers had previously used an average of 12 different drugs.

**Toro 2: Results @ 24 weeks**

| | % <400 copies HIV RNA | % <50 copies HIV RNA | HIV RNA change | CD4+ cell count change |
|---|---|---|---|---|
| O.R. Alone | 14 | 5 | -0.65 logs | +38 |
| O.R. + T-20 | 28 | 12 | -1.43 logs | +65 |

504 people (**O.R.** = Optimized Regimen)
Volunteers had previously used an average of 11 different drugs.
Study will continue for 48 weeks.

disease.

A major concern about enfuvirtide is likely to be cost. No drug of its type has ever been made in such large quantities before nor have even the raw materials from which it is made. Although no price has yet been announced, there is widespread fear that its cost will exceed that of any other anti-HIV drug. This could have widespread consequences for the already troubled programs that provide drugs for people with HIV. The expected high price will almost certainly limit the use of the drug only to people who have failed everything else..

*Unless other unforeseen side effects appear later in the study of atazanavir, the drug appears to represent an important advance in field of protease inhibitors.*

A small expanded access program for enfuvirtide is currently underway for people who have failed previous therapies. The program will provide drug for only about 600 people in the US. To sign up, doctors must fill out an application form over the internet and if accepted they will be required to take part in training as noted above. Although all currently available slots in the program were quickly taken, more may open up if drug supply increases. Also, not every person who gets accepted into the program actually goes on to use the drug. Therefore, some slots may become available between October 2002 and the expected approval date in mid-March of 2003. Applications for access are still being taken at *www.T20EAP.com*.

The small size of the program is also something of a warning that the company might be unable to meet the initial demand for the drug when it is approved. If so, there will likely be a staged rollout of the drug, focusing first on people with the most advanced disease.

## Drug Identification Chart

| INITIALS | GENERIC NAME | TRADE NAME | MANUFACTURER |
|---|---|---|---|
| **Protease Inhibitors** | | | |
| APV | amprenavir | Agenerase® | GlaxoSmithKline |
| IDV | indinavir | Crixivan® | Merck & Co. |
| --- | lopinavir + ritonavir | Kaletra® | Abbott Labs |
| 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 |
| **NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors)** | | | |
| DLV | delavirdine | Rescriptor® | Agouron |
| EFV | efavirenz | Sustiva® | Dupont Pharma |
| NVP | nevirapine | Viramune® | Boehringer Ingelheim |
| **NARTIs (Nucleoside Analog Reverse Transcriptase Inhibitors)** | | | |
| ABV | abacavir | Ziagen® | GlaxoSmithKline |
| AZT | zidovudine | Retrovir® | GlaxoSmithKline |
| AZT+3TC | --- | Combivir® | GlaxoSmithKline |
| AZT+3TC+ABV | --- | Trizivir® | GlaxoSmithKline |
| ddC | zalcitabine | Hivid® | Hoffman-La Roche |
| ddI | didanosine | Videx® | Bristol-Myers Squibb |
| d4T | stavudine | Zerit® | Bristol-Myers Squibb |
| 3TC | lamivudine | Epivir® | GlaxoSmithKline |
| **NtRTIs (Nucleotide Analog Reverse Transcriptase Inhibitors)** | | | |
| TNV | tenofovir | Viread® | Gilead Sciences |
| **Cellular Factor Inhibitors** | | | |
| HU | hydroxyurea | Hydrea® | Bristol-Myers Squibb |

### Atazanavir – A Protease Inhibitor with a Difference

Atazanavir is the newest member of the protease inhibitor class. It is expected to get FDA approval early in 2003 and is currently available in a large expanded access program. There are two main differences between atazanavir and other protease inhibitors. First, it is designed for once-daily dosing, making it easier to create a once-daily regimen that uses a protease inhibitor. Perhaps more importantly, it is the first protease inhibitor that does not appear to have a potentially harmful effect on cholesterol levels. In studies comparing atazanavir to nelfinavir (Viracept) in an otherwise common combination with d4T (stavudine, Zerit) and 3TC (lamivudine, Epivir), the group receiving atazanavir experienced no significant increase in cholesterol or triglyceride levels over 48 weeks of follow-up. Also, it appeared to at least equal the effectiveness of nelfinavir in suppressing HIV. While nelfinavir is generally considered to be among the less active PIs, it has commonly been used in comparison studies.

Another important study asked whether switching to atazanavir from another protease inhibitor would reverse the cholesterol changes caused by the other protease inhibitors. The study followed 346 people (217 men, 129 women) who had been in the earlier atazanavir vs. nelfinavir comparative study. Of the people who had previously used nelfinavir, 63 were changed to receive 400mg of atazanavir (the lower of the two doses of atazanavir used in the prior study). People who had previously been assigned to receive either 400mg of atazanavir were allowed to switch to 600mg (still once daily). All volunteers continued to receive d4T and 3TC.

Twelve weeks after the 63 people were switched from nelfinavir to atazanavir, their cholesterol levels were measured again and compared to previous levels. Changing to atazanavir obviously had the desired effect of reducing cholesterol and triglyceride levels as shown in the table above. This indicates that, at least for the first 12 weeks, switching to atazanavir has a positive effect

**Atazanavir Cholesterol Levels**

| Lab measure | Comparison to pre-switch values |
|---|---|
| Total cholesterol levels | reduced 16% |
| LDL (bad) cholesterol levels | reduced 21% |
| Triglyceride levels | reduced 28% |
| HDL (good) cholesterol levels | increased 5% |
| % with "undesirable" total cholesterol levels | reduced from 32% to 10% |
| % with "undesirable" LDL cholesterol levels | reduced from 55% to 22% |

on cholesterol. Volunteers who either stayed on 400mg atazanavir or switched to 600mg experience no significant change in these measurements.

Changes in cholesterol levels are believed to be associated with physical changes in the body, such as fat accumulation or loss of fat in the face, arms and legs. Such changes are often called *lipodystrophy*. Although some people in the original group receiving nelfinavir reported having physical symptoms of lipodystrophy, no obvious or easily measurable changes in these symptoms were noted in the people who switched to atazanavir. This indicates that 12 weeks is too short a time to see improvements, that no improvement happens or that improvements were delayed or blocked by the continued use of d4T in all study volunteers (see article on d4T on page 15).

Unless other unforeseen side effects appear later in the study of atazanavir, the drug appears to represent an important advance in field of protease inhibitors. Only time will tell if long-term switching to atazanavir will help correct some of the fat redistribution problems experienced by people on protease inhibitors and nucleoside analogue drugs.

The expanded access program for atazanavir is quite liberal, requiring only evidence of failure on existing protease inhibitors or the presence of fat distribution problems. To apply for the program, have your doctor call 1-877-726-7327.

**Emtricitabine (Coviracil, FTC)**

Emtricitabine is a new drug considered to be similar to 3TC. The drug's development has been painfully slow but has finally reached completion. The company making FTC, Triangle Pharmaceuticals, has submitted data to the FDA seeking accelerated approval for the drug.

While there is not much excitement about FTC because it so closely resembles 3TC, regulators and advocates alike must give the drug a fair hearing. Its one clear distinction from 3TC is that it is intended to be used once a day, which is an attractive feature for many people. If FTC is otherwise just a "me too" copy of 3TC, it is unclear whether it warrants either accelerated approval or expanded access. Triangle asserts that there are other important differences between FTC and 3TC, differences that they believe warrant more interest than the drug has been given.

In the earliest studies, people receiving FTC as single agent therapy (*monotherapy*) for 2 weeks achieved an average 2 log reduction in viral load. Although this finding comes from a small and uncontrolled study, it is still impressive, one that rivals any protease inhibitor and appears somewhat superior to 3TC. In laboratory studies, the drug appears to be 4 to 10 times more potent, by weight, than 3TC and more importantly, seems to be slower to develop resistance than 3TC. Rapid development of resistance is 3TC's Achilles heel.

One FTC study presented at the Barcelona conference followed the experiences of 468 people receiving treatment for the first time. They received either FTC or 3TC, along with d4T and either nevirapine (Viramune) or efavirenz (Sustiva). The main study endpoint was virologic failure, defined as either failing to achieve a viral load below 400 copies, or a return of viral load above 400 copies. Both groups had similar levels of virologic failure. The main benefit seen for FTC was that fewer of the people with virologic failure while on the drug had developed resistance to FTC, compared to those on 3TC who became resistant to that drug. This suggests that more of the failures could be attributed to the other drugs in the mix and that FTC was less likely to develop resistance. It is not clear whether this difference was statistically significant, nor is it clear whether it matters much since the overall failure rate on the two treatment regimens was the same.

In two well-controlled studies comparing FTC to 3TC, study authors concluded that the drug is equivalent to 3TC in terms of anti-HIV effectiveness.

In late September of 2002, the manufacturer announced interim results from a new study comparing a once-daily combination of FTC, efavirenz (Sustiva), and ddI-EC (Videx EC) against once-daily efavirenz and ddI-EC plus twice-daily d4T (Zerit). The study, which includes 571 people (85% male), is scheduled to run for 52 weeks, but the initial analysis looked at a mix of 24- and 52-week data accumulated to date. Results are on page 6.

The manufacturer claimed the study showed that FTC "outperformed a highly

**Emtricitabine Results**

| | % <50 copies HIV RNA (24 week data) | Probability of Viral Breakthrough (52 week data) | Mean CD4+ Increase | % with Treatment Limiting Toxicity |
|---|---|---|---|---|
| Once-daily FTC + ddI-EC + EFV | 81 | 4.7 | 152 cells | 6.7% |
| Twice-daily d4T + once-daily ddI-EC + EFV | 70 | 14.1 | 117 cells | 13.9% |

EFV = efavirenz ddI-EC = ddI enteric-coated

effective standard of care," referring to the group receiving the combination of efavirenz plus ddI and d4T. While the data supports the view that FTC was part of the superior combination, the company statement was meaningless, given new information about problems with the combined use of ddI/d4T. Consequently, the ddI plus d4T combination is not considered "highly effective" and certainly not the "standard of care." While the problems with the ddI/d4T combination may not have been clearly known at the time their study was designed, the information was available to them before they described the results of their new study. It should at least have caused them to be more cautious in promoting these new data. For more information about the problems associated with the ddI/d4T combination, see the article *New Questions about an Old Combination* on page 13.

The big picture seems to be that FTC is better proven in once-daily use and that it may be slower to develop resistance than 3TC, even though the failure rates of combinations using the drug are the same as when using 3TC. Larger or longer studies will be needed to determine whether FTC offers any practical advantage over 3TC. Whether all of this, taken together, warrants a special place for FTC, or expanded early access, is a decision that will have to be made by the FDA.

As PIP 35 goes to press, Gilead Sciences, maker of tenofovir, announced that it had purchased Triangle Pharmaceuticals, maker of FTC; Gilead also announced that it planned to create a new formulation of tenofovir that included FTC and tenofovir in a single pill. ■

## Bottom Line

**Enfuvirtide (T-20, Fuzeon)**

- Enfuvirtide is an injectable anti-HIV drug, which is likely to be approved by the FDA in March of 2003 for people with multi-drug resistance to other anti-HIV therapies.
- It appears safe, with the primary side effect of injection site reactions.
- Enfuvirtide appears to be active and useful for people who have failed other therapies and represents a hopeful new option for people.
- Being an injectable therapy, it may be difficult to use and requires training for doctors and patients alike to administer the drug to maximize benefits and minimize side effects.

**Atazanavir**

- This new protease inhibitor, designed for once-daily dosing is likely to be approved by the FDA approved in mid-2003. Thus far, it appears to be at least equal in potency to nelfinavir when used in similar combinations.
- It appears to have much less impact on cholesterol and triglyceride levels than other protease inhibitors, probably resulting in reduced risks of the fat redistribution, cholesterol-related problems (including liver problems) that have been seen with the other drugs of this class.
- It is currently available through an expanded access program to anyone who has failed on other protease inhibitors or is having cholesterol related side effects.

**Emtricitabine (FTC, Coviracil)**

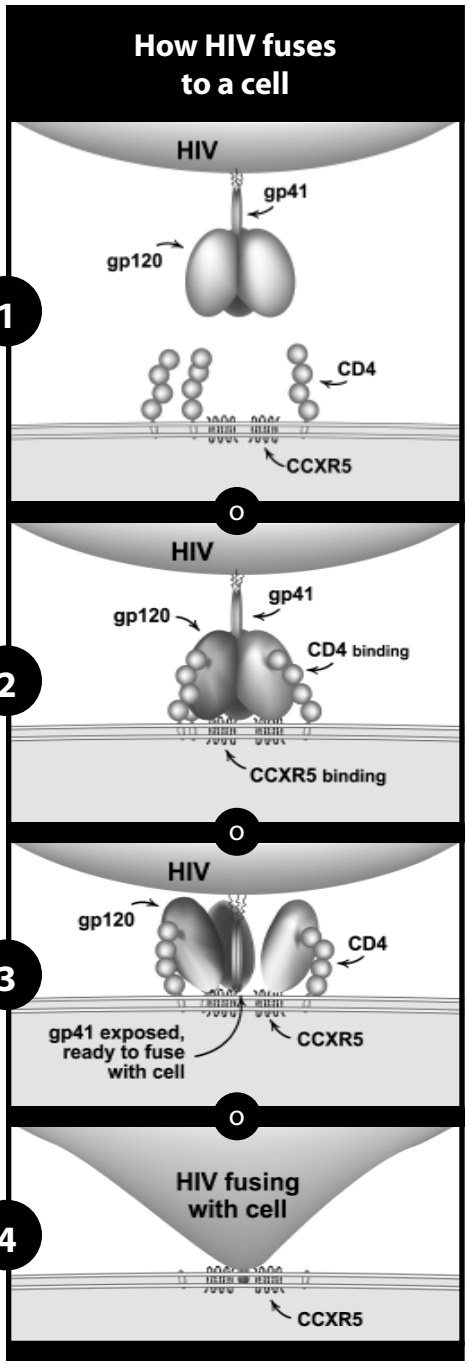
- This NARTI appears similar to 3TC (lamivudine, Epivir), but requires only once-daily dosing and resistance may be less likely to develop to FTC.
- More studies are needed to identify the true value and role of FTC.

## The Basic Message

- Learn about HIV testing options and choose one that fits your needs! Be sure your privacy is protected!
- If you're positive, don't panic. If you make your health a priority, chances are you will be reasonably healthy for many years.
- Learn about your healthcare options and local support services.
- Get a complete physical and blood tests for CD4+ cell count and HIV level. Repeat quarterly and watch for trends. Women should get GYN exams and Pap tests every six months, more often if abnormal.
- Work with a doctor to develop a long-term strategy for managing HIV disease.
- If the CD4+ cell count is below 350 or falling rapidly, consider starting anti-HIV therapy. Test at least twice before taking action.
- If anti-HIV therapy fails to reduce your HIV level below the "limit of detection" or below 5,000 copies within 3–6 months, consider a different or more aggressive therapy.
- If the CD4+ count trend stays below 300, consider treatment for preventing PCP. If it stays below 200, start treatment for preventing PCP (if you haven't already done so) and reconsider anti-HIV therapy if not on one. Learn about drug interactions and preventive treatments for opportunistic infections.
- If you started preventive therapies and your CD4+ cell count rises in response to anti-HIV therapy, ask your doctor whether it might be safe to stop certain preventive therapies.
- If your CD4+ cell count stays below 75, consider more frequent blood work—perhaps monthly. Consider therapies for preventing MAC/MAI and CMV.
- Regularly seek support for your personal, spiritual and emotional needs. It takes more than medicines to keep you well.

# New Hope from New Classes of Therapy

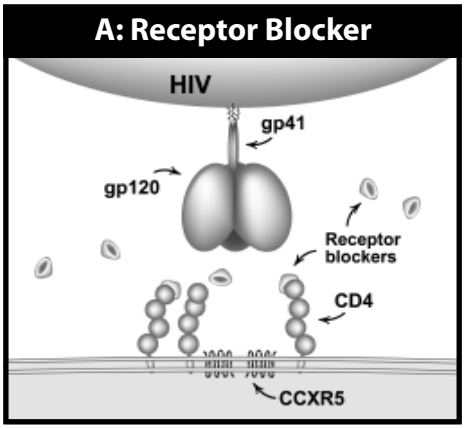
A number of very interesting new drugs were discussed in sessions at Barcelona. Two represent new classes of therapy—*entry inhibitors* and *integrase inhibitors*—while others seek to offer improvements over drugs in existing classes. Both are welcome advances.




**Entry Inhibitors**

One new class of drug is a subset of the class called entry inhibitors. The drug enfuvirtide (T-20) is one subset of entry inhibitors known as fusion inhibitors. A *fusion inhibitor* blocks the activity of HIV where the virus sends out a projectile, said to resemble an extremely small harpoon that anchors the virus to a CD4+ T-cell. The virus pulls itself in via this anchor until it makes direct contact with the cell. Once full contact is made, the virus inserts its genetic material into the cell.

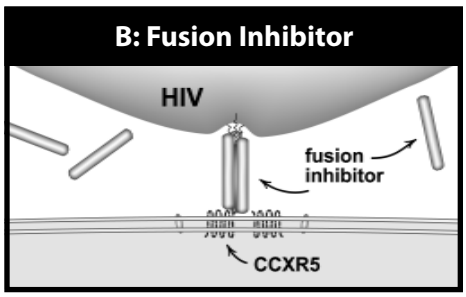
Another subset of entry inhibitors, known as a *receptor blocker (A)*, is conceptually similar to but distinct from, fusion inhibitors. Receptor blockers work one step before *fusion inhibitors (B)*. Before a virus can "shoot its harpoon" and fuse with the cell, it must first find and "dock" with the appropriate cell. This step brings the virus close enough for the "harpoon" of the fusion step to be fired. It does this by producing proteins that interlock with other proteins (called receptors) on the cell's surface. The virus will ignore cells that lack the necessary receptors.




For many years, researchers knew that HIV used a receptor called CD4 to find and link up with the cells it infected, though lab data long suggested that the CD4 receptor alone did not explain all aspects of the virus/cell interaction. In mid-1996, Robert Gallo and co-workers published a key finding that showed how HIV could be suppressed by a number of naturally occurring immune chemicals known as chemokines. Within months, other researchers, most notably Edward Berger and co-workers at the National Institutes of Health, demonstrated that these chemicals affected the virus' activity because there were receptors for them on the cells that became infected by HIV. The presence of the chemicals blocked HIV's ability to interact with those receptors and infect the cell. The first identified of these "co-receptors" is called CCXR5. A second co-receptor, CXCR4 (also called *fusin*), was soon identified and associated with a form of HIV that is considered to be more destructive of T-cells and is usually seen only in advanced or rapidly progressive disease. Other co-receptors have since been identified, including CCR7, though their importance is less understood. Most of the connection activity between HIV and infected cells, however, was explained by the CD4, CCXR5 and CXCR4 receptor interactions. (For more information about HIV Co-Receptors, call the Project Inform hotline.) It stood to reason that blocking the most common receptors would help slow the activity of HIV and a race was on to find drugs that would block them. That search has now begun to bear fruit.

These drugs all work by preventing entry of the virus into the cell, but they do it by different mechanisms.

The entry inhibitor/receptor blocker



farthest along in studies is SCH-C, or Schering C from Schering Plough. SCH-C works by blocking the CCXR5 receptor. The drug is currently in a phase 1 dose-ranging study that is using it as single agent therapy (*monotherapy*) for 10 days. The study is underway in France and the US. Although the study is uncontrolled (i.e. no one received a placebo or other drug for comparison) and results to date are from a small number of volunteers, it is clear that the drug has a significant anti-HIV effect, even at very small doses.

*One concern raised about CCR5 entry inhibitors is whether suppressing or blocking the CCR5 receptor might cause HIV to change to the form that uses the other receptor called CXCR4.*

Testing SCH-C has been a long, slow process, largely because of a potential side effect that might affect a particular heart rhythm called the QT time. QT times were altered in some HIV-negative volunteers who used the highest dose of the drug (600mg) in the first round of studies. This effect was also observed earlier in animal studies. Because of this, the Food and Drug Administration (FDA) has required that all volunteers in these early studies have their heart rhythms continually monitored while on the drug. This requires that volunteers be hospitalized and connected to monitoring devices throughout the 10-day duration of the study. It is a fairly demanding study and has been hard to find volunteers. Those who volunteer under these circumstances are making an important contribution to the development of future drugs for HIV.

To date, the studies have shown only small changes in QT times (the side effect the FDA is concerned with) that do not seem related to the dose of the drug. Researchers, however, point out that the variations seen in QT time are small and not of the size that would be considered harmful. They also note that it is has been difficult to know whether these small changes mean anything at all, since there is no standard to compare them to. No one has measured QT times continuously for ten days to determine how much variation is normal, either in HIV-positive or negative people. It may be that small variations over time are the norm. The people who showed the most significant "events" (three or more irregular heartbeats in a row) were unaware that anything had happened, and there were no other consequences. Moreover, it is known that QT times are different in men and women, further complicating analysis. Finally, it is unclear whether the effects seen in a short 10-day study are predictive of what will be seen in people who take the drug continually. For now, it is reasonable to say that no significant problems have yet been seen. The most recent round of the studies now includes a "placebo" group (people who are continuously monitored while in a hospital setting but who did not receive the drug). This may help determine what is "normal."

Schering has a second CCXR5 inhibitor in development, currently known as SCH-D. In lab studies SCH-D appears to be more potent than SCH-C and has so far not been shown to affect QT times. Studies in HIV-positive people, however, are just beginning so it impossible to predict whether SCH-C or SCH-D will prove more beneficial overall.

Pfizer Labs also has a promising CCXR5 inhibitor in the earliest stages of human testing but no data are yet available on this compound. A number of other companies are said to be working on entry inhibitors, but no others have yet begun human studies.

Bristol Myers has an entry inhibitor that blocks the other common receptor, CD4. Human studies of this compound have already begun, but the company has as yet provided no information, even about the design of the study. Combining a CCXR5 inhibitor with a CD4 inhibitor would seem to offer great hope. Best-case scenario for the Schering C drug might lead to wide availability, if warranted, approximately two years from now.

One concern raised about CCXR5 entry inhibitors is whether suppressing or blocking the CCXR5 receptor might cause HIV to change to the form that uses the other receptor called CXCR4. Versions of HIV which use CXCR4, at least when they occur naturally, tend to be more aggressive and harmful than those that use CCXR5—though this is somewhat controversial. If this switch occurs, some feel it might negate the value of CCXR5 entry inhibitors and produce a worse outcome. At least one published laboratory study, however, seems to show that this does not happen. Other scientists believe that blocking the CCXR5 receptor will have no bearing on whether the virus does or doesn't try to use the CXCR4 receptor. Time and more studies will answer this question.

**Integrase Inhibitors**

Another new, but long anticipated class of new drug that is finally entering human studies is the integrase inhibitors. The step in the virus' reproduction cycle called *integrase* or integration occurs inside HIV infected cells just prior to the stage where protease inhibitors work. In this stage, the cell is "integrating" or bringing together the pieces of new genetic material (called *DNA*) made by the infected cell as it makes a copy of the virus. Many companies gave up their work on integrase inhibitors over the last several years, concluding that the goal was too difficult to make an integrase inhibitor that did not have harmful side effects. Two such drugs, however, are now in human studies. One, from Merck, is very new and is entering human use for the first time in the fall of 2002. The company has a reputation for being very demanding of new compounds before they put them human

*Many companies gave up their work on integrase inhibitors over the last several years, concluding that the goal was too difficult to make an integrase inhibitor that did not have harmful side effects. Two such drugs, however, are now in human studies.*

testing, so hopes are high that the Merck compound might succeed. A second integrase inhibitor, currently being developed by GlaxoSmithKline, was originally created by the small Japanese company, Shinogi. This drug is now in phase 2 human studies. Some uncertainties exist about this drug. Although lab data have been reported on it for a number of years and this is the second year in which human testing was announced, the data released by the company only claims that the compound seems safe and that the formulation is adequately distributed in the body. It is odd though that there is no information about its anti-HIV effects. Anti-HIV data from phase 1 and phase 2 studies are never considered conclusive, but it often serves as "proof of concept" or proof that the compound is active against HIV in the body. No such information has been released about this drug, leading some to wonder whether it is working at all. It may be that the company is simply being very conservative. Only time will tell. ■



# Complementary Corner

Interest in nutritional health products stems from a number of observations. These include documented nutritional/vitamin deficiencies even in early stages of HIV infection and malnutrition associated with increased risk of HIV disease progression. There is great controversy, however, over whether or not using supplements is always a good idea and if it provides benefits in the long run. There has also been long-standing interest in complementary and alternative medicine (CAM) approaches to managing HIV infection and various conditions associated with HIV. The CAMs most commonly used by people living with HIV are not drugs, herbs or other pharmacologic agents, but rather things like meditation, massage, energy healing, acupuncture and the like. The following article contains summary highlights of studies of nutritional health products and CAM approaches in the setting of HIV presented at the World AIDS Conference in Barcelona.

### Selenium and HIV

Several studies have suggested that deficiencies in selenium are associated with HIV disease progression. A small study of 24 children and a larger study of 125 adults living with HIV concluded that those with selenium deficiencies were at a greater risk for HIV disease progression and death. Whether or not selenium supplementation would make a difference, however, is not known, nor did the study clearly determine whether selenium deficiency was a cause or an effect of disease progression.

Observations of selenium toxicity have been noted among people using selenium supplements. This led to warnings noting that unusual diets and vitamin supplements are the most common causes of selenium toxicity in the United States. The US RDA of selenium is generally 55mcgs. the Institute of Medicine has proposed that The maximal daily intake of selenium before causing toxic effects is roughly 400mcgs for adults.

A study conducted at the University of Miami compared the use of selenium supplementation (200µg/day) to placebo in 259 people living with HIV (147 men, 112 women). Information about CD4+ cell count, viral load and other parameters were collected at the initial study visit and then every six months thereafter for two years. While investigators concluded otherwise, it was not clear that selenium supplementation decreased the risk of hospitalization.

In a related study, investigators examined blood levels of selenium in the 112 women receiving anti-HIV therapy and looked for correlations between selenium levels and the risk for pre-cancerous cervical cells (*cervical dysplasia*). While selenium levels were lower in women who developed cervical dysplasia, supplementation made no difference in the risk of developing cervical dysplasia.

In another related presentation, investigators provided information on the impact of selenium supplementation on CD4+ cell count increases. It appears that those receiving supplements were more likely to have slightly higher CD4+ cell count increases, but problems with data reporting leave it unclear what other factors may have impacted these increases. Investigators

note that heroin use appears to decrease general nutritional status and is associated with lower levels of selenium, but no information on the distribution of heroin users in the supplement vs. placebo group were provided.

In short, the most that can be concluded from these reports is that it remains unknown if selenium supplementation offers any beneficial or harmful effects, whatsoever. Risks for cervical dysplasia appear slightly increased when selenium levels are lower, but supplementation does not appear to lessen this risk. Well-designed research is critical to evaluating the potential benefits (and risks) of selenium supplementation.

### Vitamin A (Beta Carotene and Retinoids) and HIV Drug Interactions

Deficiencies in vitamin A (retinol and its precursor, beta-carotene) have been associated with advanced HIV disease. As in many similar situations, it is unclear if the deficiencies are a cause or effect of disease progression. It also remains unclear if supplementing vitamin A with retinoids or beta-carotene is helpful for people with HIV beyond correcting the deficiency. Moreover, questions remain as to whether or not vitamin A supplements cause vitamin-drug interactions. A team in Canada set out to evaluate whether or not a variety of forms of vitamin A supplements interact with the p450 enzyme system. This system is important for the breakdown and use of many anti-HIV drugs. Things that interact with the p450 system are highly likely to have interactions with anti-HIV drugs, particularly protease inhibitors, as well as with drugs to prevent and treat some opportunistic infection.

The Canadian team evaluated six different vitamin A (beta-carotene) supplement products (four tablets and two liquid filled soft gel capsule products). All of the products tested had lower beta-carotene content then what was indicated on the label. One product had ten-fold less beta-carotene then what was advertised.

All of the constituents of vitamin A (retinal, retinol, retinate and beta-carotene) as well as all of the products tested had moderate (45 to 65%) to strong (65 to 100%) inhibitory effect on the p450 enzyme system. Therefore, these products have a very strong likelihood of interacting with anti-HIV drugs. Studies, in people as opposed to the laboratory, to look at the impact of taking vitamin A supplements (like beta-carotene) in combination with anti-HIV medications, are needed to understand the extent and impact these findings.

### Vitamin Supplements and HIV in Women (Implications for Everyone)

A study in Tanzania, Africa of the use of multivitamins among HIV-positive pregnant women showed that multivitamin supplementation led to decreases in death of the unborn child (fetal death), increases in birth weight and decreases in pre-term births. While these findings were encouraging, trends were noted that children born to HIV-positive moms who received multivitamins during pregnancy were more likely to be infected with HIV. Because of this observation, another study was initiated in Kenya to examine the impact of daily multivitamin supplementation (or placebo) among 400 women who weren't pregnant and evaluate their impact on vaginal and cervical shedding of HIV.

Women received either a daily multivitamin or placebo for six weeks. The use of multivitamins was associated with slightly higher CD4+ and CD8+ cell counts and no overall changes in HIV levels in the blood. However, multivitamin use was associated with increases in vaginal shedding of HIV, with about 1/2 log higher levels of HIV in vaginal swabs among those receiving multivitamins.

*Whether the increase in vaginal shedding of HIV associated with multivitamin supplements would be controlled with the concurrent use of anti-HIV therapy remains unknown.*

Researchers speculate that the use of daily multivitamins among women is unlikely to protect women from HIV infection and may increase the likelihood that they will transmit HIV to others.

Another study found that vitamin A deficiencies in the blood were associated with increased vaginal shedding of HIV during pregnancy, increased HIV in breast milk, higher rates of mother-to-child HIV transmission, lower CD4+ cell counts and more rapid HIV disease progression. These observations come from studies in the third world where dietary vitamin A deficiencies are notable and marked, regardless of HIV status. The same team that conducted the study of multivitamins noted above evaluated the use of vitamin A supplementation or placebo in 400 Kenyan women who were not pregnant and examined a variety of viral and immune parameters.

Women received either vitamin A (10,000 IU delivered as retinyl palmitate) or placebo, daily for six weeks. The dose of vitamin A used is the dose recommended by the World Health Organization for correcting symptomatic vitamin A deficiencies in women of childbearing potential. The study found that vitamin A supplementation had no effect (positive or negative), whatsoever, on vaginal shedding of HIV, blood levels of HIV, CD4+ or CD8+ cell counts compared to placebo. These observations held true even among women with notable vitamin A deficiencies at the start of the study (about 59% of the women). These findings suggest that while vitamin A deficiencies may be associated with poorer outcomes in mother-to-child HIV transmission and poorer outcomes of HIV disease in general, supplementation is unlikely to address these problems.

The women in these studies were not receiving anti-HIV therapies and thus the results are perhaps most relevant to settings where anti-HIV therapies are not available and/or to individuals who choose not to use them in conjunction with supplement approaches. Whether the increase in vaginal shedding of HIV associated with multivitamin supplements would be controlled with

the concurrent use of anti-HIV therapy remains unknown.

### Vitamin E, Vitamin A and Anti-HIV Therapies

Previous reports have suggested that vitamin E levels are decreased in people living with HIV and low levels of vitamin E in the blood have been associated with increased risk of HIV disease progression. Researchers in the United Kingdom sought to evaluate vitamin E levels among 33 people before and six weeks after starting anti-HIV therapy and compare them to levels observed in healthy HIV-negative people.

Investigators found that prior to starting anti-HIV therapy, vitamin E levels were lower among people with HIV compared to healthy HIV-negative people. Contrary to previous reports, people with HIV who had AIDS had slightly *higher* vitamin E levels (24µmol/l) compared to people with HIV who did not have AIDS (19µmol/l). After six weeks of anti-HIV therapy, vitamin E levels normalized among people with HIV (28µmol/l) compared to HIV-negative people with vitamin E levels measured six weeks after the start of study (26µmol/l).

Vitamin A levels were also evaluated before and six weeks after starting anti-HIV therapies. No differences were observed in vitamin A levels either before or after starting anti-HIV therapy. Moreover, vitamin A levels were in normal healthy ranges, roughly equivalent to those observed in HIV-negative individuals, both before and after six weeks of anti-HIV therapy use. Further, no differences were observed in vitamin A levels between healthy HIV-positive people and those with AIDS.

This study suggests that for people taking anti-HIV therapy, vitamin E supplementation is likely not necessary. Moreover, vitamin A deficiencies were not noted with HIV infection, regardless of stage of disease. It remains unknown if vitamin E supplementation among people not on anti-HIV therapy will provide benefits.

### Nutrition and Exercise to Manage Lipodystrophy

A group in New York conducted a small study to evaluate the impact of individualized nutrition and exercise advice (delivered by a registered dietitian in accordance with recommendations by the American Heart Association) on lipid levels in people with HIV experiencing lipid elevations associated with the use of anti-HIV therapy. Twenty-five people were enrolled in the study (1 Asian, 10 African Americans, 7 Hispanics and 7 white/non-Hispanic), which included 10 women and 15 men.

Nutritional and exercise advice had little to no impact on lipid levels. Virtually no changes were seen in cholesterol levels (either HDL or LDL cholesterol). There were slight decreases in triglyceride levels, but not to healthy target levels defined by the National Cholesterol Education Program. While only a small study, the investigators propose that nutrition and exercise advice alone are unable to improve lipid abnormalities seen in people on anti-HIV therapy.

There are several limitations to this study that may confound conclusions. One is the relatively small size of the study. Another is that dietary assessments were not conducted (while people were given advice on nutrition and exercise, it's unknown if they actually followed the advice). Despite underwhelming results from this study, improving nutrition and exercise habits and routines will likely benefit a person's general overall health even if it has apparently little effect on lipid profiles.

### Managing Side Effects of Anti-HIV Therapy with Acupuncture

Acupuncture is an ancient Chinese healing art, involving placing small, fine needles at various points through the skin. These points are believed to conduct an energy, called *qi*, between the surface of the body and internal organs. Putting fine needles in various points is believed to direct this energy and promote healing and balance. Acupuncture is sometimes used with Chinese herbal remedies, though not always. A Boston study evaluated acupuncture as a treatment for digestive side effects associated with anti-HIV medications.

The study included 26 people who were taking anti-HIV medication and experiencing digestive side effects of therapy. Half received symptom-specific acupuncture for three weeks and half received non-specific acupuncture for three weeks. At the end of three weeks the groups switched modes of acupuncture therapy.

Preliminary results were presented on the effect of symptom-specific and non-specific acupuncture for nausea, excessive gas and loss of appetite associated with the use of anti-HIV therapy.

These results suggest that symptom-specific acupuncture may be more effective than non-specific acupuncture in managing digestive side effects of anti-HIV therapies. Of note, adherence to anti-HIV therapies improved following symptom-specific treatment (80%) compared to non-specific treatment (68%). Current plans are to expand the pilot study to see if these results hold true in a larger and more diverse group of people. ■

| Side Effect | % reporting symptom after *symptom-specific* acupuncture treatment | % reporting symptom after *non-specific* acupuncture treatment |
|---|---|---|
| Nausea | 25% | 37% |
| Excessive Gas | 50% | 63% |
| Appetite Improvements (only includes those reporting lack of appetite at study entry) | 85% | 58% |

# New Questions About an Old Combination – ddI + d4T

For the last several years, the combination of ddI (didanosine, Videx) and d4T (stavudine, Zerit) as a backbone of three-drug therapy has been popular both in treatment and in research. Together, the two nucleoside analog reverse transcriptase inhibitor (NARTI) drugs offered relatively high strength and fairly simple use. Despite this, some researchers have long questioned the wisdom of the combination as it violates one of the key rules of combining drugs: combine only drugs with different side effect profiles. Both drugs are associated with the development of peripheral neuropathy and pancreatitis. Pancreatitis is more commonly seen with ddI and neuropathy with d4T, but both occur to a significant degree with each drug and to a higher degree than was seen with other drugs of their class. However, few if any studies were run comparing the ddI/d4T combination to alternatives such as AZT/3TC (Combivir) or even 3TC/d4T. Both ddI and d4T come from the same company, Bristol Myers Squibb.

In 2001, a study conducted by the AIDS Clinical Trials Group (ACTG) looked at combinations that included ddI, d4T and hydroxyurea (HU). The study was stopped early because of a high incidence of pancreatitis and neuropathy in the ddI/d4T/HU group. Study investigators blamed the problem on hydroxyurea, but some critics charged that they missed the more obvious point—that the combination of ddI and d4T was responsible. The most troublesome side effects seen were not typical of HU, but rather of ddI and d4T. Still, the same researchers had another large study underway comparing the use of ddI and d4T in a combination to other combinations that included AZT and 3TC.

This year, the ACTG reported the results of the second study. They added to the growing concern about the combined use of d4T and ddI and have led to many scientists now openly opposing the use of the combination. In short, the study showed the ddI/d4T combination not only to be less effective than the main alternative of AZT/3TC, but also to be substantially more toxic. Drug toxicity was much quicker to cause volunteers to quit the ddI/d4T-containing regimen than others who used AZT/3TC-containing regimens.

When questioned, even the drugs' manufacturer no longer encourages combined use of the two drugs. They have not, however, sent warning notices to doctors about the reduced effectiveness and higher toxicity the combination produces, as many feel they should.

Researchers are divided about what all the new data mean about the use of d4T in any combination. Some feel that even though the evidence is not yet irrefutable, the overall weight of the accumulating data fares poorly for continued use of d4T. Others have suggested that it should perhaps only be used in salvage therapy, when a patient has run out of other options for this type of drug. A number of independent studies—some small, some larger—have been conducted in recent years attempting to analyze the contributions of d4T vs. other drugs on newly described side effects such as lactic acidosis, heart disease, diabetes, cholesterol disorders and lipo-atrophy (loss of normal fat deposits in the face and limbs). While none of these studies could be seen as conclusive, nor were they all originally designed to answer such questions, 12 of the 16 studies found that regimens using d4T were more likely than alternatives to produce such side effects. Most of the regimens used d4T in combination with ddI, but significant side effects of this type were even more common in studies using d4T with other NARTI drugs, most commonly 3TC (lamivudine, Epivir). Most recently, a new study comparing tenofovir to d4T showed d4T to be more toxic on all the measures associated with lipo-atrophy, cholesterol elevations, mitochondrial toxicity and lactic acidosis.

Perhaps the greatest concern was raised on March 29, 2002, when the FDA and Bristol Myer Squibb notified healthcare providers caring for persons with HIV of the potential for lactic acidosis as a complication of therapy with d4T in combination with other antivirals. Doctors were warned to watch for rapid onset of neuromuscular weakness (including respiratory failure) which could easily be mistaken for Guillain-Barré syndrome. Some cases were fatal and most were reported in relation to lactic acidosis. Many doctors feel that while this looks like a new side effect of d4T, it has in fact probably been happening all along but was often misdiagnosed.

While other drugs in the NARTI class also can produce mitochondrial toxicity and possibly related effects such as lactic acidosis and lipo-atrophy, d4T seems to be the largest

culprit in such matters. Today, with the advent of better, less toxic drugs like tenofovir and simple co-formulations like AZT/3TC (Combivir) and AZT/3TC/abacavir (Trizivir) in a single pill, they feel that there is no compelling need for d4T. Given that there are alternatives that cause lesser problems in all these areas, it may be difficult to justify using d4T as part of an initial therapy regimen. Still, others may argue that d4T has been used successfully for many years and that only a minority of people report serious levels of the side effects now known to be associated with the drug. They point to a new formulation of d4T soon be available which will allow the drug to be used only once a day and see this as important advantage.

Despite these growing concerns, there is little reason to expect the manufacturer to stop selling d4T (though there is good reason to expect them to stop promoting the combination of ddI plus d4T). But on an individual basis, these new findings are important and must be factored into the choice of a regimen. People who are experiencing the side effects discussed above might be the first to reconsider their regimen if d4T plays a role in it and other NARTI options are available.

*While other drugs in the NARTI class also can produce mitochondrial toxicity and possibly related effects such as lactic acidosis and lipo-atrophy, d4T seems to be the largest culprit in such matters.*

With 17 drugs now available for the treatment of HIV (and soon to be 20), people have the option, if not the responsibility, to be more demanding of the drugs they take. When fewer drugs were available, putting up with side effects was an unfortunate necessity, especially when we didn't even understand which drugs caused which effects. It is no longer a necessity. Although we are not yet at the point where people can easily choose a regimen that is free of side effects for all users, there is increasingly enough information to make thoughtful choices and decide just what side effects they are willing to risk. ■

## Prostate Cancer Screening in African American Men

A group in New York evaluated Prostate Serum Antigen (PSA) levels among HIV-positive and HIV-negative African American men forty years of age and older. PSA is a laboratory marker that helps doctors to diagnose prostate cancer. Because PSA levels can be affected by other conditions, including urinary tract infections, inflammation of the prostate, etc., men with these conditions were excluded from the study. In all age ranges examined (40-49, 50-59, 60-69), HIV-negative African American men had consistently higher PSA levels than HIV-positive African American men. Researchers speculate that this might be caused by decreased immunity, the use of anti-HIV medications, low testosterone levels (which is associated with advancing HIV disease) and possibly variations in the PSA test itself. The following chart displays the differences observed in the study:

This study is important as it is estimated that about 14% of HIV-positive African American men are over the age of forty and should be undergoing age-appropriate screening for prostate cancer. Doctors should be aware that African American men living with HIV may have lower PSA levels compared to their HIV-negative counterparts and be aware that this may make early detection of prostate cancer by relying on PSA more difficult. It is likely that this information also applies to men of different races and ethnicities. ■

| Age Range | Median PSA level (HIV-) | Median PSA level (HIV+) | p-value* |
|---|---|---|---|
| 40 – 49 | 0.71 (n*=48) | 0.54 (n=52) | 0.03 |
| 50 – 59 | 0.96 (n=87) | 0.68 (n=76) | 0.0002 |
| 60 – 69 | 1.5 (n=44) | 1.33 (n=24) | 0.66 |
| Over 70 | 1.86 (n=47) | (n=0) | - |

n = the number of men included in the age range and HIV grouping.
p-value = the statistical power of the difference between the two groups. At a minimum, an observation needs to have a power of .05 to be considered meaningful and significant. The smaller the p-value, the more statically important or significant the observation. Thus a p-value of .0002 is considered very powerful.

# New Uses for Tenofovir; More Questions about d4T

In fall of 2001, the drug tenofovir (Viread) was approved based on data showing its effectiveness in people who had previously developed resistance to one or more of the older anti-HIV drugs of the NRTI class (nucleoside analogue reverse transcriptase inhibitors, such as AZT, ddI, 3TC, d4T, etc.). The drug filled an important niche since tens of thousands of people had been on such drugs for many years already. Since tenofovir also offered the advantage of once daily usage and an excellent side effect record, many people wondered how the drug would fare when used as a person's first therapy or in the early years of treatment. They didn't have long to wait for an answer, which was announced at the Barcelona Conference.

In a newly presented study, tenofovir was compared to the use of d4T (stavudine, Zerit). All 600 volunteers received efavirenz (Sustiva) and 3TC (lamivudine, Epivir) in addition to either d4T or tenofovir. The outcome was very good in both groups (Table 1).

Since three-drug combinations using d4T have long been recommended for first-time treatment use, and these data show tenofovir to be at least its equal, tenofovir will now be used for initial therapy and not just as a salvage drug for people with resistance to NRTI drugs.

Although both groups achieved almost identical suppression of HIV, there were a number of important differences. The group receiving tenofovir showed little change in triglyceride and cholesterol levels, while the group receiving d4T experienced a more pronounced rise. Increased triglyceride and cholesterol levels are believed to be associated with increased risk of fat distribution problems, diabetes and heart disease. The level of increase seen here from d4T, however, is not by itself large enough to create a serious increase in the risk of these problems. Protease inhibitors and even some non-nucleoside drugs, including efavirenz, also can increase these levels, which may be why some increase is seen in both groups in the study. These side effects, however, are consistently worse in the group receiving d4T.

d4T has also frequently been suspected of being a major contributor to mitochondrial toxicity. Mitochondria are the critical energy source of cells. Laboratory tests have shown that d4T may inhibit production of mitochondria more than other drugs of its type. Many researchers believe that mitochondrial toxicity, which is not normally tested for, is a factor in the development of such side effects as lactic acidosis, peripheral neuropathy and pancreatitis. Moreover, some preliminary findings suggest that it contributes to increases seen in total cholesterol and triglycerides and the side effects associated with these changes (lipodystrophy, diabetes, heart disease). In a further analysis of the new tenofovir study, Johns Hopkins University researcher Joe Gallant showed that people assigned to use d4T showed evidence of substantial mitochondrial damage, while those receiving tenofovir did not. So far, tenofovir has not been associated with mitochondrial toxicity in either laboratory or human studies. A summary of these find-

**TABLE 1: Results after 48 weeks using strict "Intent to Treat" Analysis**

| | % <400 copies HIV RNA | % <50 copies HIV RNA | Triglyceride levels | Ttl. cholesterol increase | "bad" (LDL) cholesterol inc. |
|---|---|---|---|---|---|
| **d4T + EFV + 3TC** | 87 | 81 | 84mg/dl | 57mg/dl | 28mg/dl |
| **TNV + EFV + 3TC** | 87 | 82 | 12mg/dl | 29mg/dl | 15mg/dl |

*Intent to treat analysis measures results from all volunteers based on the drug they were assigned to receive, regardless of whether they ever took the drug. A less strict, "as treated" analysis only counts volunteers who actually used the assigned drugs. Using an "as treated" analysis, roughly 97% of volunteers achieved viral load below the 400-copy limit of detection.

** lower numbers are better TNV = tenofovir; EFV = efavirenz

**TABLE 2**

| Outcome Measure | d4T group | tenofovir group |
|---|---|---|
| Median increase in mitochondrial DNA *** | 18 copies/cell | 82 copies/cell |
| % with normal lactate levels *** | 64% | 93% |
| % with nucleoside analogue toxicities ** (such as neuropathy and lipodystrophy) | 10% | 3% |

** Lower numbers are better

*** Higher numbers are better

ings from the study is shown **in Table 2.**

While some of these outcomes may also be affected by the other drugs used, the effect of the other drugs should be the same in each group since the same other drugs were used in each group. These numbers reflect the genuine differences between d4T and tenofovir. (For more information on Mitochondrial Toxicity, call the Project Inform hotline. For more information on d4T side effects, see articles on **page 13 and 15**.)

Given these interesting findings, tenofovir is rapidly becoming a favored drug among many doctors and their patients. Additional studies of tenofovir are being planned or are underway including new comparative regimens, simplified treatment maintenance, prevention of mother-to-child transmission and pre-exposure prevention in high-risk populations.

It is less clear where these new findings leave d4T. Accumulating evidence seems to suggest that it is disproportionately associated with a number of recently identified side effects. While it remains a potent drug, potency alone is no longer enough to justify its widespread use. The availability of new and less troublesome drugs such as tenofovir suggests that it may be time to retire d4T to less a prominent role in the treatment of HIV. ■



# Interleukin-2 (IL-2, Proleukin) and Immune Function

IL-2 is an immune-based therapy that results in dramatic increases in CD4+ cell counts when used in conjunction with anti-HIV therapy. Although IL-2 has been discussed in previous issues of *PI Perspective*, new information warrants a further look at the product.

The value of the large CD4+ cell count increases realized with the use of IL-2 therapy remains unknown. Two large studies are underway to see if IL-2 use among people with HIV prolongs life and improves quality of life. A small study, conducted by the AIDS Clinical Trials Group (ACTG 328), sought to assess immune function in IL-2 treated people who had CD4+ cell counts between 50 and 300 at study entry.

ACTG 328 included people who had never taken either protease inhibitors or 3TC (lamivudine, Epivir). All volunteers received indinavir (Crixivan), 3TC and another NARTI drug (like AZT, d4T, etc.). After 11 weeks of anti-HIV therapy, those who achieved viral load suppression to below 5,000 received intravenous IL-2 (high dose, cycled), IL-2 administered by injection under the skin (high dose, cycled) or no IL-2, in addition to continued anti-HIV therapy. Results from this study showed that IL-2 is able to bolster CD4+ cell counts above what is observed with anti-HIV therapy alone.

In an attempt to glean information about the function of CD4+ cells, a substudy of ACTG 328 evaluated responses to HIV-1 Immunogen (Remune), tetanus, hepatitis A and hepatitis B vaccines. More people in the anti-HIV therapy alone group demonstrated skin test reactivity to the Remune vaccine than those receiving IL-2 (60% vs. 20%). Antibody responses to Remune were similar between both groups, however. There was no apparent difference in antibody responses induced by hepatitis A vaccination between those receiving IL-2 compared to those who did not. While there were no *statistically significant* differences in hepatitis A vaccine responses, there was a trend toward slightly better responses among those receiving anti-HIV therapy alone.

Researchers note that this is a very small study and it's quite possible that a few very stellar responders in the anti-HIV therapy alone group could be driving trends in favor of this group and thus masking the activity of IL-2. In other studies, IL-2 therapy has shown to promote more pronounced and sustained responses to various vaccinations. At best, the results of this study suggest that the function of CD4+ cell increases resulting from IL-2 therapy remain unknown. It is clear, in this study, that responses were not notably better among IL-2 users. Rather, trends favored the anti-HIV therapy alone group. More research is needed to understand the discrepancy between this observation and contrary observations from other studies.

As we went to press, Chiron Corporation, the company that is developing IL-2, has announced the closure of its large study of IL-2, called SILCAAT. The company states the reason for the study closure is a "business decision." Project Inform and other advocacy groups have strongly protested this action by the company. Non-Chiron scientists involved with the study are struggling to find a way to continue this important research, which external safety monitors state is proceeding as planned and should continue. Chiron says that those currently receiving IL-2 in the study are guaranteed to continue receiving the drug for a minimum of one year. As this story evolves, more information will be available. For more information about IL-2, call the Project Inform hotline. ■

# Human Growth Hormone for Thymus Reconstitution

The thymus is an important immune organ necessary for development of new T-cells (like CD4+ and CD8+ cells.) Without some residual thymus, immune reconstitution with a wide varietyof functional CD4+ cells is not believed to be possible. Thus, the state of the thymus in HIV disease and the impact of therapies on the thymus are of great interest to those researching immune restoration approaches.

Striking data were presented on the use of human growth hormone (rHGH) and its impact on thymus reconstitution in people with HIV. A study evaluating the use of rHGH for treating lipodystrophy (body composition changes) was conducted using doses ranging from 1.5 to 3.0mg/day for six to twelve months. In a sub-study, CT scans (a type of x-ray) were taken of the thymus on five volunteers before, during and after using rHGH. All had been on stable anti-HIV therapy for 1–4 years and had very low HIV levels in their blood, most below the limit of detection of the viral load tests. The mean CD4+ cell count was about 419.

Marked increases in thymus mass at six months were noted, beyond what have been seen using anti-HIV therapy alone. This increase was sustained over the course of rHGH therapy and correlated with an increase in naïve T-cells, most notably naïve CD4+ cells—suggesting that the thymus is functioning properly and contributing to new T-cells. The development of new, naïve T-cells is critical to true immune restoration. When rHGH therapy was stopped, there was a coincident deterioration in thymus mass. CD4+ cell count increases observed over the course of therapy, however, were sustained despite this deterioration.

While these data are encouraging, they do not yet lead investigators to the conclusion that broad and general use of rHGH be recommended for immune restoration therapy. Two of the five volunteers discontinued rHGH therapy due to side effects. Of note, rHGH can cause arthralgia (joint pain) and glucose intolerance, increasing risks for diabetes. Further, investigators caution against the use of over-the-counter or through-the-internet purchase of products claiming to contain human growth hormone. Some of these products claim to contain plant-derived growth hormone, others claim to contain cow (bovine) or goat-derived growth hormone and still others claim to contain substances that increase the body's production of HGH. There is no evidence that any of these products contain either a relevant product or a dose needed to induce the types of effects seen in the study. Over-the-counter and internet-based sales of claimed growth hormone products are a major source of health fraud. Moreover, Dr. Napolitano cautioned that this was a small study and it is too early to draw conclusions about the role of rHGH in immune reconstitution. A larger study has been designed and is enrolling volunteers.

Another study evaluated immune responses in 12 people with lipodystrophy who received, in conjunction with anti-HIV therapy, 12 weeks of 4mg/day growth hormone and then received either placebo, every other day, rHGH or twice weekly rHGH for an additional 12 weeks. Volunteers were then followed and monitored for 24 weeks off all rHGH therapy. HIV-specific CD4+ and CD8+ cell responses were evaluated before, during and after rHGH therapy.

After 12 weeks of rHGH therapy, marked improvements in HIV-specific CD4+ and CD8+ cell responses were observed in 9 of 12 volunteers. These improved responses did not correlate with improvements in overall CD4+ or CD8+ cell counts or decreases in HIV levels. Improved HIV-specific CD4+ cell responses were lost by week 24, regardless of whether an individual continued on any rHGH regimen or received placebo. Improved HIV-specific CD8+ cell responses were sustained in all groups (including the placebo group) for this second 12-week period. By the end of the 48-week study period, HIV-specific CD8+ cell responses were waning and HIV-specific CD4+ cell responses remained undetectable.

Herpes-specific CD4+ cell responses were present at study entry and improved over the 12 weeks of rHGH therapy. During the maintenance phase of the study, the subsequent 12 weeks of lower rHGH doses or placebo, these responses fell to below pre-study levels. The loss of herpes-specific CD4+ cell responses correlated with symptoms of herpes.

Investigators conclude that 4mg/daily rHGH therapy may be able to improve both HIV-specific CD4+ and CD8+ cell function. The effect on CD4+ cell function does not appear to be sustained with reduced doses or when rHGH is stopped.

Herpes-specific immune responses are also improved over the 12-week rHGH therapy period and lost thereafter. While rHGH may bolster cellular immune responses in the short-term, during higher dose daily therapy, it might also be correlated with a longer-term loss of these functions—as herpes-specific responses were actually higher prior to initiating rHGH than after the end of the first 24 and 48 weeks of study. This provides reason for caution around the use of rHGH for immune reconstitution outside of studies. While there is certainly interesting and compelling information coming out about the use of rHGH, enthusiasm should be tempered as further work is needed to define the true risks and benefits. ■

# Cell Cycles, Anti-HIV Drugs and Treatment

New research regarding how and when anti-HIV drugs are effective (and ineffective) raise questions about many of the combination treatment regimens in use today. The data seem to provide additional insights into why drugs fail, and consequently suggest new strategies for improving the effectiveness of combination therapy.

### Current Reasons for Drug Failures

Two closely connected reasons are commonly used to explain why anti-HIV drugs fail over time. Part of the blame is assigned to the drugs themselves and part is assigned to the person who uses them.

First, let's look at the way the drug itself contributes to failure. At the simplest level, the most common reason for drug failure is because HIV develops resistance to them. How easily and quickly this happens is at least partially determined by the design of the drug. The most effective drugs remain stable in the blood for long periods. As a result, the level of the drug in the blood rarely falls below the amount needed to sustain full suppression of the virus, and thus, there is little opportunity for the growth of resistant forms of HIV. In contrast, some drugs are quickly flushed out of the body. As a result, the level of drug in the blood is constantly rising and falling as people take their daily doses. This often creates periods in which the level of drug in the blood is too low to fully suppress the virus, and this is precisely the condition which encourages the development of resistance, and thus, drug failure.

*New research suggests the startling conclusion that not everyone using a 3-drug regimen is actually getting the effect of three drugs.*

Next let's look at how the drug's user can contribute to the problem. The key issue here is adherence—how carefully the user follows the instructions on taking the drug. This is particularly critical with drugs that are quickly flushed out of the body. The only way to make such drugs work well is to constantly replenish the drug supply in the bloodstream. For some drugs, this means taking them on a precise time schedule two or three times a day. The worse the drug is at maintaining a high, steady level in the bloodstream, the more important adherence becomes. Yet, we are all human and it's hard to expect people to adhere to their drug regimens' perfectly year after year.

### New Research Provides New Reason

In theory, these two issues should explain most incidences of drug failure, assuming that people are using a minimum of three anti-HIV drugs together in a combination. However, any doctor who treats large numbers of people with HIV sees cases where drugs seem to fail despite careful selection and near perfect adherence. What explains this discrepancy?

New research suggests the startling conclusion that not everyone using a 3-drug regimen is actually getting the effect of three drugs. A new study, conducted by Drs. Robert Redfield, Charles Davis and Alonso Heredita, reported in the Journal of Human Virology (Vol. 4: pages 113-122), shows that another variable, called *cell-cycle dependency*, is also at work and affecting the outcome of anti-HIV therapy.

Simplistically, there are two basic states for every type of cell, including the cells that are infected by HV. In the ACTIVE state, a cell is engaged in the process of replication, or making copies of itself. In the RESTING state, a cell is quietly awaiting a signal to turn itself on. The cells, however, can produce copies of HIV or become infected in either state. What makes this an issue for anti-HIV therapy is that some drugs only work in ACTIVE cells, some work only in RESTING cells and some work in both cell states. Ideally, a drug should work without regard for the cell cycle. Drugs that work only in one state of the cell are said to be CELL CYCLE *DEPENDENT*. Drugs that work regardless of the state of the cell are said to be CELL CYCLE *INDEPENDENT*. In contrast, HIV can infect cells in either the

| Drug | Drug works in: active cells | resting cells |
|---|---|---|
| **NRTI's** | | |
| 3TC (Epivir) | yes | yes |
| abacavir (Ziagen) | yes | yes |
| AZT (Retrovir) | yes | no |
| ddI (Videx) | no | yes |
| d4T (Zerit) | yes | no |
| FTC (Coviracil) | yes | yes |
| tenofovir (Viread) | yes | yes |
| **NNRTI's** | | |
| delavirdine (Rescriptor) | yes | yes |
| efavirenz (Sustiva) | yes | yes |
| nevirapine (Viramune) | yes | yes |
| **Protease Inhibitors** | | |
| indinavir (Crixivan) | yes | no |
| ritonavir (Norvir) | yes | no |
| saquinavir (Fortovase) | yes | no |
| amprenavir (Agenerase) | yes | no |
| nelfinavir (Viracept) | yes | no |
| ritonavir boosted lopinavir (Kaletra) | yes | no |
| atazanavir | yes | no |

active or resting state.

The implications of this appear to be highly significant. Unless all three drugs in a combination are CELL CYCLE INDEPENDENT, the person using the combination is not really on a 3-drug combination all the time. If the combination includes one drug that doesn't work in resting cells, the user is for all intents and purposes only on a 2-drug combination in regard to resting cells. Some combinations even use two drugs that have little or no effect in resting cells.

Most, but not all, drugs work in active cells. The exception is ddI, which works mostly in resting cells. The biggest differences occur in the effect of drugs on resting cells. Here, two of the most common nucleoside analogue drugs, AZT and d4T, and all protease inhibitors have little effect in resting cells. Fortunately, there are a number of drugs that work well in both cell states. The chart (previous page) summarizes the activity of various drugs in the two different activity states.

**Limitations**

The data suggest that many commonly used 3-drug combinations do not provide full 3-drug coverage all the time. But this is perhaps an oversimplification, as the implications of the new data are not yet clear. The data are based in laboratory findings (*in vitro*). The lab data don't conclude that certain drugs have no activity against one or the other cell state, but only that the drug's effectiveness is sometimes significantly diminished. We also don't know the relative contribution of viral reproduction that is made by active cells and resting cells, and therefore can't yet predict how big an impact these finding will have. Nor is it entirely clear whether full 3-drug combinations are needed for both active and resting cell types.

This data raises many important questions that can only be answered by human trials. On the surface, though, these findings may help explain why some people experience drug failure despite good adherence.

Can any conclusions be drawn while awaiting further research? Possibly. For example, it seems reasonable to want to make sure that every combination include at least two (if not three) drugs that are effective against cells in both the ACTIVE state and the RESTING state. In some cases, this might require using more than three drugs in total, or at least carefully selecting three.

Looking at the chart, it is clearly possible to meet the goals implied by this data. For example, any of the following combinations would provide full coverage in both cell states:

Other factors, however, would also have to be considered in a typical situation, such as a person's drug history, any known resistance to individual drugs, relative potency, etc. In most situations, there won't be simple solutions like those implied above. Any protease inhibitor, for example, lacks effectiveness against resting cells. Thus, care should be taken when selecting a regimen based on a protease inhibitor to include at least two drugs that are effective in RESTING cells.

**Any two from column A plus one from column B:**

| Column A | Column B |
|---|---|
| abacavir (Ziagen) | delavirdine (Rescriptor) |
| tenofovir (Viread) | efavirenz (Sustiva) |
| 3TC (Epivir) | nevirapine (Viramune) |
| FTC (Coviracil) | |

**Conclusion**

The challenge of this new data will be to determine how to integrate into our thinking about combination therapy. The basic findings seem reasonable and logical, but it is unclear what relative value to place on them in the overall context of factors that are considered in putting a treatment regimen together. Initially, it might make sense for this data to be considered first for people who are having difficulty establishing and maintaining an effective regimen. This provides one more piece of the puzzle in understanding why things happen the way they do. For people already on stable, effective therapy, the new data may be less important, unless they find they are on two drugs that fail to address one or the other cell state.

In the long term, these observations must be factored into the search for new drugs, so that ideally, new therapies that work in both ACTIVE and RESTING cells might be given priority. ■


**In the Dog House:**

*Chiron Corporation*, maker of interleukin-2 (IL-2), the most promising immunotherapy for HIV, for dropping the most important study of the drug without completing it. The company has given various excuses and reasons, but the bottom line is money and an intention to become less involved in HIV. Negotiations are underway to revive a streamlined version of the study, but Chiron continues to offer less financial support than needed.

**Want to tell them how you feel about this? Write or email:**

Sean P. Lance, CEO
Chiron Corporation
4560 Horton Street
Emeryville, CA 94608-2916
*sean_lance@chiron.com*

# Progress Report: Organ Transplantation in HIV

As people with HIV are living longer due to advances in HIV medicines, there is a rise in death rates from conditions not historically associated with HIV. This includes an increase in risks and rates of both liver and kidney failure, often caused by hepatitis B or C, and underlying kidney disease or HIV-related harm to the kidneys (*called HIV-associated nephrotoxicity or HIVAN*). Anti-HIV therapies that are processed through the liver or kidney can also, in some cases, worsen these conditions and there have been some instances where the damage to the organ has been wholly caused by the side effects of therapies to treat HIV. For people with very advanced liver disease, liver transplantation is often the only option. People with kidney disease have slightly greater options, including dialysis, which involves being hooked up periodically to a machine to circulate and cleanse the blood. It is critical to assess the effectiveness of organ transplantation in people with HIV in order to determine if it prolongs life, improves quality of life and if so then costs should be covered by third-party payers (insurance, Medicaid/MediCal, etc.). The answers to these questions are not obvious since the kind of surgery associated with organ transplants can be very hard on anyone, let alone people suffering from HIV infection.

**Background**

Historically HIV has been a contraindication for organ transplantation, meaning that if a person were living with HIV they were not considered a candidate to receive an organ. Transplant surgeons were often unwilling to perform the surgery and third-party payers were not willing to pay the costs for the required supportive long-term care, as they considered the transplants unproven and "experimental" in HIV-positive people. A number of years ago AIDS activists, including activists from Survive AIDS in San Francisco and Project Inform, got involved with this issue. With the support and leadership of two researchers at the University of California San Francisco, HIV specialist Michelle Roland and transplant surgeon Peter Stock, a local pilot project has blossomed into a national project providing important information to move this field forward.

**The Study**

Dr. Roland presented an overview of findings from 53 people undergoing kidney or liver transplantation in the setting of potent anti-HIV therapy. To be eligible people must have:

- no prior history of opportunistic infections,
- a CD4+ cell count greater than 200 for kidney transplant candidates and greater than 100 for liver transplant candidates, and
- a viral load below 50 copies/ml for kidney transplant candidates and *either* a viral load below 50 copies/ml for liver transplant candidates or if the person is unable to tolerate anti-HIV therapies due to their liver condition, a protocol HIV specialist must determine that after transplantation the individual will be able to construct an effective anti-HIV regimen that will result in maximal viral suppression.

Of the 53 patients reported on at the conference, 45 fit the above eligibility criteria and 8 did not. The reason it's important to include the information on the 8 ineligible people is it helps to determine whether or not the eligibility criteria is appropriate, or if it is perhaps too rigid.

**The Results**

Focusing first on the 45 eligible study participants, 26 received kidneys and 19 received livers. There were six deaths among eligible volunteers receiving transplants, two among those receiving kidney and four among liver transplant recipients. For the most part deaths were happening at similar rates and were due to the same causes that would typically be seen among HIV-negative transplant recipients, such as recurrent HCV disease or post-operative pancreatitis.

In one instance, death was deemed to be caused by a person stopping their anti-HIV medication without consulting the study team. When a person undergoes organ transplantation, they are given immune-suppressive therapy for the rest of their life in order to prevent their body from rejecting the new organ. Anti-HIV therapies have notable interactions with these anti-rejection medications. A great deal of care is taken in monitoring levels of anti-rejection medica-

*…when a person receives an organ transplant they have less flexibility in implementing choices around anti-HIV therapy.*

tions and adjusting doses as needed. When the individual stopped anti-HIV medication abruptly, their blood levels of the anti-rejection medication fell dramatically and they died due to a serious organ rejection event. The important lesson here is that when a person receives an organ transplant, they have less flexibility in implementing choices around anti-HIV therapy. Moreover, adherence to medications has even more critical and potentially life-threatening consequences. Implementing a decision to discontinue the use of anti-HIV therapy, for example, must be done in careful consultation with the transplant team so that dose adjustments for anti-rejection drugs can be made and carefully monitored. Even the simple act of switching anti-HIV drugs can alter blood levels of anti-rejection drugs and must be done with a higher degree of care.

*Results to date are quite encouraging and may already be enough to begin dialog with third-party payers around reimbursement policies.*

For the most part, liver and kidney transplantation had little to no effect on either viral load or CD4+ cell counts. CD4+ cell counts among kidney transplant recipients were about 441 pre-transplant and about 436 post-transplant. CD4+ cell counts were about 280 pre-transplant for liver recipients and about 218 afterwards. Viral loads were basically undetectable in both groups pre-transplant and remained so afterwards. In terms of the short-term safety issues, this is all good news. The median follow up on the entire group is about 314 days, so almost 1 year (with some people having been followed only 3 days but others having been followed for close to 1,700 days—nearly five years).

When comparing the outcomes of the transplant recipients to the larger population of people receiving kidney and liver transplants, survival outcomes thus far appear to be very similar after one year. Some scientists have worried that a higher rate of organ rejection would be seen among people with HIV compared to transplant recipients in the general population. So far, this has not occurred. Among the kidney transplant recipients there was a 38% rejection rate and among liver patients the rate was 21%. Rates of patient survival appear to be similar among the study observations and survival rates observed in the UNOS registry (a registry of outcomes for transplantation in the general population).

Among the eight ineligible subjects who also received transplants, two have died of severe neurologic condition associated with HIV infection called progressive multifocal leukoencepthalopathy (PML). There is currently no way to know whether this was in any way related to the transplants. The reasons folks were deemed ineligible included: one was undiagnosed with HIV at the time of transplantation, a few kidney transplant recipients had viral load above the requisite 50 copies/ml, low CD4+ cell counts and altered mental status (which is also disallowed by the protocol). Of note, those with detectable viral load prior to study entry are currently doing fine as are those with CD4+ cell counts lower than the required threshold. The deaths occurred in the individual with altered mental status and the individual who was not known to be HIV-positive at the time of transplantation.

**Where do we go from here?**

NIH funding is pending for the formal national multi-center study. Results to date are quite encouraging and may already be enough to begin dialog with third-party payers around reimbursement policies. In the meantime, the study is enrolling and providing an option for people with HIV who are or may be in need of kidney or liver transplantation. It is critical that the community push for this study to be expanded to include other organ transplantation approaches, such as heart transplants, as well. While there may be openness by investigators to include such approaches in the study, there remain barriers to overcome. For more details about these study results, and for a list of transplant sites participating in the multi-center study, call the Project Inform hotline. Moreover, your help is needed in political action to insure that organs are available to all those who need them. See page 27 to learn more. ■

## Bottom Line

- Initial information on kidney and liver transplantation in people with HIV in the current era of potent therapy looks very encouraging.
- Though data remain preliminary and on only a small number of people, survival rates after one year of transplant look similar between people with HIV and the general transplant recipient population.
- The study will continue and likely expand with anticipated government funds, and eligibility criteria around prior history of opportunistic infections have already relaxed. In the longer-term eligibility criteria around viral load is hoped to loosen as well.
- Of course wherever possible, preventing and managing conditions that lead to organ damage is preferable to organ transplantation and this should be discussed with a provider—this might include hepatitis B vaccination, implementing HCV prevention/risk reduction or considering HCV treatment.

# The Challenge of Barcelona

Forty million infected with HIV; five million dead in 2001. Fourteen million children orphaned. And, perhaps most startling, the prediction that seventy million people will have died by 2020 unless there is decisive intervention. The horrifying numbers that describe the international AIDS pandemic provided the backdrop for the 14th International AIDS Conference in Barcelona. It is easy for numbers like these to paralyze those of us who live far from where the epidemic is taking its most deadly toll—in places where HIV treatment, care and prevention programs are more generally available. We wonder what we can possibly do in the face of so much suffering and death.

The message of Barcelona, however, was that we can do something, and, in fact, we must. The tools for addressing the epidemic exist, even if the political will and funding are seriously lagging in most countries throughout the world. Everyone has a role to play and those of us living in the US and other rich countries need to hold our leadership accountable to the fight against the epidemic. All of our actions, from the personal to the political, can make a difference.

The international conference convenes every two years. It is an opportunity for scientists, community members, government officials, clinicians, health experts and others from all over the world to come together and assess the state of the epidemic. For many years the conference focused on the science that drove treatment, care and prevention efforts. While that continues, the conference in Durban, South Africa two years ago saw the emergence of another area of strong focus. It was clear in Barcelona that the state of the epidemic in developing countries, the politics that surround it and the social, cultural, gender, infrastructure and clinical issues that drive the unfolding tragedy are squarely at the center of the international conference.

From a political perspective, this conference was important in at least two broad areas. The first was the general acknowledgement of a fundamental paradigm shift in the way we view the pandemic. The shift was at the heart of the international policy and treatment access sessions and discussions. The conference provided an opportunity to recognize the change and to gain broader consensus on how to move forward.

The importance of this can't be underestimated. When delegates left Durban two years ago, "the silence had broken" and the international pandemic took on a reality that was new for many of us; a reality shaped by the HIV-positive people we met and with whom we shared experiences and knowledge. But there were still many questions being asked. Among them were "could prevention and treatment and care work on a large scale in developing countries?" and "should treatment be delivered in resource-poor settings?".

The conversation in Barcelona was fundamentally different. The need to deliver treatment and care, the need to scale up prevention programs and integrate prevention and care was clear and the lack of action was seen primarily as a moral and political problem, not one of feasibility. The questions asked in Barcelona were not whether treatment, care and prevention programs should be mounted but: how can we hold leadership accountable and how quickly can we move?

The paradigm shift in the way we think about the epidemic is multi-faceted and includes:

- The knowledge that the epidemic is in its early stages and its course is unknown. Many thought that the epidemic would burn itself out, and that we would eventually see a slowing of transmission. That hasn't happened in sub-Saharan Africa, where HIV has taken its most horrific toll. Some areas and populations have sero-prevelance rates of 80%, an unthinkable number of people affected. There are many other areas of the world where a similar picture could unfold. We can't accurately predict what will happen, but we do know that our action—or lack of action—will be a factor in the outcome.
- Many wondered whether prevention efforts would work in developing countries, particularly in the absence of treatment. We now see successful, proven prevention approaches, including shining examples in Thailand, Uganda and other places. Effective prevention takes leadership, funding and community involvement, but we know it can be done.


*Join Project Inform's Treatment Action Network*

Since the beginning of the AIDS epidemic, grassroots advocacy has been the heart of many political victories. In the current political environment, your involvement is needed more than ever. Join over 2,000 Treatment Action Network members and become an influential advocate for AIDS care, treatment and research funding and policies!

If you would like to sign up to be a part of the Treatment Action Network, call Project Inform at 415-558-8669, FAX to TAN Coordinator at 415-558-0684, or email ***TAN@projectinform.org.***

- Community mobilization is at the core of any adequate response to the epidemic. Some questioned the effectiveness of community with scarce resources. It is clear, across all borders, that community develops support systems, creates political will, holds leadership accountable and provides the personal experience necessary in all aspects of the fight against HIV. HIV-positive people and those who support them are responding to the epidemic throughout the world, sometimes with few resources and at great risk.
- Prevention and access to care and treatment are linked and synergistic. Prevention and treatment have often been pitted against one another as strategies for addressing the epidemic. We know from experience that access to treatment and care boosts prevention efforts, if only by increasing the number of people who seek voluntary testing and counseling. We also know that the arguments that prevention gets "more bang for the buck" are simplistic and fail to take into account the cost of human lives and the human resources and infrastructure that make society viable.
- Access to comprehensive care and treatment is possible and it is not optional. Many questioned the feasibility of delivering treatment and care in developing countries. However, the cost of anti-retrovirals has decreased dramatically, particularly in countries that take advantage of generic competition. Although the healthcare infrastructure in developing countries presents challenges, it is not the reason that treatment is unavailable. Groups are treating people now in places such as Kayalitsha, South Africa and Haiti, where the infrastructure is among the poorest. What is lacking now is the willingness to pay for the further development of needed infrastructure and for the lives of those most at need. Lack of treatment and care is not primarily a problem of feasibility but rather of moral and political failure.
- We have to address the gender, economic, political, social and cultural factors that make people vulnerable to HIV. We know that a fairly comprehensive and reasonably funded prevention and care effort can make great strides against HIV. However, unless we address the inequities that make people vulnerable to infection, we can't eliminate or radically decrease new infection for all people. Many understand this and are working hard to address the epidemic on several levels.
- The argument that developing countries can't effectively utilize new money or resources to fight the epidemic is not an excuse for delaying resources. We know from the first round of applications to the Global Fund to Fight AIDS, TB and Malaria that there is a huge unmet need that is ready for significant funding and resources right now.

The second important note at Barcelona was the changed emphasis of the conference and the tenor of the international policy debate. The science reported was important, fueled many debates and provided those with access to treatment and care with some new information to consider. But the conference was essentially political and the spotlight was on those without the basic tools to fight the epidemic.

Confrontational protest seemed, for many of us, to have regained an important place in the spectrum of political approaches and a new energy. The policy track report-back may have summed it up best, stating that there was a "clear consensus, across all disciplines and backgrounds, from all parts of the world, a sense of urgency for effective action and a clear frustration between knowledge of what is possible and what is happening now."

It was notable that the challenge to movement and accountability wasn't exclusive to the policy track but had a place in all parts of the conference. Many of those in leadership positions, including Dr. Peter Piot, Executive Director of UNAIDS, Bill Clinton, Nelson Mandela and Graca Machel, former First Lady of South Africa, challenged delegates to action.

Peter Piot opened the conference with the statement that, "We did not come to Barcelona to renegotiate the promises. We must make an uncompromising attack on stigma—that's not negotiable. We must strengthen the alliance that will deliver HIV vaccine—that's not negotiable. We must deliver both prevention and treatment at full scale—that's not negotiable. We must find $10 billion—that's not negotiable. Defeating the epidemic is possible but it's not inevitable."

*…treatment works, by saving and improving lives, and, therefore, treatment should be made available as soon as possible when clinically indicated to those who need it, in the north and in the south.*

Even amongst those known for their expertise in, commitment to and focus on the science of care and treatment, the call for action was clear. Dr. Anthony Fauci, Director of the National Institute of Allergies and Infectious Disease (NIAID) gave a plenary speech focused on HIV pathogenesis, but included a message for access to treatment, "… treatment works, by saving and improving lives, and, therefore, treatment should be made available as soon as possible when clinically indicated to those who need it, in the north and in the south."

Women were very visible in the political discussion at the conference. As the numbers of women and girls infected continue to rise at alarming rates, women and men are struggling to address issues for positive women, including the gender inequities that fuel the epidemic. A woman with HIV opened the conference and an HIV-positive woman closed the conference with an eloquent and compelling speech urging, among many things, a greater role for community at the next conference in Bangkok. Women at high levels of government and in leadership positions spoke about their own actions, the

concept of leadership, what was needed for women living with HIV and the importance of gender equality. Calls were made for a gender analysis for funding applications. This would mean that applicants for various types of funding, including Global Fund support, should be required to outline what they would do with and for women living with HIV. Women also developed a Barcelona Bill of Rights that is currently being endorsed and will be distributed in advance of World AIDS Day, December 1, 2002.

Project Inform and other organizations joined with activists from throughout the world to protest the Bush Administration's domestic and international HIV/AIDS policies. Secretary of Health and Human Services, Tommy Thompson's speech regarding the US role in the international epidemic was drowned out by angry protestors. Protestors demanded increased US funding and accountability in the domestic and international fight against the epidemic. Secretary Thompson, to his credit, met with several community members after the protest to discuss substantive policy issues, including prevention efforts, particularly in communities of color, needle exchange, domestic and international funding, the US contribution to the Global Fund and the concept of Medicaid expansion for people living with HIV. Secretary Thompson also committed to continued dialogue with community members and another meeting.

*There were protests against rich countries for their lack of funding and leadership and multinational corporations, including Coca Cola for allowing their employees in developing countries to go without HIV treatment.*

There were political challenges to increase and diversify the voices of people living with HIV. One young woman, an out HIV-positive active drug user, from Australia made an impassioned plea to attendees of one session to help at least one out HIV-positive active drug user attend the next international conference. She hadn't met anyone else who was out about active drug use during her time in Barcelona.

Many delegates were unable to attend the conference due to a Spanish government decision to deny visas to positive people without insurance. This decision affected many from developing countries who may have benefited greatly from the information and the contacts of the conference and who would have educated others through their efforts to fight HIV in their countries. Spanish activists spearheaded a noisy protest of their Minister of Health during her speech at the conference opening to denounce the action.

There were protests against rich countries for their lack of funding and leadership and multinational corporations, including Coca Cola for allowing their employees in developing countries to go without HIV treatment. Since the conference at least three corporations have joined Heineken International in providing treatment for employees. As always, there were protests against pharmaceutical companies. But overall, the challenges, debates and protests seemed to resonate through the conference. The sense of urgency and frustration expressed in the policy track summary was palpable throughout the conference.

From a political perspective, the take home message from Barcelona was at once profoundly significant and very simple.

- There is a tragedy unfolding.
- Women and girls are at its center.
- We have the tools necessary to address the epidemic and save millions of lives.
- The political will to make that happen is lagging in many countries, including the United States.
- Community plays a vital role in initiating and sustaining responsible action and leadership.
- Each of us has a part addressing and perhaps averting at least some of the tragedy.
- All of our actions count.

For more information on global issues, or to receive regular policy updates and action alerts on domestic and international issues, email *tan@projectinform.org*. ■


## In the Dog House:

*Hoffmann-La Roche*, maker of saquinavir (Invirase and Fortovase) and ddC (HIVID) for setting the price of their new drug for hepatitis C, called Pegasys, even higher than that charged by Schering Plough for a similar drug.

Schering's price, at around $14,000 per year, was already so high that most people considered it immoral, but despite the impending crisis in funding for drugs, Roche topped them, charging nearly $15,000. Pegasys must be used in combination with a second drug, ribavirin, so the true price is higher still.

**Want to tell them how you feel about this? Write or email:**

George Abercrombie
President & CEO
Hoffmann-La Roche
340 Kingsland St.
Building 85, 8th Floor
Nutley, NJ 07110
*george.abercrombie@roche.com*

## Action Alert:

**Call Congress on January 15 and Demand Action on AIDS!**

On January 15, a coalition of HIV/AIDS advocates will have a press conference and lobby visits at the U.S. Capitol to demand that Congress pass a final appropriations bill with adequate funding for HIV programs. Shortly after the November elections, Congress adjourned for the year without finishing its appropriations work and passed a "continuing resolution"—or temporary spending bill—to keep programs funded until a final bill could be negotiated. Because this continuing resolution does not include any increases for HIV/AIDS programs, it puts additional pressure on programs like the AIDS Drug Assistance Program that are already facing a financial crisis and having difficulties meeting the needs of those they serve.

You are encouraged to be a part of this effort by calling your U.S. Representative and two U.S. Senators on January 15 and urge them to:

1. make sure a final appropriations bill is passed immediately and
2. support the highest possible funding levels for all HIV/AIDS programs.

If you are unable to make these calls on January 15, please call as close to that date as possible. A strong grassroots effort is needed to ensure that HIV is a priority for the new Congress. You can find an Action Alert with more information and sample phone message on Project Inform's website, or by emailing *tan@projectinform.org*.

# Re-Infection: Is it a Concern for People Living with HIV?

Re-infection is a term used to describe a new or secondary infection by a virus that has already infected a person. In most viral diseases, re-infection with the same virus doesn't occur because once the immune system conquers the original viral infection, it creates immunity against that virus. Re-infection occurs almost constantly, however, in some types of infection, such as the cold or flu viruses, because each new version of those new viruses is substantially different from the last. This is why a person may develop immunity to the flu strain that is common in one year, but still be at risk from the strain that becomes dominant the next year.

The question of re-infection with HIV has long been debated. There is no theoretical reason to think re-infection isn't possible, since the immune system never fully conquers the initial HIV infection. Still, many people, including many physicians, clung to the hope that re-infection with HIV either does not happen or that it only happens rarely. This view is the basis of the belief held by some HIV-positive people that having sex or sharing needles with another HIV-infected person poses little or no risks. Many if not most virologists, however, have long believed that re-infection is both possible and perhaps even likely. What is not known are the individual short- and long-term clinical consequences (which may vary from person to person for wholly unknown reasons).

For many years, there were no clear cases of re-infection presented at scientific conferences, but this did not mean such re-infection wasn't occurring. Instead, we know that finding and documenting cases of re-infection is extraordinarily difficult, if for no other reason than that no structured program has looked for them. Finding a case of re-infection has largely been a matter of chance. Yet, several observations over the years support the notion that re-infection is possible, including observations of sex workers in Africa infected with several different recombined "clades" of HIV as well as detailed genetic analysis of a few people's virus suggesting that re-infection was possible. This research is very difficult to conduct. Perhaps the only simple example of re-infection is in western Africa, where people are routinely found who carry both HIV-1 and HIV-2. At the very least, this proves that having HIV-1 does not protect a person from infection with HIV-2.

Recently, there has been considerable media attention about a few well documented cases of suspected re-infection with two versions of HIV-1. The most interesting case, presented by Dr. Bruce Walker, was the result of an almost accidental observation. While researching the effects of Structured Treatment Interruption (STI) in some newly infected volunteers, Walker's team was intrigued by one particular case in which the volunteer responded well to two initial cycles of STI. After each, the person's viral load remained undetectable for several months without treatment. Shortly after a third STI, however, the viral load remained low for only a brief period and then suddenly soared upward. The team wondered what made things different this time? After conducting extensive genetic analysis, they found their answer: the volunteer had become infected with a second, slightly different strain of HIV. Most striking, and discouraging, was that the genetic makeup of the new infection differed by only 12% compared to the original infection. Despite this small difference, the

second infection had completely escaped control by the immune system, breaking through the suppression achieved against the original virus. This discovery, while important enough in regards to re-infection, also had discouraging implications for vaccine development, suggesting that as little as 12% variation between viruses might be enough to make a vaccine fail.

Several questions remain in regards to re-infection. Will re-infection lead to more rapid disease progression? Will re-infection with HIV result in transmission/acquisition of drug-resistant HIV that will limit a persons' anti-HIV treatment options? Both of these concerns are theoretically possible, and both have now been demonstrated in case studies. Currently there is not a large amount of data to assess the actual risk to the individual. Although only a little data currently exists and it is extremely difficult to gather more, it does not lessen the real potential for re-infection or its consequences.

There are several reasons why people living with HIV would want to maintain safer sex activities. While the clinical implications of re-infection remain unknown (and will likely be unknown for many years to come), there is some evidence of harm and no evidence of harmlessness. We also know for certain that safer sex does protect against many blood-borne infections that are major causes of life-threatening diseases and death in people with HIV. These likely include CMV, some forms of hepatitis virus, genital herpes, possibly the JC virus (cause of a particularly destructive condition known as PML), to name a few.

Ultimately people living with HIV need to consider this information and make informed decisions about safer sex for themselves. In the early 1980s many did not want to believe that HIV was caused by unsafe sex. Many people have dearly paid the price for that belief. The optimal outcome here is for people not to fight against data and shy away from acknowledging the potential consequences of re-infection. Some people will come to a conclusion that it's better to be safe than sorry. Others will choose the risk of being sorry rather than safe and will continue to participate in unsafe sex with positive partners. What matters most is that people make a conscious decision based on the available information. ■

## Managing Nelfinavir-related Diarrhea

The use of the protease inhibitor nelfinavir (Viracept) has been associated with diarrhea. Some community-based clinics report that upwards of 80% of their clients who are using nelfinavir experience this side effect to varying degrees. While this figure is higher than what has been reported in studies, it underscores the need to prepare for and take preventive action against this side effect if you're considering the use of the drug.

A small study reported at the Barcelona conference evaluated strategies for managing nelfinavir-associated diarrhea. The study included 47 people who reported experiencing diarrhea while receiving nelfinavir (1,250mg twice daily) as part of their anti-HIV therapy regimen. Volunteers received one of three regimens for diarrhea: (1) calcium (500mg twice daily) with dietary counseling; (2) loperamide (Imodium), 2mg a day three times a week with dietary counseling; or (3) dietary counseling alone. Those receiving either calcium or loperamide along with dietary counseling experienced far greater improvements in symptoms of diarrhea compared to those who received only dietary counseling alone. No one receiving dietary counseling alone experienced normalization of diarrhea. Only ten percent experienced any improvements in diarrhea symptoms and 7% noted a worsening. In contrast, 36% and 40% of those receiving calcium and loperamide respectively experienced normalization. Over 50% of those receiving either calcium or loperamide experienced improvements in symptoms and no one receiving these interventions experienced worsening symptoms.

These findings show that dietary counseling alone is not enough to manage nelfinavir-related diarrhea and perhaps suggests that people starting nelfinavir consider the use of loperamide or calcium as a preventive measure.

In addition to calcium and loperamide, as described above, the following dietary advice may help to reduce nelfinavir-associated diarrhea:

- Take nelfinavir with food
- Reduce lactose intake
- Supplement diet with soluble fibers (such as oatmeal or psyllium husk)
- Increase foods in diet known to reduce symptoms of diarrhea (bananas, apples, rice and toast) ■

# We Must Have Presumed Consent

**By Larry Kramer**

More and more people with HIV and/or hepatitis are going to need organ transplants, particularly liver transplants. As more of us all over the world discover we are carrying one or more of these viruses, even if we are being treated for them—or particularly if we are being treated for them—the more likely it becomes that one of our organs is going to cease working effectively. And the longer we are being treated, the longer we live and the more that chance grows.

With all the new drugs for HIV and viral hepatitis, it is now safe, ok, kosher to transplant "coinfecteds." The New England Journal of Medicine has even written approvingly of such transplants. Insurance companies can no longer simply refuse to pay for these expensive procedures on the grounds that they are "experimental." Too many of them have been done successfully.

Right now there are hundreds of thousands of people in this country waiting for organs. Most of them will die before they get them. Many will die after they have been put on a waiting list. Why is this? Because not enough people in America donate their organs to be used after they die. It is as simple and as complicated at that. There are more than five people waiting for every organ made available by donation.

In many countries this extreme shortage does not exist. That is because these countries (including Austria, Belgium, Denmark, Finland, France, Italy, Norway, Singapore and Spain) have what is called a Presumed Consent organ collection system. That means that every person is deemed to be an organ donor unless s/he specifically opts out. When an accident occurs to a person who has not opted out, and brain death is declared, organs can be taken immediately without the time-wasting rigmarole America requires for "approval." An organ only has a few hours to get from one body to the next. In America, you sign the back of your driver's license if you are willing to be a donor, and even then most centers still require permission from a family member, which, believe it or not, may not be given.

I have been trying, since my transplant, to find a way of changing America's organ donor system to one of Presumed Consent. Well, you would have thought that Presumed Consent was akin to the biggest blasphemy known to civilization. Opponents from the right, the conservatives, the orthodox, you name it, including the ACLU (did you know that the organs of dead people have rights?) have screamed in opposition. These opponents do not care that Spain, a very Catholic country, has the most successful organ procurement system in the world.

And no one I can find knows how the system can be legally changed. Who does it? Congress, by passing a law? HHS, by issuing an edict? State-by-state or community-by-community, by putting it on a local ballot? As Robert Bazell, the chief medical correspondent for NBC Nightly News, warned me when I embarked upon this new activist journey, "Larry, you will find that it is like punching air."

One person who can help change this system more than anyone else is Senator Bill Frist (R-TN). He is a transplant surgeon himself. He knows the hideous horrors of watching people desperate for organs die. But he is a politician with Presidential ambitions, so he is not exactly willing to be Mr. Flag Waver for organ transplants. He has prepared a bill, with Sen. Christopher Dodd (D-CT), to investigate Presumed Consent. But this bill has no hope of getting passed, which is not so bad because it is such a wishy-washy piece of legislation that we are better off without it. It is an all-talk no-action kind of bill.

Frist needs to be reminded that going out further on this issue is not only the morally right thing to do, but also will ultimately help him win voter support. Despite what people think, voters like candidates who take moral, life-saving positions. And all the people who need organs have lots of relatives and friends.

AIDS activists have been here before. It is the beginning of a new crisis and no one of any importance wants to pay it an iota of attention. In the coming years, the number of people around waiting for new organs is going to rise to the millions from the several hundred thousand currently in need. Once again I find myself screaming out loud about a huge and coming catastrophe and no one is listening.

I would like to close words from Dr. John Fung, who saved my life: "Patients are dying and the public still does not understand that saying no to donation means someone will die. No one wants to be so blunt. No one wants to raise the American conscience to make people feel that it is their human obligation to pass along their body to the living when they die. This is a systematic deficiency in American culture, the idea that you are out only for yourself and have little or no obligation to society as a whole."

*This is a systematic deficiency in American culture, the idea that you are out only for yourself and have little or no obligation to society as a whole.*

Tell Senator Bill Frist: America must have presumed consent for organ donation! Email him and tell everyone you know to email him or call his office: *Bill_Frist@frist.senate.gov* or 202-224-3344. ■

# PI Perspective and In Focus are going electronic!

Project Inform's plans for 2003 include developing electronic notices and/or e-newsletter versions of *PI Perspective* and *In Focus*. This will further enhance the timeliness of the information that we provide to you, along with reducing our paper, production and postage costs.

We hope you will consider receiving future issues of these publications through your email account. So, to help us out, we need your email address. Please fill out your name and address below, clearly print your email address and mail back in the enclosed envelope. **You may also quickly email us this information at *support@projectinform.org.*** And, as always, we do not spam and we do not sell, trade or otherwise distribute any portion of our mail list to anyone else.

We will let you know later in 2003 when these new versions are available to you. Thank you for your continued interest in Project Inform. We wish you a happy, healthy and safe New Year.

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