

When to Start Treatment

New findings presented at this year's Conference on Human Retroviruses and Opportunistic Infections were overshadowed by public discussion of a change in the US Guidelines on the Use of Antiretroviral Therapies. The changes represented something of a correction, or some say, a repudiation of the "hit it hard and hit it early" approach promoted at the International AIDS Conference in Vancouver in 1996. Researchers whose views were considered "state of the art" in 1996 were now all but hiding from the press. As usual, the truth wasn't quite that simple nor are the changes as dramatic as some think. They do, however, offer an important clarification on the use of treatment.

The issue of when to start anti-HIV therapy has been debated since 1986. While there are good theoretical reasons to support early treatment of HIV, doing so means coping with a complex interplay of drugs, HIV evolutionary processes (resistance), short- and long-term side effects and issues of personal choice. If there is any clear message from the last fifteen years of research, it is that there is no single treatment strategy that is "best" for everyone, no matter how much people might wish to have one. The decision to start treatment is a personal choice that can be informed—but not dictated—by the available scientific and medical evidence.

Although there were various opinions on when to start therapy prior to the use of Highly Active AntiRetroviral Therapy

(HAART) in 1996, the availability and success of protease inhibitors led to a wide swing in favor of early treatment. Talk of the potential of "eradicating" HIV led many physicians to believe that everyone should be placed on treatment without regard for clinical symptoms or how long a person was infected. A careful examination of what researchers were saying, however, showed that they were only raising the hope of eradication in people who started treatment literally within a few weeks or months of first being infected. Nonetheless, the media translated the call to "hit it hard and hit it early" into a mantra that was interpreted to mean "treat everyone."

During this period, the Federal government called together a panel of experts to

draw up "official" recommendations for the use of anti-HIV therapy in adults. They recommended then that people with CD4+ cell counts below 500, and/or with a viral load of 5,000 to 10,000 copies, should be "offered" treatment, and that treatment should be strongly encouraged for people with CD4+ counts below 200. The Guidelines never said that people "should take treatment"—only that it should be discussed and offered. For people with CD4+ cell counts above 500, the Guidelines concluded that treatment was a matter of personal choice and opinion since there were no data either supporting or firmly discouraging its use. Still, many physicians interpreted the Guidelines as recommending that everyone should be on treatment, regardless of lab values or stage of disease.

The Outcome – Four Years Later

There are several possible long-term consequences of the "hit it hard, hit it early" era of therapy, many of which were not initially recognized.

- 1 It may cause people who had no urgent need for therapy to be unnecessarily exposed to drug side effects.
- 2 It may cause people to begin cycling through the list of the available drugs earlier than necessary. No drug lasts forever and most are eventually weakened by the development of resistance. By starting treatment earlier, people may have begun using up their treatment before the drugs were capable of providing a meaningful benefit.

March 2001

**In
This
Issue**

© 2001
Project Inform, Inc.

1 *When to Start Treatment*

4 *Anti-HIV Therapy Update*

4 *New Formulation of ddI Approved*

5 *Caution: Garlic Supplements*

5 *Drug Identification Chart*

6 *Tenofovir Expanded Access*

6 *Head to Head Study of Two Protease Inhibitors*

7 *Cidofovir*

8 *Making Decisions About Treatment*

9 *Lipodystrophy Update – The Continuing Saga*

11 *Women and Pharmacology ♀*

12 *Women's Highlights from the 8th Retrovirus Conference ♀*

13 *Spotlight on IL-2*

15 *New Presidential Administration*

♀ - May be of special interest to women

- 3 Pressure to start therapy too early may discourage some from taking treatment altogether. Those who felt healthy before starting treatment suffered through rigorous daily regimens, disrupted eating and sleeping habits, and side effects like nausea, diarrhea and liver damage. These people may later oppose or fear the use of treatment when they need it most.
- 4 Many who start “early therapy” might become careless in their adherence or use of the drugs because they feel little if any pressure from the disease. They feel fine, with or without treatment.

With factors complicating the use of early therapy becoming more apparent over time, the US Federal Guidelines Panel revisited their recommendations, as had their European counterparts and the International AIDS Society. Though there really aren't any new data regarding the potential benefits of early treatment, there are now a lot of data about the potential risks. After a year-long review, the new Federal Guidelines now recommend that physicians discuss and “offer treatment” to people with CD4+ cell counts below 350 or viral loads over 30,000 to 50,000 copies. Some newly available data continue to suggest that most people will fare well even if they wait until the CD4+ cell count falls to around 200, though this provides little safety margin to accommodate individual differences or the differences seen between men and women on some lab tests.

Therefore...?

For HIV-positive people and their doctors who wish only to read the charts of the new Federal Guidelines but not the accompanying text, things sound very simple: just put everyone on treatment when their CD4+ cell counts fall below 350 or when their viral load exceeds 30,000 to 50,000. Following such a rule, however, might still result in a good deal of inappropriate use of drugs because the health of a person's immune system cannot be described solely by the CD4+ cell count or viral load, nor can their response to treatment be predicted.

Studies cannot predict how any individual will respond to treatment, or how

they would fare without it. All a study can do is report the average response seen in the groups studied. Some of the people in those studies will indeed have the “average” response described by the study analysis, but many others will do much better or worse. While it is true, for example, that there is a serious risk of getting pneumocystis carinii pneumonia (PCP) when a person's CD4+ cell count falls below 200, some people get the infection with a CD4+ cell count of 300 or even 400, while others coast along with counts below 50 CD4+ cells without any infections. *Monitoring not just lab values, but also overall measures of general health including weight, minor symptoms and your overall sense of well-being can provide important clues as to your individual risk of disease progression and help you decide if intervening with therapies is right for you.*

The fact that we currently lack proof of the benefit of treatment when CD4+ cell counts are above 350 or even 500 does not prove that starting treatment early is wrong.

People with the same CD4+ cell counts and same viral load do not all have the same risk of disease progression. By itself, the CD4+ cell count doesn't tell us enough. It's a good starting point, nothing more, nothing less. It's perhaps most useful when looked at over time, in the context of general trends. Other factors that should be considered in making a decision to start treatment include:

- **CD4+ percentage:** No test measures the exact number of CD4+ cells in the blood. Instead, laboratories measure the number of white blood cells and then roughly determine what percentage of a person's white blood cells (WBC) have a marker called “CD4+”. That percentage is then multiplied by the number of white blood cells, giving us a calculated

In Memory Of . . .

We dedicate this issue of the
PI Perspective to:

Frank Goyer
Jim Botsko

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

number called the “absolute” CD4+ cell level. But this number is anything but absolute. This process makes the count of the CD4+ cells dependent upon the number of white blood cells, and that WBC fluctuates widely over time, usually for reasons that have nothing to do with the health of the immune system. Every time the WBC goes up or down for any reason, the “absolute” number of CD4+ cells circulating in the blood moves up and down with it, sometimes producing a very misleading number that can either frighten people or cause them to overlook a developing problem. In short: a high WBC results in an artificially elevated CD4+ cell count, while a low WBC causes an artificially suppressed CD4+ cell count. Because of this, many physicians also track the CD4+ percentage, which is provided by the same lab tests. The advantage is that the CD4+ percentage does not fluctuate along with the WBC and therefore reflects a more realistic picture of the balance of cells in the immune system. Many physicians recommend checking the CD4+ percentage as well as the absolute CD4+ before taking any action, as it filters out the fluctuations in cell numbers.

- **CD4+ change over time (or trajectory):** If the CD4+ cell absolute count rapidly declines from one test period to another, a fall below 350 might be a very important warning of danger to come. But if the number is largely stable over time and perhaps just moves a little above or below 350 (or is contradicted by the CD4+ percentage), treatment may not



Board of Directors

Joseph R. Garrett, *President*
 Mark Cloutier, *Vice President*
 Michael Mendiola, *Secretary*
 Ken Turner, *Treasurer*

Diane Cenko
 Martin Delaney
 Kathleen Fisher
 Brenda Freiberg
 Linda Grinberg
 Jim Gutschick

Curtis Ingraham
 Tom Kelley
 Alonzo Reese
 Bill Sprick
 Steve Suacci
 Jeff Wiggins

National Board of Governors

Percival Beacroft
 Suzanne Benzer
 Thomas Blount
 Ernesto Caldeira
 Richard C. Dailey
 Don Davis, MD
 Lynda Dee, Esq
 Rebecca Denison
 John Dwyer, MD
 Robert Gallo, MD
 Michael Gottlieb, MD
 David Ho, MD
 Suzanne Ildstad, MD
 John S. James
 Cleve Jones

Barry Krost
 Sharon Lee, MD
 J. Michael McCune, MD, PhD
 Jerry Moss
 Gwyneth Paltrow
 Betsy Fels Pottruck
 Adan Rios, MD
 Michael Saag, MD
 Nava Sarver, PhD
 Robert Schooley, MD
 Erik Sterling
 Paul Volberding, MD
 Irv Weissman, MD
 Jason Winters

Staff Members

FOUNDING DIRECTOR
 Martin Delaney

EXECUTIVE DIRECTOR
 Ellen LaPointe

ACCOUNTING
 Glen Tanking

ADMINISTRATION
 Edd Lee

CONSTITUENT SERVICES
 Reuel Sherwood Doug Ronning

DEVELOPMENT
 Julie Doherty Carol Varney

HOTLINE
 Adrian Elwell Freddie Oaks

INFORMATION AND ADVOCACY
 Brenda Lein Ben Cheng Angela Garcia

MATERIALS PRODUCTION
 Alan McCord Kirby DeMott

OUTREACH AND EDUCATION
 Judy Leahy Sana Chehimi

PUBLIC POLICY
 Anne Donnelly Ryan Clary

VOLUNTEER AND INTERN SERVICES
 Mark Owens Esmeralda Pereira

Volunteer Groups

Board of Directors, Hotline, Institutional Review Board,
 Internet Team, Mailing & Office Assistance, Project
 Immune Restoration, Speaker's Bureau,
 Special Events, Treatment Action Network.

PI Perspective® is published three times per year and is distributed free of charge. *PI Perspective* is a publication of:

Project Inform

205 13th Street, Suite 2001

San Francisco, CA 94103-2461

PHONE 415-558-8669 FAX 415-558-0684

EMAIL SUPPORT@projectinform.org

WEBSITE www.projectinform.org

be critical at all. For some, a count of 350 might represent a brief step in a rapid decline from 400 or 500 to 200 or below. In this latter case, a test result of 350 CD4+ cells might be an important warning sign. Rapidly declining cell numbers are probably a more important warning sign than any particular threshold number or percentage of cells.

- **Presence or absence of symptoms:** A person who experiences repeated symptoms associated with HIV disease progression, such as frequent skin infections, difficult to control thrush (candida) infections, mouth or skin infections, etc. might be wise to consider therapy earlier than standard recommendations might imply. Conversely, someone who shows no symptoms and generally robust health might be safe to wait for the later extremes of CD4+ cell count decline. Almost everybody recommends anti-HIV treatment when CD4+ cell counts fall below 200, but even in this situation, personal choice can be a factor in decision-making.
- **Personal needs, beliefs and preferences:** The fact that we currently lack proof of the benefit of treatment when CD4+ cell counts are above 350 or even 500 does not prove that starting treatment early is wrong. Scientists have changed their views a number of times already, and may well change them again when new data or new drugs become available. Some people prefer to try to halt any decline of their CD4+ cell counts, even if this means starting treatment with a high CD4+ cell count. There is nothing irrational or unscientific about trying to preserve one's immune system or to prevent any loss of cells of their functions. In fact, if drugs didn't produce side effects and people didn't have to worry about resistance, physicians would probably favor the earliest possible treatment. Some people would rather take their chances with side effects than with any permanent damage to their immune system. There is in fact some evidence that very early treatment—starting within the first month or two after

infection—preserves some aspects of the immune system that are almost always lost when treatment is delayed.

- **Personal situation:** Some jobs, such as working in an office or driving a cab or a truck, might make it very difficult to cope with a drug that produces diarrhea as a side effect. For such people, delaying treatment as much as safety permits might seem a reasonable choice. Similarly, people unable or unwilling to share knowledge of their condition with family members may prefer the greatest possible delay. Women and men who are victims of domestic violence or who must hide their HIV status may find that their home life makes adherence or even regular access to medications difficult. None of these situations represents an insurmountable barrier to starting therapy, but each requires more planning and preparation and may factor into a decision to start therapy now or defer.
- **Personal readiness:** It makes little sense to force a person who fears anti-HIV treatment or its potential complications to start a treatment regimen. While some degree of fear of therapy may be normal, it's important to explore the extent and roots of those fears. Unless the person has come to grips with the situation and the necessity of treatment, that person may not use a treatment wisely. They may have great difficulty with adherence, leading to rapid development of drug resistance. Such a person may be better off to wait and continue preparing for treatment than to rush into something he or she isn't yet prepared for. This may be true even if it means waiting until after reaching the critical "200 CD4+ cell count" level. People can still be protected against most major opportunistic infections through simple, preventive medications before committing to anti-HIV therapies.

Commentary

HIV-positive people and their doctors must understand that the US Federal Guidelines or the International AIDS Society Guide-

lines—anyone’s guidelines—are not meant to be rigid formulas that dictate the practice of medicine. They are just a generalized starting point for making decisions about treatment. There is no one “right” time for starting treatment that will work for everyone, and no planned or possible study will ever result in a precise universal recommendation. Over time, studies may add to our knowledge about how the various factors affect the decision to start treatment. They will help clarify matters, but they too will never lead to a “cookbook” solution that fits everyone and every circumstance.

In deciding when to start, many factors should be considered, including a mix of all we have learned from studies, and all that is known about the individual and his or her life situation. Once this is understood, it is generally easier to find the “right” time for an individual to start therapy.

There is no one “right” time for starting treatment that will work for everyone, and no study will ever result in a precise universal recommendation.

While there may be no one “right” time to start anti-HIV therapy, there is certainly a “right” time to start managing HIV disease. Learning about and lining up benefits and support systems; improving diet, exercise and general health habits; choosing and developing a relationship with a doctor; setting up routines of regular health check ups, including Pap smears for women, (quarterly and twice yearly, respectively); learning about HIV disease and treatment options; and cultivating a philosophy of well-being are ways to intervene in HIV disease and take charge of one’s health that can start today. There is no question that starting these activities earlier rather than later is beneficial. Project Inform has resources to help people consider these approaches to health and well-being. ■

Anti-HIV Therapy Update

Several new anti-HIV therapies have recently entered human studies. Most of these drugs belong to the currently existing classes of therapies (i.e. protease inhibitors or non-nucleoside reverse transcriptase inhibitors). Laboratory studies suggest that their resistance patterns are different from the existing drugs and so may be effective against drug-resistant viruses, rendering them of potential interest for people seeking third line therapy options.

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Tibotec, a new company based in Belgium, reported results from a small study of their new NNRTI, TMC-120. In laboratory study, this drug remains sensitive to virus that are resistant to the currently approved NNRTIs. However, this initial human study was conducted among people who had not previously received anti-HIV therapies, and so it is not known how effective this drug really is for people who are resistant to current NNRTIs.

Forty-three people with an average viral load of about 32,000 copies and CD4+ cell counts of about 600 participated in

this study. Participants received 50mg of TMC-120 twice a day, 100mg of TMC-120 twice a day or placebo for seven days, after which everybody received three-drug therapy. There was essentially no difference in viral load or CD4+ cell count response between the two doses of TMC-120, with about a one and a half log (32 times) reduction in viral load. CD4+ cell increases of 120 were seen at the end of the seven days.

One of the primary concerns with the NNRTIs is the potential for rapid development of resistance, especially when used alone or part of a sub-optimal regimen. No resistance was found among any of the individuals at the end of this study.

New Formulation of ddl Approved

After numerous failed attempts at developing a new formulation of ddl (Videx), Bristol-Myers Squibb has finally secured Food and Drug Administration (FDA) approval for a new version of the drug. The advantages of the new formulation are:

- It can be taken once a day.
- It can be taken at the same time as the protease inhibitors and other commonly used drugs, including indinavir (Crixivan), dapsone, ciprofloxacin (Cipro) and ketoconazole (Nizoral).
- It can be swallowed rather than chewed or mixed with water.

Unlike the old version, the new formulation does not contain any buffer so the likelihood of diarrhea as a side effect should be reduced. However, the studies using the new formulation did not show a reduction in diarrhea compared to the old version, but this is likely due to the fact that everybody in the study also took nelfinavir, a protease inhibitor that commonly causes diarrhea. The new formulation still has to be taken on an empty stomach, at least 30 minutes before or two hours after eating. ■

Nevertheless, the true test for this drug will be in how effective it is for people who have developed resistance to the current NNRTIs. Only when those studies are conducted will we learn whether this drug is really different from what is currently available.

The future of the new NNRTI capravirine is up in the air. Laboratory studies suggesting long-term side effects in some animals have put future studies on temporary hold. Inflammation of the blood vessels (vasculitis) was seen in some animals receiving a high dose of the drug. This has not been observed in any of the human studies of capravirine.

Preliminary results were reported from a study of capravirine in people who were experiencing increases in viral load while on a NNRTI-based regimen. The 61 participants had an average viral load of about 10,000 copies HIV RNA and CD4+ cell count of about 300 at the start of the

study. No one had previously used a protease inhibitor. All of the volunteers received nelfinavir (Viracept) + two new nucleoside drugs and 1,400mg or 2,100mg of capravirine twice a day or placebo. There was little difference in response rates after sixteen weeks among the three groups with 60–75% of participants having viral loads below 400 copies HIV RNA. However, people receiving capravirine experienced more side effects (diarrhea), especially those receiving the higher dose. Based on this small short-term study, it is difficult to determine exactly how much, if any, capravirine is contributing to the overall anti-HIV response.

Fusion Inhibitors

New results from a study involving T-20 (pentafuside) continue to show that the drug might be useful for people constructing a third line regimen. Seventy-one people with an average viral load of about

20,000 copies HIV RNA and CD4+ cell counts of about 230 received abacavir (Ziagen) + efavirenz (Sustiva) + ritonavir (Norvir) + amprenavir (Agenerase) with or without T-20. The dose of ritonavir and amprenavir used in this study was 200mg and 1,200mg respectively both taken twice a day and the dose for T-20 were 50mg, 75mg or 100mg all dosed twice a day by injection under the skin (subcutaneous). All of the participants had previously taken a protease inhibitor but not a NNRTI.

Caution: Garlic supplements

A recent study shows that garlic supplements decrease saquinavir (Fortovase) levels by an average of 51% and are therefore likely to greatly reduce saquinavir’s anti-HIV activity. This can lead to the rapid development of resistance to saquinavir. What effect this might have when saquinavir is used with small doses of ritonavir is unknown.

Many people use garlic supplements to reduce cholesterol levels or naturally manage yeast infections, and this is the second study to show that herbal or natural therapies can significantly reduce the levels of the anti-HIV drugs. A previous study showed that St. John’s Wort significantly reduced indinavir (Crixivan) levels.

Garlic supplements are likely to significantly reduce levels of the other protease inhibitors as well as the non-nucleoside reverse transcriptase inhibitors. As this study illustrates, there’s a definite potential for some herbal and nutritional supplements to lower the effectiveness of anti-HIV therapies or other medications. People who use these herbal or natural therapies should always discuss possible interactions with their doctors and pharmacists. ■

Drug Identification Chart

| INITIALS | GENERIC NAME | TRADE NAME | MANUFACTURER |
|--|-----------------------------|-------------|----------------------|
| Protease Inhibitors | | | |
| APV | amprenavir | Agenerase® | Glaxo SmithKline |
| IDV | indinavir | Crixivan® | Merck |
| LPV | lopinavir | 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® | Glaxo SmithKline |
| AZT | zidovudine | Retrovir® | Glaxo SmithKline |
| AZT+3TC | --- | Combivir® | Glaxo SmithKline |
| AZT+3TC+ABV | --- | Trizivir® | Glaxo SmithKline |
| ddC | zalcitabine | Hivid® | Hoffman-La Roche |
| ddI | didanosine | Videx® | Bristol-Myers Squibb |
| d4T | stavudine | Zerit® | Bristol-Myers Squibb |
| 3TC | lamivudine | Epivir® | Glaxo SmithKline |
| NtRTIs (Nucleotide Analog Reverse Transcriptase Inhibitors) | | | |
| TNV | tenofovir | | Gilead Sciences |
| Cellular Factor Inhibitors | | | |
| HU | hydroxyurea | Hydrea® | Bristol-Myers Squibb |

The results of the three T-20 doses were pooled together and after 16 weeks of the study 71% of people receiving T-20 had viral loads below 400 copies HIV RNA compared to 58% for those not receiving the drug. The percentage of people with viral load below 50 copies HIV RNA was 48% for those receiving T-20 and 37% for those not receiving the drug. Additionally, volunteers receiving T-20 had about a 50 CD4+ cell count increase whereas there was no change in CD4+ cell counts for those not receiving the drug.

A small expanded access program for T-20 should open within the next few months for people needing the drug to construct a third line regimen. Watch for announcements about the program and when you hear it, call the Project Inform Hotline to get the details on how to apply.

A second generation fusion inhibitor is now being studied. In laboratory studies T-1249 remains sensitive to virus that have developed resistance to T-20. Preliminary results from a small study shows that the drug does have activity against HIV; however, there were also a large number of mild-to-moderate side effects.

Seventy-two people with an average viral load of about 100,000 copies HIV RNA and CD4+ cell counts of 100 participated in this study. Almost all of the participants had been on previous anti-HIV therapies. Six different doses were studied ranging from 6.25mg once a day to 25mg twice a day all dosed by subcutaneous injection. Volunteers receiving the highest dose had an average 1.3 log (20 times) reduction in viral load after 14 days on the drug. Side effects included injection site

reaction (mostly pain or redness in the skin), headaches and dizziness. Two serious side effects were observed, a hypersensitivity reaction to the drug and neutropenia (a reduction in neutrophils, a type of white blood cell used to fight infections).

Protease Inhibitors

It is not clear whether the new protease inhibitor BMS-232632 will be effective against viruses resistant to the currently approved protease inhibitors. Nevertheless, one apparent benefit of the drug is there have been no reports of increases in triglyceride or cholesterol levels among people taking it.

The study enrolled 420 people with an average viral load of 50,000 copies HIV RNA and CD4+ cell counts of about 350. None of the participants had previously received anti-HIV therapies. All the volunteers received d4T (stavudine, Zerit) + ddI (didanosine, Videx) and either 200mg, 400mg, 500mg of BMS-232632 once a day or 750mg of nelfinavir (Viracept) dosed three times a day. Results were similar for all four groups with 63-68% of the participants achieving viral loads under 400 copies HIV RNA after 24 weeks and about 100 cell increase in CD4+ cell counts. Participants receiving nelfinavir had increases in cholesterol and triglyceride levels whereas those receiving BMS-232632 had no changes in either of these markers. A number of people had to reduce from the 500mg to the 400mg dose primarily because of an increase in bilirubin levels, a measure of liver function. As a result of this, future studies will be using the 400mg once a day dose.

Commentary

People who have exhausted their treatment options need new potent drugs, especially those that are effective against drug-resistant virus. Studies of these newer drugs suggest that they will offer some improvement over the current drugs. Furthermore, newer classes of drugs have recently entered studies, including drugs that block the chemokine receptors CCR5 and CXCR4, two 'pathways' that HIV uses to infect cells. ■

Head-to-Head Study of Two Protease Inhibitors

Results from a study comparing the recently approved protease inhibitor lopinavir (Kaletra) to nelfinavir (Viracept) as first line therapy were reported at a major International AIDS conference in Glasgow, Scotland. Lopinavir includes a new protease inhibitor along with a small dose of zidovudine in a single capsule. Seven hundred and fifty-three people with average viral loads of about 80,000 copies HIV RNA and CD4+ cell counts averaging 260 received either lopinavir or nelfinavir in combination with d4T (stavudine, Zerit) and 3TC (lamivudine, Epivir). After forty-eight weeks the results were as follows, using a strict "intent to treat" analysis:

| | < 400 copies HIV RNA | < 50 copies HIV RNA | Change in CD4+ cell counts |
|------------|----------------------|---------------------|----------------------------|
| Lopinavir | 75% | 67% | 207 |
| Nelfinavir | 63% | 52% | 195 |

Significantly more people receiving lopinavir achieved viral suppression below 400 copies and 50 copies, though there were no differences between the two groups in the magnitude of CD4+ cell increases. There were no significant differences in side effects, including changes in triglyceride levels, between the two groups although fewer people receiving lopinavir discontinued drug primarily due to rebound in viral load (virological failure).

These results are not completely unexpected. Previous studies have shown lopinavir to have very potent activity against HIV, even among people who have previously received protease inhibitors. Additionally there have been concerns about the long-term potency of nelfinavir. ■

Cidofovir

Results from an Italian study suggest that cidofovir (Vistide) may be useful for people with progressive multifocal leukoencephalopathy (PML). PML is a relatively rare disease in people living with HIV, affecting the brain. It is caused by a virus, called the JC virus. Most adults (about 80%) are exposed to this virus but it usually only causes disease in people with very low CD4+ cell counts. In rare circumstances, PML can occur in people with higher CD4+ cell counts (e.g. above 200).

PML is typically an aggressive and extremely unpleasant disease, often leading to a rapid and complete loss of mental faculties. Historically, the average time from PML diagnosis to death was about 90 days. Since the availability and use of potent anti-HIV therapies, however, the incidence of PML has fallen sharply and survival time after a diagnosis with PML has extended significantly, with a number of people having post-PML diagnosis survival of two to five years (and counting!).

Because PML affects the brain, diagnosing the disease is difficult and frequently it is diagnosed presumptively (i.e. based on symptoms and not definitive laboratory tests, which would include a brain biopsy). Treatments for PML are, at best, rather ineffective. The most common approach to treatment was an antiviral drug called ARA-C, although that drug was never proven to have a major effect against PML. Because ARA-C has many side effects and must be delivered directly into the brain, many people choose not to treat PML. Fortunately, some people have had an effective response against PML simply from using potent anti-HIV therapies.

The most recent study involved 40 people with PML all of whom were taking potent anti-HIV therapy. Fourteen were also given cidofovir, a drug approved for the treatment of cytomegalovirus (CMV). The dose of cidofovir used in this study was 5mg/kg every week for the first two weeks then 5mg/kg every other week. People receiving cidofovir had a more pronounced increase in CD4+ cell counts and prolonged survival compared to people receiving only potent anti-HIV therapy.

Further analysis of the results show that several factors contributed to prolonged survival: use of cidofovir, lower JC virus levels at the start of the study and starting potent anti-HIV therapy prior to developing PML.

Cidofovir is a very difficult drug to take. It has to be given by injection directly into the vein (intravenously) and has to be given with probenecid to reduce the risk of developing kidney toxicities. Even with the use of probenecid, a fair number of people have problems tolerating the drug. Still, the side effects of cidofovir seem less significant than those of ARA-C and pale when compared to the effects of a bad case of PML.

Commentary

While there are no standard of care guidelines for PML, this study suggests that the addition of cidofovir to potent anti-HIV therapy should be considered. However, the side effect profile for cidofovir is still of great concern. ■

Gilead Provides Expanded Access Program for Tenofovir

Gilead Sciences, the developers of a new nucleotide analogue, tenofovir (PMPA), will start a small expanded access program in January.

The most important use of this drug, for now, will probably be in people who have developed resistance to several of the NRTI drugs, like d4T (Zerit) and AZT (Retrovir), and need something new to shore up their combination therapy. It is less clear whether the drug will compensate for protease inhibitor failure. The initial program will begin small and expand during 2001 as drug supplies increase.

To qualify, people must have all of the following:

- Over 10,000 copies HIV RNA and CD4+ cell counts below 100 or CD4+ cell counts below 200 and a opportunistic infection within the past three months;
- Intolerance to and/or viral load increases to at least two protease inhibitors or one protease inhibitor and one NNRTI (for a list of the names and types of anti-HIV drugs, call Project Inform's Hotline); and
- Unable to construct a viable drug combination without tenofovir.

To register patients in the program, physicians should call 800-GILEAD-5 (800-445-3235).

As more drug supplies become available, the criteria to qualify will change. ■



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

www.projectinform.org

Making Decisions About Treatment

Making treatment decisions can feel overwhelming. Developing a personal plan to help you think about, plan for and make decisions can help. It's important that your plan is one you're comfortable with and feel empowered by. This article summarizes issues to consider as you develop your own decision-making plan.

Get informed! Learn about HIV disease and your treatment options! Whenever possible, get informed about treatments well before it's time to start. Starting treatment discussions with your doctor will greatly increase the chances that you will avoid starting therapy either too early or too late.

Find out what the research shows. Understanding HIV treatment research can be difficult at first and there is an overwhelming amount of information in circulation, often with widely differing points of view. Project Inform can help. We have objective information about HIV, treatment options and strategies. Though we try to make it the best source, Project Inform is not the only place to get information about HIV treatments and strategies. For a list of references, call the National HIV/AIDS Treatment Hotline and ask for the *Resource Guide to HIV/AIDS Related Resources*.

Explore, examine and challenge your beliefs about therapy. Concerns and fears about starting therapies are common. Learning about therapy can lessen concerns and help you decide whether and when treatment is right for you. In exploring your beliefs about a therapy or combination of therapies, you might find that you have come to a conclusion based on personal fears, rumors or biased advertising. Grounding yourself in knowledge, rather than fears, and challenging where possibly unfounded beliefs might be clouding decision-making is critical to making wise treatment decisions.

If, after considering the facts, you believe that an approach may be more harmful than its potential benefits, you might be better off considering another option. There

are many possible therapies and strategies to choose from, and none of them are right for everyone. You can always revisit your decision at a later time. Don't reject what you believe about therapy—explore, examine and challenge those beliefs—and weigh them in with other considerations.

Learn about the experience of friends and people you trust. Talk to friends, support groups and others who are experiencing similar health conditions. Ask about what kinds of treatments they're using. Why did they choose certain treatments and what have their experiences been?

While learning about the experiences of others can be helpful, it's important to keep an open mind. Just because someone you know had a bad or good experience with a particular therapy doesn't mean that *you* will. The most reliable picture of a therapy's actions will come from well-designed studies, and even these cannot predict how *you* will respond.

Ask your doctor's opinion about the therapy that you are considering—what is it and what is it based on? Does the doctor have advice about whether a particular therapy might be helpful for you? Has the doctor followed other people using the same approach?

Get as much information as possible, from a variety of sources you trust. It's better to make an informed decision that you feel comfortable with than a hasty one.

Once You've Made A Treatment Decision, Then Consider ...

When to start? There is no one proven "right" time to start anti-HIV therapy.

There are differences of opinion about starting therapy early in the course of HIV infection vs. later. Either choice has possible long-term consequences. Deciding on your own criteria, with the guidance of your doctor, lets you be in control of your treatment decisions. The article on page 1 of this *PI Perspective* provides an in depth discussion on when to start therapy.

How to monitor whether a therapy is working for you? *Before* starting a therapy, it's important to have realistic expectations about what it will do and determine how to monitor its effectiveness. For anti-HIV therapy, typically you will look for decreases in viral load (HIV RNA), increases in a measure of immune health (CD4+ cell counts) and improvements in overall general health.

Determining if a complementary therapy is working, when it doesn't have any direct anti-HIV activity, can be more difficult. Talk to your doctor and work together to develop realistic ways of determining if the product you want to use is working. If after some agreed upon period of time you are not achieving your goals, agree to revisit the use of the therapy you are trying. Have these discussions *before* you start taking the therapy.

Consider what you might do if your current or pending option doesn't work, causes too many side effects or for other reasons doesn't fit with your lifestyle.

How to monitor (and manage) potential side effects? *Before* you start a therapy, learn about potential side effects, how to monitor for them and how to manage them. But don't automatically assume that you will experience any particular side effect. Many people who start or switch to a new anti-HIV regimen will experience some side effects or symptoms. These may include headache, nausea, diarrhea and/or tension. Often these go away within four to

six weeks and not everyone experiences them. Some therapies have potentially life-threatening side effects that occur only very rarely. You can learn to watch for early signs of serious effects and what to do if they arise. (Read Project Inform's *Drug Side Effects Chart for more information*.) It's just as true, however, that many people do not experience any significant side effects, and that some people perceive the severity of side effects differently.

When to switch therapy and what you might switch to (if necessary)? Many people are making strategic decisions about therapy that look years into the future instead of days or weeks. To do this, think about how the therapies started today will affect options later. Consider what you might do if your current or pending option doesn't work, causes too many side effects or for other reasons doesn't fit with your lifestyle.

When to stop? How do you determine when a given therapy or approach just isn't working for you? At what point do you say that the cost or potential risks associated with using the therapy isn't worth the potential benefits of staying on it? Working with your doctor before you start therapy to develop some criteria around this—that you both feel comfortable with—is important.

In all of these areas you might come to decisions and agreements with your doctor that change over time. Your expectations of a therapy may change as you learn more and as new information becomes available. Changing your mind and rethinking your strategies are healthy and normal parts of evolving a decision-making process.

Conclusion

Developing a treatment decision-making plan offers many benefits, but it also takes effort on your part. The likelihood of benefiting from therapy increases and the likelihood of experiencing serious side effects decreases when you are involved in decision-making and monitoring. For a more complete discussion of these issues, contact Project Inform's Hotline at 1-800-822-7422 and request, *Making Decisions About Therapy*. ■

Lipodystrophy Update — The Continuing Saga

The different manifestations of lipodystrophy syndromes have been extensively reported on in the past few issues of *PI Perspective*. Small studies are now shedding light on how some anti-HIV therapies may play a role in the syndromes, but these findings are by no means conclusive.

Mitochondria and Anti-HIV Therapy

Early results from a small study show that people on nucleoside analogue reverse transcriptase inhibitors (NRTIs) have fewer mitochondria in cells compared to HIV-positive people not taking NRTIs or HIV-negative people. Mitochondria can be likened to the energy source of cells. This reduction in mitochondria was only seen among people taking d4T (stavudine, Zerit) and was not seen among people on any other NRTI. The average number of mitochondria in cells decreased by 44% among people on d4T. One interesting but unexplained observation from this study was that people with fat loss in the face, arms or legs (called *lipoatrophy*) had decreased number of mitochondria in cells whereas people who had developed an accumulation of fat at the base of the neck (sometimes called *buffalo hump*) had an increase in the number of mitochondria. For more information, call Project Inform's Hotline and ask for *Mitochondrial Toxicity and Lactic Acidosis*.

Another recent study also looked at the number of mitochondria in cells. Forty people participated in this study, ten with fat wasting (group A), ten without any signs of fat redistribution (group B), ten people who had never taken anti-HIV therapies (group C) and ten HIV-negative people (group D). The number of mitochondria in cells was looked at from tissue samples from the back of the neck, the abdomen area and the mid thigh. This study found that people in group A had fewer mitochondria in cells than those in group B who in turn had fewer mitochondria in cells than those in group C or D. There were no differences

in the number of mitochondria found in cells between people in groups C or D. This clearly suggests that the reduced level of mitochondria is a result of anti-HIV therapies rather than HIV disease itself.

New results suggest that each protease inhibitor may make different contributions to the changes in body composition that have been observed in some people with HIV.

Protease Inhibitors and Changes in Body Composition

New results suggest that each protease inhibitor may make different contributions to the changes in body composition that have been observed in some people with HIV (called *lipodystrophy syndrome*). A group in Seattle previously reported when ritonavir (Norvir) was given to HIV-negative people for two weeks, they experienced a significant rise in cholesterol and triglyceride levels. Now a group from San Francisco has given indinavir (Crixivan) to HIV-negative individuals for four weeks. There were no significant increases in cholesterol or triglycerides but people had a marked decrease in insulin sensitivity (a marker associated with diabetes), something that was not studied by the Seattle group. Changes in these markers associated with the way the body uses fats and sugars are believed to be part of the lipodystrophy syndrome.

One small study suggests that the use of human growth hormone may be of some benefit for people with fat accumulation. Seven people, four of whom had a buffalo hump and three with accumulation of fat behind the muscle in their midsection (called *abdominal or central obesity*), received 3mg/day of human growth hormone for six months. Five people completed the six months course of treatment, one person had to stop because of elevated glucose levels and another moved away from the study site. All five who completed the six-month course of growth hormone had a decrease in fat accumulation with an average reduction of 4.4kg (about 10 pounds) in total fat and a 5.4kg increase in muscle mass (also called *lean body mass*). It is not clear, however, whether this loss of fat represented a correction of the problem of lipodystrophy at specific sites or was just the normal outcome of the use of growth hormone, which favors the growth of muscle tissue over fat accumulation in general.

After many years of detailing the different syndromes associated with lipodystrophy, there are finally some hints on the cause. However, these are preliminary results and they need to be confirmed. Another complicating factor is whether all of the therapies belonging to the same class of drugs will have the same effect and therefore cause the same side effect. It may be necessary to do these types of studies for each drug.

Two Studies Provide Additional Information

A study of 100 people shows that those taking d4T (stavudine, Zerit) are more likely to have fat loss compared to those taking AZT (zidovudine, Retrovir). All of the participants had previously taken AZT, ddI (didanosine, Videx) and/or ddC (zalcitabine, Hivid) but not any other anti-HIV therapies.

During this study, volunteers received 3TC (lamivudine, Epivir) + indinavir (Crixivan) and either AZT or d4T. There was no difference in anti-HIV response between the two groups after 30 months. Additionally no differences in fat accumulation, cholesterol, glucose or triglyceride levels were seen between the two groups. However, people taking d4T had more fat loss in the arms, legs and buttocks. Seventy percent of people taking d4T experienced some fat loss compared to 43% of people taking AZT.

This study found that older age, lower CD4+ cell counts and female gender were associated with increasing risk for fat loss. This is the first study to show that women may be more likely to experience fat loss, whereas several other studies have already shown that women are more likely to experience fat accumulation than men.

Results from a small study show that gemfibrozil (Lopid) may help lower triglyceride levels. Thirty-two people with elevated triglycerides, and who were on a protease inhibitor-based regimen, participated in this study. All were on a low saturated fat diet and received gemfibrozil or placebo. People receiving gemfibrozil had a small reduction in triglyceride levels, but only one had a return to 'normal' levels. There were no changes in cholesterol or glucose levels for the two groups.

These results suggest that gemfibrozil by itself is not sufficient to lower triglyceride levels, especially in people who are continuing a protease inhibitor-based regimen. Gemfibrozil may need to be used in combination with another lipid lowering drug for optimal effect in people with HIV. ■

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 results 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.

National HIV/AIDS Treatment Hotline



Project Inform's toll-free hotline provides HIV/AIDS treatment information to people living with HIV, their healthcare and service providers, and family members.

1-800-822-7422

Women and Pharmacology ♀

There are known and potential considerations for women with regard to how drugs are processed in the body, a field of study called *pharmacology*. Studies describing some of these note sex differences in metabolism, drug levels and/or side effects. This article highlights some important observations for women living with HIV.

Delavirdine Study

Project Inform has previously reported on a study that looked at differences in blood levels of the NNTRI drug, delavirdine (Rescriptor) in men and women. As with almost all drugs, the amount of delavirdine in the blood rises to a high or peak level after taking the drug and then gradually declines to a *trough* or lowest level just before taking the next dose. But this study showed that women who took delavirdine (Rescriptor) + AZT (Retrovir) had nearly twice the amount of delavirdine (1.8 times more) in their blood at trough levels than men, even though both were taking exactly the same doses.

... it is critical that sufficient numbers of women participate in studies of new therapies, as well as other studies that may reveal potential sex differences.

Potential explanations for this difference include weight and body mass differences and hormonal influences. Whatever the cause, the study suggests that women may absorb drugs differently than men in some cases and that researchers should be careful to watch for this effect.

Ritonavir Study

In addition to higher drug levels in blood, some studies have reported increased or varied side effects associated with anti-HIV drug use in women. A study looking at ritonavir (Norvir) showed that women ex-

perienced more nausea, vomiting and malaise than men. Some women also experienced a unique and potentially dangerous side effect caused by ritonavir—excessive menstruation.

While the cause of these differences remains unknown, like the delavirdine study, it also suggests that women and men might need different dosage levels of drugs to lessen these effects. Little research has taken place to evaluate different dosing schemes in women, and it remains unknown if or how people might safely decrease doses and maintain potency and durability of a drug when faced with side effect concerns. In the short-term, it's probably unwise to simply decrease doses of anti-HIV drugs to manage side effects. Reduced dosing might result in lower side effects, but it may also cause the drug to fail or the virus to develop resistance to it.

Therapeutic drug monitoring, a testing process that may tell people the actual blood levels of the drugs they are taking, is currently being evaluated and may shed light in these areas. While still in the research phase, it's important that women seek out and participate in studies that include this new technology so that more information is gleaned that includes the experiences of women.

Drug Interactions

Drug interactions between anti-HIV therapies and other drugs commonly used by women are another important pharmacologic consideration. For instance, it is known that some protease inhibitors decrease the level of estrogen among women receiving hormone replacement or oral contraceptives, whereas the protease in-

hibitor indinavir (Crixivan) and the NNRTI efavirenz (Sustiva) increases the level of estrogen.

Practically speaking, women on protease inhibitors should be counseled on how to alter the dose of their oral contraceptives or hormone replacement therapy to maintain effectiveness and/or use alternative methods of birth control. Additionally, this also suggests that some protease inhibitors might decrease the natural level of estrogen in women, leading to other potential health considerations associated with low estrogen levels (such as early menopause and/or loss of bone density).

Commentary

As the field of HIV drug pharmacology becomes more complicated, many basic questions remain regarding differences in women. In order to answer these questions, it is critical that sufficient numbers of women participate in studies of new therapies, as well as other studies that may reveal potential gender differences. Industry, government and community must work together to prioritize these research areas and to address the barriers that remain for women's involvement in research. ■

Project WISE, Project Inform's HIV treatment information and advocacy program for women, is pleased to announce the availability of its publication, *"Positive? How are you feeling?"* This colorful and informative booklet for women living with HIV focuses on physical and emotional wellness in the context of providing basic information on HIV disease and its management. The latest issue of *Wise Words* (#7) "Is Switching or Stopping Therapy Right for You?" is also available.

These publications are available in English and Spanish and can be ordered by calling Project Inform's National HIV/AIDS Treatment Hotline at 1-800-822-7422. They are also available on Project Inform's website at www.projectinform.org.

Women's Highlights from the 8th Retrovirus Conference ♀

The eighth conference on Retroviruses and Opportunistic Infections was recently held in Chicago. Below are some items that may be of particular interest to women.

Pregnancy Issues

A recent and highly celebrated study (HIVNet 012) showed that one dose of nevirapine (Viramune) given to a woman in labor and one dose given to the newborn within the first 72 hours can reduce the risk of mother-to-child HIV transmission by about 50%. A new study shows that, when the two-course nevirapine regimen is added on top of other anti-HIV regimens commonly used during pregnancy (including AZT, AZT+3TC, and other combinations with and without a protease inhibitor), it offers no additional or unique preventive benefit. Thus, nevirapine is not needed if the HIV-positive woman is already on an effective HAART regimen, but it has clear value when used alone as a simple two-dose regimen for reducing the risk of transmission.

These days, use of powerful anti-HIV therapies have helped make transmission of HIV from mother to child a rarity. However, at the same time, there have been several cases of mother-to-child transmission of drug-resistant HIV, including multi-drug resistant HIV. Most of these have occurred in the setting of detectable viral load or high viral load during pregnancy, despite the use of anti-HIV therapies.

A few studies explored concerns about the prevalence and effect of drug resistance during pregnancy. One found that resistance to AZT at time of delivery was common among those who had received the drug prior to pregnancy. After adjusting for maternal viral load, CD4+ cell count and duration of labor, it also found that AZT resistance was independently linked to an increased risk of HIV vertical transmission. Additionally, the nevirapine study discussed above also found that resistance mutations

associated with nevirapine at the time of delivery and six weeks after are common and may increase with lower CD4+ cell count (below 400). It also found that resistance to reverse transcriptase inhibitors and protease inhibitors were common. It is unknown whether resistance to these drugs increases risk of HIV transmission.

While there is still a lot to learn about the prevalence and risks of resistance during pregnancy, it remains an important concern. The prognosis for babies born with drug-resistant virus is poor. Pregnant women who are taking anti-HIV therapies, especially before pregnancy, are now encouraged to undergo a resistance test. This will help women and their doctors construct the most effective anti-HIV regimen in the course of pregnancy, minimizing potential risks linked to drug resistance, including the potential increased risk of mother-to-child HIV transmission.

While there is still a lot to learn about the prevalence and risks of resistance during pregnancy, it remains an important concern. The prognosis for babies born with drug resistant virus is poor.

Finally, a European study investigated the impact of pregnancy on CD4+ cell counts in women that became pregnant in the course of the study. All women had a known date of when they became HIV-positive (seroconversion). The study found that

pregnant women had slightly lower CD4+ cell counts than non-pregnant women (401 vs. 450). In general, pregnant women have lower CD4+ cell counts than women who are not pregnant. During pregnancy CD4+ cell counts decline temporarily, but return to pre-pregnancy levels after the child is born. This return to pre-pregnancy CD4+ cell levels occurred in this study as well. These results suggest that pregnancy—and potentially hormonal changes that occur therein—does impact CD4+ cell count, though they do not seem to have an overall negative impact on HIV disease progression rates.

HPV Update

Human Papillomavirus (HPV) is the sexually transmitted disease that causes genital warts, anal and cervical pre-cancerous conditions (called *dysplasia*) and, in severe cases, cancer. More serious HPV-related problems are common in HIV-positive women than HIV-negative women. In order to prevent this, it's recommended that HIV-positive women have a Pap smear at least every six months and more frequently if results are abnormal.

Women with abnormal Pap results usually undergo what is considered a more sensitive screening technique called colposcopy. Sometimes, but not always, colposcopy is accompanied by biopsy. The results of these tests are then used to determine the most appropriate course of treatment.

A new study by the Women's HIV Interagency Study (WHIS) shows that colposcopy alone, without an accompanying biopsy, does a poor job showing cervical abnormalities. Because identifying the degree of the problem is critical in treating it, the study suggests that biopsy—which can best show the degree of damage—should become a routine component of colposcopy. But because biopsy can hurt and cause bleeding, it may not be preferable for everyone. Colposcopy plus biopsy may best be warranted in women most at risk for high-grade cervical abnormalities, such as those women with a history of problems related to HPV and/or lower CD4+ cell counts. ■

New Warning for Pregnant Women on the Use of ddI and d4T ♀

A recent warning has been issued cautioning pregnant women about the use of ddI (Videx) in combination with d4T (Zerit) because of increased risk of *lactic acidosis*, a potentially life-threatening condition. Lactic acidosis occurs when the cells in the body cannot convert food into usable energy and as a result there is an excess accumulation of the acid that can damage different organs (primarily the liver) in the body. The new recommendation suggests that pregnant women only use this combination when the benefits may outweigh the risks and that they should be closely monitored for lactic acidosis and liver damage.

Lactic acidosis is a recently recognized side effect now believed to be associated with the nucleoside analogue drugs (AZT, ddI, d4T, 3TC and abacavir). Several recent studies suggest that people on ddI and d4T may be more likely to develop this side effect. In early stages of lactic acidosis, people sometimes experience a shortness of breath, nausea, vomiting and a pain in the gut. If any of these symptoms occur, contact your doctor as soon as possible. For more information on lactic acidosis, contact Project Inform's Hotline and ask for *Mitochondrial Toxicity and Lactic Acidosis*. ■

Spotlight on Interleukin-2 (IL-2, Proleukin)

Interleukin-2 (IL-2) is a naturally occurring immune chemical that stimulates CD4+ cells to reproduce. A manmade version is undergoing evaluation as a therapy for HIV infection in two large international studies, called SILCAAT and ESPRIT respectively. Prior to the Conference on Retroviruses and Opportunistic Infections, investigators from both studies met to discuss new data and update one another on the progress of their studies. Additionally, a number of studies involving the use of IL-2 therapy were presented at the Chicago conference.

How Does IL-2 Work?

When someone has increases in their CD4+ cell counts, there could be several explanations as to where these cells are coming from. Dr. Cliff Lane of the National Institutes of Health (NIH) summarized a collection of experiments to shed light on what might be influencing CD4+ cell count increases seen with IL-2. During IL-2 therapy there is a dramatic increase in CD4+ cell reproduction, but overtime IL-2 actually results in a decrease in CD4+ cell reproduction. Interestingly, the way IL-2 therapy may be affecting increases in CD4+ cell counts overtime is by prolonging the survival of cells. This is a new theory and will likely become the focus of further research.

IL-2 Study Results

Unlike anti-HIV drugs that are taken daily, IL-2 therapy is taken twice daily for five days, usually every eight weeks. If people experience large and lasting CD4+ cell count increases, they are then encouraged to decrease the frequency of five-day courses of IL-2 in an attempt to maintain CD4+ cell counts. In this article, when IL-2 therapy is referred to, it infers intermittent five-day courses of IL-2 therapy. Most studies used either a twice daily dose of either 4.5 or 7.5 million international units (MIU) of IL-2. In all studies, unless otherwise noted,

IL-2 therapy was delivered through injection under the skin (called subcutaneous injection).

CPCRA 059 is a 511-person study of IL-2 in people with CD4+ cell counts of 300 and above. People received IL-2 or no IL-2 in addition to anti-HIV therapy. Volunteers had CD4+ cell counts of about 540 when they entered the study. Among those receiving IL-2, CD4+ cell counts increased to about 850 over the 12 months of study. Those who received only anti-HIV therapy experienced no change in CD4+ cell count over the study period. Viral load levels were similar between the two groups. It is anticipated that volunteers in the CPCRA 059 study will "rollover" into the larger IL-2 study called ESPRIT, which will follow people for about six years.

Unlike anti-HIV drugs that are taken daily, IL-2 therapy is taken twice daily for five days, usually every eight weeks.

An *ESPRIT Vanguard* study in the United Kingdom enrolled 36 people with CD4+ cell counts above 300, 24 received IL-2 and 12 did not. Neither group received anti-HIV therapy. There were no

differences in viral load between the two groups at 64 weeks. Those receiving IL-2 experienced CD4+ cell increases from about 400 to 650. Those receiving no IL-2 therapy experienced a slight CD4+ cell count increase from about 480 to 500. The CD4+ cell count increases observed were less pronounced than those seen in other *ESPRIT Vanguard* studies that included anti-HIV therapy. The researcher speculates that more profound increases can be realized with the concurrent use of anti-HIV therapy.

Women of color had the most pronounced increases in CD4+ cell counts, men of color and white women had equivalent responses and white men had the least dramatic increases.

An AIDS Clinical Trials Groups study (ACTG 328) evaluated the use of IL-2 in people with CD4+ cell counts between 50 and 350, who achieved viral load suppression to below 5,000 copies/ml after twelve weeks of anti-HIV therapy. After twelve weeks of anti-HIV treatment resulting in viral control, people received IL-2 therapy

intravenously (in the vein), by injection or no IL-2 therapy in addition to their anti-HIV treatments. A total of 161 volunteers were included in the 84-week analysis. Results after 84 weeks are summarized below in Table 1.

After 84 weeks those receiving IL-2 had substantial increases in CD4+ cell counts compared to those receiving only anti-HIV therapy. Viral levels were similar between the three groups. Those receiving IL-2 experienced expected side effects associated with five-day courses of therapy, primarily flu-like symptoms.

A study in France, ANRS 82, delivered IL-2 therapy to people who despite long-term anti-HIV therapy had not had their CD4+ cell count go above 200. Participants had CD4+ cell counts between 25 and 200 and viral load below 1,000 copies/ml, despite at least six months of anti-HIV therapy. Most had been on anti-HIV therapy for about 1½ years. At study entry the average CD4+ cell count in the IL-2 group was about 150 and about 140 in the group that did not receive IL-2 therapy (Table 2).

After 24 weeks, the group receiving only anti-HIV therapy was offered IL-2. In essence, after the 24 week (6 month) mark, everyone received IL-2 and thus differences between the two groups can be viewed as the difference between immediate or delayed IL-2 therapy in people with CD4+ cell counts below 200.

This study led the French government to approve IL-2 therapy for people with CD4+ cell counts below 200. After 80 weeks, except for one case of KS progression seen early in the course of the study, there have been no new AIDS-defining diseases in the group.

The National Institutes of Health (NIH) has conducted the most studies using IL-2. They have followed a number of people who have been receiving IL-2 therapy for six to seven years. The NIH conducted an analysis combining groups receiving injectable IL-2, which included 77 people who elected to participate in the extension phases from three different studies. CD4+ cell counts increased from a mean of 540 to about 1,130 over the course of observation. Each person has used about 10 five-day courses of IL-2 to achieve and maintain these numbers. The mean interval since the last course of therapy is 26 months, slightly over two years, to maintain counts.

This collection of studies show that IL-2 therapy can produce a dramatic and sustainable increase in CD4+ cell counts in people living with HIV.

Table 1

| | Increase in CD4+ Cell Count | % < 50 copies/ml HIV RNA |
|------------------------|-----------------------------|--------------------------|
| Anti-HIV therapy alone | 100 | 84% |
| Subcutaneous IL-2 | 240 | 83% |
| Intravenous IL-2 | 310 | 71% |

Table 2

| | % CD4 >200 @ 24 Week | % CD4 >200 @ 80 Weeks |
|------------------------|----------------------|-----------------------|
| Anti-HIV Therapy Alone | 33% | 83% |
| IL-2 | 81% | 93% |

Factors Associated with CD4+ Response to IL-2 Therapy

In the CPCRA 059 study it was found that white race and nadir (lowest ever) CD4+ cell count were associated with less robust CD4+ cell count responses. People of color had a better CD4+ cell count increase after three courses of IL-2 therapy compared to the white people. Women of color had the most pronounced increases in CD4+ cell counts, men of color and white women had equivalent responses and white men had the least dramatic increases. CD4+ cell count increases were dramatic among all groups, however. Also, the lower a person's lowest ever CD4+ cell count (nadir CD4+ cell count), the less likely the person is to experience robust CD4+ cell count increases in response to IL-2 therapy.

Conclusion

This collection of studies show that IL-2 therapy can produce a dramatic and sustainable increase in CD4+ cell counts in people living with HIV. After an initial increase is realized, typically occurring within four to six cycled five-day courses of IL-2 therapy, maintaining CD4+ cell count increases with IL-2 usually requires only yearly therapy in people who start IL-2 when CD4+ cell counts are high (above 300). Among those who initiate IL-2 when CD4+ cell counts are lower, increases greater than what is seen in people taking anti-HIV therapy alone are realized. Those with CD4+ cell counts below 200 who do not experience increases above 200 despite initiating anti-HIV therapy are likely to realize this gain with the use of IL-2.

Nearly everyone taking IL-2 does experience some side effects during the course of therapy, usually worsening over the five days and resolving when therapy is stopped at the end of the five-day course.

IL-2 is not without side effects and those contemplating study participation or using IL-2 “off-label” are advised to learn about potential side effects and side effect management before initiating IL-2 therapy. IL-2 users note that side effects can be lessened and managed with proper planning. Nearly everyone taking IL-2 does experience some side effects during the course of therapy, usually worsening over the five days and resolving when therapy is stopped at the end of the five-day course. For more information on these and other studies of IL-2 presented in Chicago and/or a discussion of IL-2 and side effects, call the Project Inform hotline. ■

New Presidential Administration Presents New Challenges

The inauguration of George W. Bush as President has created anxiety and uncertainty among HIV/AIDS advocates. For the first time in eight years, we have a new President and Administration. This change brings many unknowns and some definite challenges.

President Bush said little during his campaign about HIV/AIDS, and does not have much of a record on the issue as governor of Texas. However, as governor, his actions on healthcare do raise concerns. In addition, one of the first actions from the Bush administration was a renewal of the ban on funding for international organizations engaging in family planning. This is a serious and troubling indicator of the Bush Administration’s approach to health policy.

President Bush did make a few statements on HIV/AIDS issues as a candidate. He has “promised to do his part” to fight AIDS. He has proposed doubling the National Institutes of Health’s budget, which should increase AIDS research activities proportionately, and he is on record as supporting the Ryan White CARE Act.

In a letter to *Numedix*, a quarterly HIV medical journal, Bush stated his support for a “permanent extension of the research and development tax credit for pharmaceutical companies that are currently conducting research and development on drugs to combat AIDS.” In that same letter, Bush stated that he supports increased funding to sub-Saharan Africa to fight HIV, with unspecified safeguards to ensure that U.S. money is actually being spent on those in need. He also pledged his support for medical privacy legislation.

However, while Bush has indicated his support for HIV prevention programs, he is on record opposing needle exchange programs. He has also pledged that he will make funding for abstinence education a priority.

President Bush’s choices for his Cabinet send more mixed messages about his commitment to fighting HIV/AIDS. He appointed Wisconsin Governor Tommy Thompson as Secretary of Health and Human Services. According to many advocates in Wisconsin, Governor Thompson has demonstrated a strong commitment on HIV/AIDS issues. He has ensured adequate funding for the AIDS Drug Assistance Program and supported

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 x313, FAX to TAN Coordinator at 415-558-0684, or email TAN@projectinform.org.

