



AIDS 2002 Barcelona

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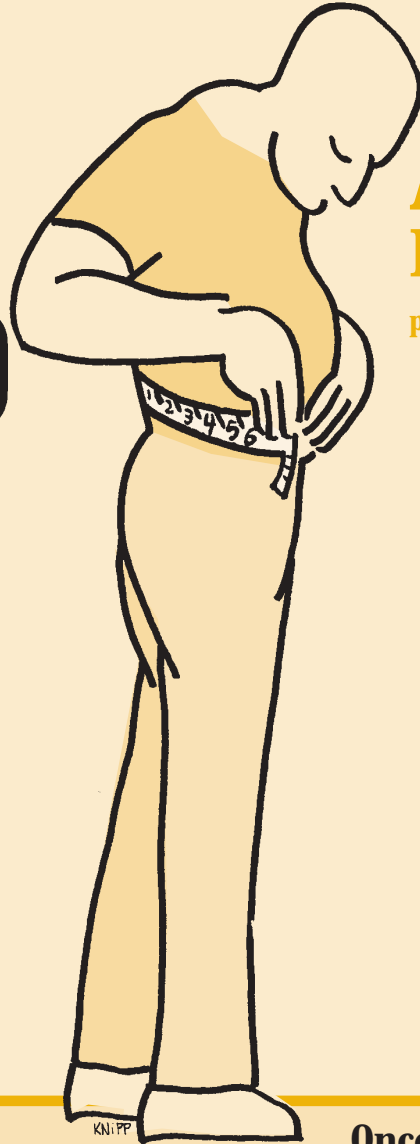
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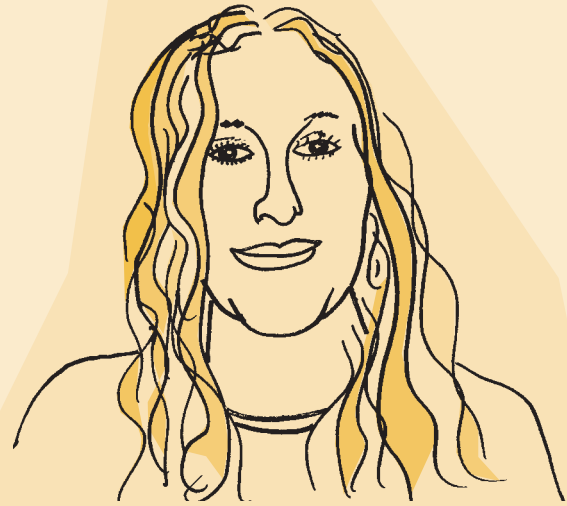
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your HIV/AIDS treatment journal



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One Last Item

Our mission is to supply up-to-date, factual information of the pros and cons of promising treatments for HIV infection and its manifestations. We believe that such information empowers persons with HIV to make intelligent decisions in consultation with their healthcare providers. Participation in the preparation of a STEP *Perspective* article does not imply an endorsement by a PAC member. Rather, it is merely a reflection of their donated time and professional expertise.

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AIDS 2002 Barcelona & Seville

XIV International AIDS Conference & HIV Resistance Meeting



This year, the biannual International AIDS Conference (IAC) was held in Barcelona, Spain, preceded by the HIV Resistance meeting in Seville, Spain. While STEP did not attend these meetings, we have followed closely the reports from these meetings and present the highlights below. The focus and emphasis of this year's IAC was clearly on getting antiretroviral drug treatment to the vast majority of people living with HIV in the developing world. The United States has about 900,000 cases of HIV infection, while Southern Africa has over 28 million people living with HIV infection! About 5 million people have died of AIDS since the last IAC, two years ago in South Africa. In spite of all the talk about funding AIDS treatment programs, the funding for the UN's Global AIDS Fund remains very poor. Also, AIDS treatment activists were very vocal and visible, protesting high drug prices and a speech by U.S. Secretary of Health and Human Services Tommy Thompson.

International AIDS Conference Highlights

The highlights of the HIV treatments studies reported at the IAC are summarized below. These were follow-up reports on T-20, reports of early human trials of the new class of drugs called integrase inhibitors, the report of a large strategy trial conducted by the AIDS Clinical Trials Group (ACTG), and the report of the use of Viread (tenofovir) in previously untreated people.

T-20: An Entry Inhibitor

T-20 is known as an entry inhibitor, because it is a compound that interferes with the ability of HIV to enter into the T-cell. Trimeris, who owns T-20, has filed with the FDA for approval in the U.S., and approval is expected later this year. The drug is a small protein that is not absorbed in the stomach and must be given as an injection under the skin, twice a day. However, T-20 has been shown to cause impressive reductions in levels of the HIV virus in the blood (or viral load) when added to other drugs in people with multiple drug-resistant mutations.

Two presentations reported on results from ongoing T-20 trials, in which T-

20 added to other HIV drugs is compared to a placebo injection. Both studies observed that the group that received T-20 had twice the viral load decrease compared to the placebo group. These results were maintained over 24 weeks, although it is known that resistance to T-20 does develop in some people. Almost all people had nodules develop at the injection sites that did not go away completely over time. This drug will be of help to people with HIV with multiple drug resistances.

Integrase Inhibitors Finally in Clinical Trials

Many compounds have been evaluated for their ability to inhibit integrase, the unique HIV enzyme that allows the virus to copy its genetic message into the body's cellular DNA. In the past, all of these compounds were too toxic to move into human trials, but reported at the IAC were two more integrase inhibitors that have passed all the animal toxicity testing and are moving into early clinical trials to determine safety and dosing. These are S-1360 and L-870,810. S-1360 was administered to 18 HIV-negative

people for 14 days and no significant side effects were observed. L-870,810 was well absorbed in animal testing and had good levels in the blood. This compound will now move into human testing. Thus, the search for a new class of drugs to target another HIV enzyme may finally be producing some compounds.

A Large Strategy Trial in Previously Untreated People

The ACTG presented for the first time the results of a large, complicated study in treatment-naïve (never treated before) people, Study 384. The study included two separate sets of comparisons in what is called a factorial design. The nucleoside reverse transcriptase inhibitor (NRTI) combination of AZT/3TC was compared to d4T/ddI. Also the initial use of a non-nucleoside reverse transcriptase inhibitor (NNRTI) (Sustiva) was compared to a protease inhibitor (PI) (Viracept), and also to a combination of the PI plus the NNRTI. In the PI and NNRTI groups, when virologic failure or toxicity developed, participants were switched to the alternate combination of NRTI

continued next page



and either the PI or NNRTI. There were two basic questions being asked in this study. First, how does the use of AZT/3TC compare to d4T/ddI? Second, how does the strategy of the use of a 4-drug combination compare to the use of two sequential 3-drug combinations? Since this is a complex study, the table below may be helpful in understanding the six possible treatment groups that the 980 people participating in this study were randomized to.

	NNRTI (Sustiva)	PI (Viracept)	NNRT/PI
AZT/3TC	A	B	E
D4T/ddI	C	D	F

When people in group A failed, they were switched to group D, when people in group B failed; they were switched to group C, and so forth. The groups E and F were considered treatment failures when they failed their first 4-drug regimen.

The most important result of this study is that the success rate of using two sequential 3-drug regimens was the same as using a 4-drug regimen. A secondary finding of the study was that the group that performed the best on their first regimen was group A, the group that received Sustiva/AZT/d4T.

A subsequent preliminary presentation was given a few weeks later at the summer Adult AIDS Clinical Trial Group (AACTG) meeting in Washington, D.C., reporting on the metabolic substudy of 384. The future results of the metabolic substudy may be of more interest than the primary study, as comparison can be made between an NNRTI versus a PI-containing regimen, and between AZT/3TC and d4T/ddI. The preliminary data presented in Washington showed that peripheral fat loss was greater in the d4T/ddI group. There was also greater toxicity associated with the d4T/ddI combination, particularly neuropathy. Fu-

ture results will include measures of cholesterol, insulin resistance, and other metabolic comparisons from Study 384.

Viread (Tenofovir) in Previously Untreated People

Results of a trial comparing Viread/Sustiva/Epivir to Zerit/Sustiva/Epivir in 600 people were reported. Study 903 found that these two regimens were equally effective in viral load suppression and T-cell increases after 48 weeks of treatment. Between 81 and 82 percent of people achieved viral loads below 50 copies per mL of blood in both groups at 48 weeks. Viread was approved by the FDA to be used as part of a salvage regimen. The results of this trial also support consideration of the use of Viread in previously untreated people. Gilead will be asking the FDA to include this use in its product labeling. Viread is taken once a day, with food, and is well tolerated by most people. It does not appear to cause mitochondrial toxicity. (See the article on mitochondrial toxicity in this issue of the *STEP Perspective*.)

Bare-Backing Superinfection Dangers

There was a great deal of press attention given to a report of what appears to be a very well documented case of infection with a second, stronger strain of HIV, in someone doing well and not on antiretroviral therapy. The person had been treated at the time of initial (primary) HIV infection and did well after a couple of treatment interruptions, maintaining a low viral load. However, the person had a sudden large increase in their viral load and very sophisticated testing demonstrated that the person was infected with a second strain of HIV, which the immune system was unable to contain. The fact that a person could be reinfected (so-called "superinfection") has been known for some time, but this was the first well documented superinfection. What is of greater significance, however, is that while the person had evidence of strong HIV-specific immune

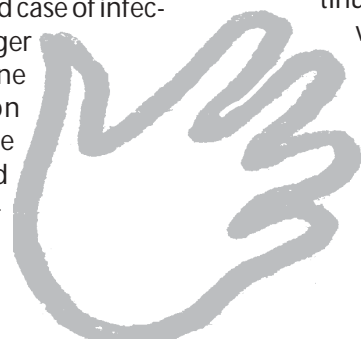
responses, these immune responses did not protect from a second HIV infection. This raises serious concerns about the ability of any HIV vaccine to protect someone from HIV infection. This case also reinforces the dangers of "bare-backing" amongst HIV-positive persons. **It is possible to be reinfected—with a more aggressive, or even drug-resistant, strain of HIV.**

Changing HIV Treatment Guidelines: Is It Safe to Stop HAART?

A reassuring, but small, study reported on the outcome of stopping treatment in people who had started antiretroviral treatment under the old HIV treatment guidelines, for whom treatment would not be recommended under the new HIV treatment guidelines. Most major HIV treatment guidelines have changed from recommending treatment for people with less than 500 T-helper (CD4) cells, to recommending that people with between 200 and 350 T-helper cells consider therapy, and that people with fewer than 200 T-helper cells definitely begin HIV therapy.

A group from Argentina randomized 36 people who had pretreatment T-cell counts above 350 and a viral load less than 60,000 copies per mL to either continue or stop HIV therapy. The viral load in the group that stopped therapy returned to close to the pretreatment viral load, and the T-cell decreases were not very rapid, only about a 14-cell decrease. The average follow-up in this small study is less than 1 year. However, it should offer

some reassurance to people who are considering stopping highly active antiretroviral therapy (HAART) because they started under the old guidelines, and would not be recommended to start HAART were they being evaluated to start HAART today. For many people who are tolerating their regimen well, continuing HAART is still also a very reasonable consideration.



PI Interactions

Another small study of concern and interest is yet another report of the complicated interactions of two protease inhibitors (PIs) that are commonly prescribed together. Kaletra and Agenerase may be a very useful combination in people with multiple PI-resistant mutations. However, there appears to be a complicated and not completely predictable interaction between the two drugs. There is a two-way interaction: Agenerase appears to decrease to blood levels of Kaletra, and Kaletra appears to decrease the blood levels of Agenerase. So, a higher dose of Kaletra (533 mg versus 400 mg) may be needed when these two drugs are combined. The dose of Agenerase studied varied from 600 mg to 900 mg twice a day. Also, NNRTIs are known to decrease Kaletra blood levels.

The major concern with the results of this and other studies of the interactions of Kaletra and Agenerase is that there is a great deal of variation in the blood levels from person to person. Therefore, this study, like others, concluded that it would be advisable to measure blood levels of the PIs when they are prescribed together. This is not currently routinely done in practice in the U.S.

Drug Holidays Before Starting a New Regimen

Dr. Katlama presented results from a trial in which 70 people were randomized to either start a new salvage regimen immediately or to take an 8-week "drug holiday" prior to starting the new HAART regimen. The group who had the 8-week drug holiday had twice as great a chance of achieving a viral load decrease of 1 log or more (a 10 times bigger decrease) after 24 weeks on the new regimen. Half (50 percent) of the group that had the 8-week drug holiday achieved at least a 1- log reduction in viral load, compared to only 24 percent for the group that did not have the drug holiday prior to starting their new treatment regimen.

All people were started on the same new regimen, which included 4 NRTIs,

an NNRTI, hydroxyurea, and 3 PIs, also known as mega-HAART. Most people reportedly tolerated this very aggressive regimen. However, there is a risk of a significant decrease in T-cells during the drug holiday and more than 24 weeks of follow-up is needed to determine if this type of structured treatment interruption is of benefit. A similar study found no difference with this approach. There still needs to be a larger study, with longer follow-up, to resolve this issue.

HIV Resistance Meeting Highlights

Atazanavir Resistance Findings

The next PI to be approved will probably be atazanavir (ATV.) It is a once-a-day drug that does not cause changes in cholesterol or triglycerides. Early trials in people with PI-resistant virus were not too encouraging; however, a report from the meeting in Seville found that the first mutation that develops to ATV does not appear to cause resistance to the other PIs. So this raises the possibility that ATV could be used first and then if resistance were to develop, HIV would still be sensitive to the other PIs. However, clinical trials will need to confirm if this is in fact what would happen in people.

A Toxic Second-Generation NRTI Resurrected?

An NRTI known as FTL was dropped from development in the early 1990s due to serious toxicity, including some deaths from hepatitis. Another company has purchased this drug and is trying to resume clinical trials. They reported at the resistance meeting that the mutation that develops to this drug does not cause cross-resistance to other NRTIs. While this is an encouraging

finding, the serious toxicity of this drug observed in earlier trials needs to be addressed before further testing of this drug resumes.

Trimeris also reported was that the resistance that develops to T-20, the entry inhibitor, does not confer resistance to the next entry inhibitor in development called T-1249. Another encouraging report is that the transmission of drug-resistant HIV appears to have decreased slightly in the United States in the last 2 years. This is good news, since the rate of increase was significant for the prior few years. Most people still expect the next revision of the Public Health Service HIV Treatment Guidelines to recommend HIV resistance testing prior to beginning HIV treatment, even in people who have been infected for some time.

(The above highlights from the HIV Resistance Meeting in Seville are based on a summary of the significant findings presented by Dr. John Mellors at this summer's ACTG meeting, with some editorial comments added by the author of this STEP Conference Review.)

HIV in Women



A stereotype exists in the United States that AIDS is a gay disease. Although AIDS was first documented among homosexual men in this country in 1981, according to the U.S. Centers for Disease Control (CDC), the total AIDS cases attributable to women in the U.S. has increased from 7 percent in 1985 to 20 percent in 1996. Today, the CDC reports that over 40,000 new HIV infections occur in the U.S. each year and about 30 percent are women. AIDS stereotypes can prevent women, and their healthcare providers, from seeing themselves at risk for HIV infection. Other HIV stereotypes include the female prostitute and the injection drug user. However, the CDC estimates that approximately 75 percent of new infections among women were through heterosexual sex, and 25 percent were through injection drug use.

Worldwide, the CDC reports that as of December 2000, 16.4 million women were living with HIV/AIDS, accounting for 47 percent of the 34.7 million adults living with HIV/AIDS, and that over 80 percent of adult HIV infections are due to heterosexual transmission. AIDS is not a gay or straight or a male or female disease. AIDS is a human disease.

What are some of the issues that are unique to women living with HIV/AIDS? Here are some alarming CDC statistics:

- One in five HIV-infected women is uninsured.
- Approximately 50 percent of women with HIV have at least one child under the age of 15 years.
- African American women are 13 percent of the U.S. female population, but

represented 63 percent of newly reported female AIDS cases in 1999.

- In 1999, the AIDS case rate for African American women was 49 per 100,000, compared to 14.9 for Latinas, and 2.3 for white women.
- HIV/AIDS is now the third leading cause of death among women ages 25 to 44, and the leading cause of death among African American women in this age group.

- Although AIDS deaths in this country are down overall, AIDS deaths in women are rising.

Why are women, especially African American women, not accessing care and treatment as readily as men? The reasons are multiple and complex. Women have families and life difficulties

that they often put before their own healthcare. They may be isolated geographically and culturally and may fear rejection by family, church, or community. There is often distrust of the healthcare system, especially among minority women, because of a history in this country of abuses of people of color in research. Since it is more difficult to get women involved in necessary research, we don't know a great deal about the differences in treating men versus women as far as medication doses or side effects. We do know that esophageal candidiasis is an opportunistic infection that occurs more often in women than men, and conversely, that Kaposi's sarcoma is commonly seen in gay men but rarely in women.

What else do we know about women with HIV/AIDS? We know that menstrual disorders, such as amenorrhea (lack of

menstruation), and hypermenorrhea (excess menstruation) are frequently reported by HIV-positive women. There is lack of evidence whether low CD4 counts or high HIV viral load levels have an effect on menstrual function. Menstrual disorders in women with HIV infection may be related to a combination of factors such as chronic disease, weight loss, contraception, agents used to stimulate appetite, or substance abuse. More studies are needed to understand the relationship between HIV in women and abnormal menstrual periods.

Women with HIV/AIDS are 10 times more likely to have abnormal Papsmears of the cervix than women who are HIV negative. These abnormal Paps are associated with the presence of HPV (human papilloma virus or genital wart virus) and low CD4. In 1993, the CDC included cervical cancer as an AIDS-defined diagnosis. Even with treatment of abnormal Papsmears, women with HIV infection tend to have higher recurrences of abnormal Pap smears than women without HIV infection. Adequate screening and treatment programs are needed to prevent progression of abnormal Pap smears to invasive cancer. In 1998, the CDC recommended that women with HIV have a Pap smear every 6 months and that if they have two consecutive normal Pap smears, then an annual Pap can be done.

Some studies suggest that women with HIV tend to have more vaginal yeast infections, especially those with declining CD4 counts. Women should consult their healthcare providers for the most effective treatment of yeast infections.

There are many other topics such as pregnancy and menopause that need to be considered when discussing women and HIV. Although we've made

significant advances in the decline of transmission of the virus from mothers to babies during pregnancy, we need many more studies on the safety and doses of HIV drugs used for women during pregnancy. There is very little information on treatment of menopause in women with HIV infection. Likewise, there is almost no information on hormonal replacement therapy and interactions with HIV drugs for post-menopausal women.

Women with HIV may need extra assistance to overcome the multiple barriers to accessing healthcare and treatment. Women often need intensive case management, peer advocacy, mental health and chemical dependency services, help with childcare and transportation, and specialized prenatal care, as well as easier access to treatment and clinical trials. All of these measures can have an impact on transmission, death rates, and more effective treatment for women with HIV/AIDS. ♣

HIV/AIDS is now the third leading cause of death among women ages 25 to 44, and the leading cause of death among African American women in this age group.

RESOURCES

Additional resources for HIV+ women:

BABES Network
Seattle, WA

206-720-5566 local
1-888-292-1912 toll free
www.babesnetwork.org

WORLD

414-13th Street, 2nd Floor
Oakland, CA 94612
510-986-0340
www.womenhiv.org

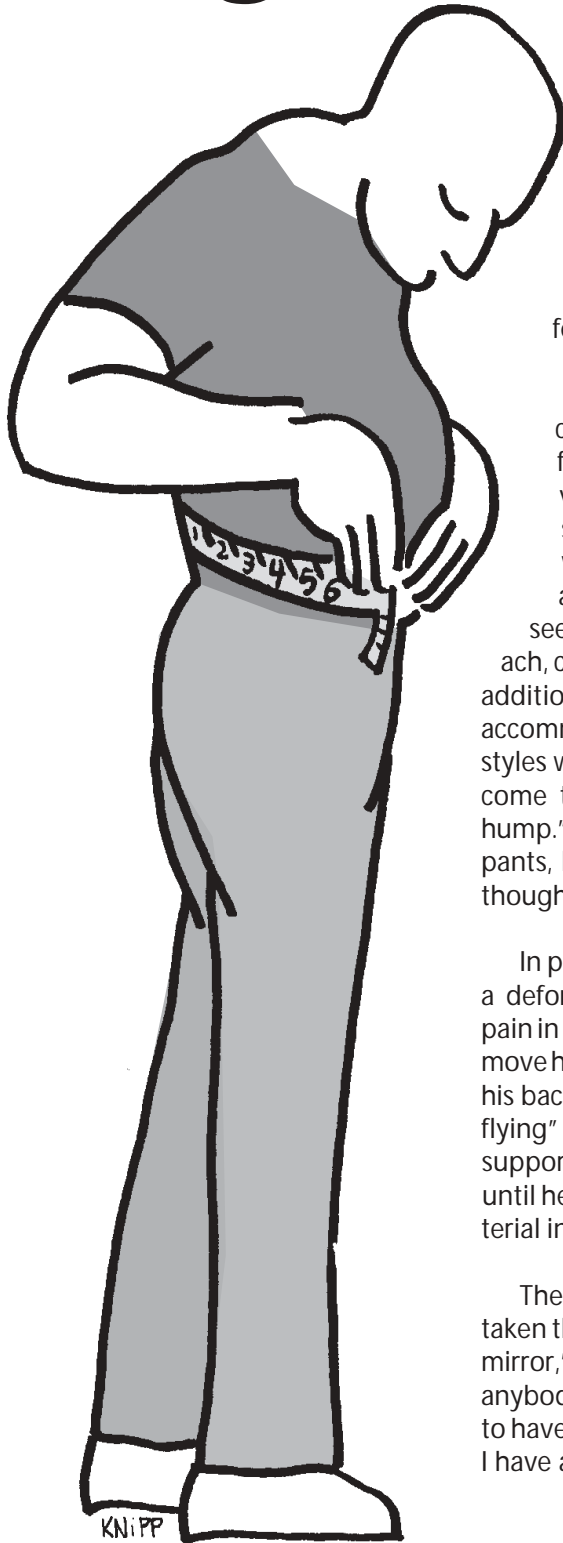
Postive Women's Network
3701 Broadway
Everett, WA 98201
425-259-9899 local
1-888-651-8931 toll free
www.pwnetwork.org

Wise Words (Project Inform)
205-13th Street, Suite 2001
San Francisco, CA 94103-2461
415-558-8669
www.projinf.org/pub/ww_index.html

Women Alive
1566 Burnside Ave.
Los Angeles, CA 90019
323-965-1564 local
1-800-554-4876 toll free hotline
www.women-alive.org

Womens' HIV Support Group
Pierce County AIDS Foundation
Tacoma, WA
253-383-2565
www.piercecountyaid.org

An AIDS Body — Living with Lipodystrophy



Like many of us these days, Juan's (not his real name) denial was overcome by reality when his pants wouldn't button any more. However, Juan's problem wasn't too much food and too little exercise, but lipodystrophy, a common side effect of HIV medications.

He's been on a variety of medications over the last 8 years, and for the first 5 years, he noticed very little change in his body shape. Then he began to lose weight in his face, arms, and legs, and about 3 years ago began to see fat accumulation over his stomach, chest, and the back of his neck. In addition to needing a bigger shirt to accommodate his chest, he can't wear styles with a collar because of what has come to be referred to as a "buffalo hump." In addition to needing bigger pants, he also has to wear a belt, even though it often cuts into his skin.

In particular, that hump is more than a deformation of posture, it's a literal pain in the neck. It hurts when he tries to move his head and when he lies down on his back, he says it feels like his head "is flying" – dangling loose. An expensive support pillow brought some relief – until he developed an allergy to the material inside the pillow.

These changes in body shape have taken their toll. "I don't see myself in the mirror," Juan says. "I don't want to see anybody and I believe nobody will want to have sex with me. It seems to me as if I have an AIDS body and face."

To deal with the neck pain, Juan has used stretching and exercises recommended by a physical therapist, but he tries not to take pain medications because they make him feel sleepy and depressed. His insurance covers medications, but covers massage just once a month. For a while he found help at the Northwest Institute of Oriental Medicine (NIOME), where acupuncture, massage, and Chinese herbs provided some relief, but the Institute has closed now, and Bastyr is a difficult commute.

Juan's family lives in Mexico, and his friends haven't been very helpful. Even though he's tried to explain that it's the HIV medications, they tell him not to eat so much. "They tell me I am a weird fat man." So he attends a support group for people living with AIDS, but even though the other participants are also Hispanic, most are younger men, and haven't been on medications nearly as long, and he doesn't have much in common with them.

So he feels isolated "insecure, ashamed of myself. Sometimes I feel like a monster." He's afraid of the opinion of his family when he meets them next. When asked if he's thought about liposuction or plastic surgery he says, "Yeeeeesssss. Every day, all the time. But it's kind of expensive and I can't afford it." And his insurance wouldn't cover it.

Over the last 8 years, Juan has had to change medications several times and is currently on his "last cocktail." So he's run out of alternatives to the drugs that he's currently taking, and that are the cause of the lipodystrophy. In addition to fat accumulation, side effects include

elevated cholesterol and triglyceride levels, and digestive problems including bloating, cramps, and diarrhea.

When STEP talked with Juan, he was about 10 weeks into a drug trial with the AIDS Clinical Trial Unit (ACTU) with both metformin and rosiglitazone. [These are drugs that increase the body's sensitivity to insulin and are commonly used to treat diabetes. It is thought that some of the problems of lipodystrophy are due to decreased sensitivity to insulin, or insulin resistance.] So far, the feelings of bloating and problems with gas have improved, and he's even lost a little weight. The combination seems to be more effective for him than taking metformin alone. Since he can't take over-the-counter remedies for gas because of their interactions with his HIV

"I don't see myself in the mirror," Juan says. "I don't want to see anybody and I believe nobody will want to have sex with me. It seems to me as if I have an AIDS body and face."

medication, any improvement is welcome. The study will run for several years more.

He's not seen any change in the fat accumulations yet. But even if the trial helps him only a little, he's not in the trial just for himself. "I wanted to be part of the solution, so I asked my doctor if I could participate." However, because of other health problems, including a bout of pancreatitis and lymphoma (and hepatitis brought on by the lymphoma), he wasn't strong enough to participate as soon as he wanted to.

What's been most helpful in dealing with the emotional, social, and physical effects of lipodystrophy has been a 12-step program called Neurotics Anonymous, which he's been in for over 10 years. In Latin America, Juan says, *neurotic* means that you have emotions you can't control, whether it's feeling depressed, or guilty, or joking uncontrollably. He was first referred to the group by a doctor who believed he didn't have long to live. Juan credits the group with giving him the support he needed to take responsibility for his own health. They've

been with him all the way, visiting him daily when he was hospitalized. "Without them, I'd be dead," he says, and means it.

Even though his friends aren't convinced that lipodystrophy is real, Juan says that all of his healthcare providers have been supportive "and very compassionate." It's been a "team effort" of his doctor, nurses, case workers, and support groups.

Juan has a little advice for readers. "Don't be afraid to ask your doctor for answers. Take responsibility for your own health – it's 80 percent your job." ✕

Lipodystrophy website link:

www.medibolics.com/FacialWasting&Cosmetics.htm



Do you feel **ISOLATED** from the community because of the your HIV status?

ANGRY that some in the negative gay community have so little willingness to talk about the effects of HIV on our lives?

Have you felt **UNCOMFORTABLE** disclosing your status to someone you want to engage sexually?

HIV & AIDS is being conveniently forgotten. Though still life changing, threatening, and lethal, it has ceased to rally us as a community.

It is time to begin a dialogue! We need to find ways to get HIV back out of the closet. A coalition is forming of people surviving HIV & AIDS to explore how to end the deafening silence that has settled over our community.

If you're interested in helping, join us on **Oct 23, 6:30–9pm** at the STEP offices at 1115 E. Pike St. LGBT Center, corner of 12th & Pike.

For more information, please call STEP at 329-4857



Once-Daily Antiretroviral Options

Numerous studies have now shown that very high levels of adherence to medication regimens are necessary for adequate HIV suppression. The ideal antiretroviral (ARV) regimen is simple, effective, and well tolerated. An increasing number of approved once-daily regimens are being used to minimize pill burden and optimize adherence. There is already data showing the efficacy of once-daily dosing of Videx, Efavir, Viread, Viream, Sustiva, Fortovase/Norvir and Agenerase/Norvir.

The long half-life of the active breakdown product of both Videx and Efavir favors a once-a-day dosing regimen. The plasma half-life of Videx is only 1.5 hours, but its intracellular half-life is approximately 25 to 40 hours. The clinical studies of these two nucleoside reverse transcriptase inhibitors (NRTIs) show that the effectiveness and side effects of a once-daily regimen are equivalent to twice-daily dosing. Once-daily (with a 400 mg dose) and twice-daily (with a 200 mg dose) Videx are equally effective in reducing viral loads and increasing CD4+ cell counts. Efavir once daily (300 mg) compared to twice daily (150 mg) also had similar clinical results and has been approved in Europe. There are also ongoing trials for once-a-day Abacavir.

Viread belongs to a new class of antiretroviral drugs, the nucleotide (as opposed to a nucleoside) reverse transcriptase inhibitors. It is given in a single daily dose of 300 mg. The main advantage

of Viread is that it does not appear to have cross-resistance with the other available classes of antiretrovirals and therefore can often be used in individuals with HIV that has many resistance mutations due to prior highly active antiretroviral therapy (HAART) exposure.

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) Viream (400 mg) and Sustiva (600 mg) are both given once daily with good clinical results. The once-daily dosing regimen for Viream has yet to be approved by the FDA. Although Sustiva has always been marketed as a once-a-day drug, the only formulation available was a 200 mg pill. The FDA has just approved a 600 mg version of Sustiva (which is about the same size as the 200 mg pill), decreasing the pill burden from three 200 mg tabs to a single 600 mg pill.

The addition of low-dose Norvir to many of the protease inhibitors (PIs) often increases the blood levels of effective drug, allowing for once-daily drug dosing. Peter Cardillo et al. recently published promising data for once-daily dosing of Fortovase (saquinavir) soft gelatin capsules in combination with Norvir (Fortovase 1600 mg/Norvir 100 mg). HIV-infected individuals with an undetectable viral load on a stable HAART regimen of twice-daily Fortovase/Norvir and two NRTIs were switched to once-daily Fortovase/Norvir while continuing the NRTIs. Once-daily

Fortovase was well tolerated and after 24 weeks; 93 percent of the participants still had a viral load less than 50 copies/mL. CD4 cell counts improved significantly on once-daily Fortovase/Norvir therapy as well. The data supports the use of once-daily Fortovase/Norvir with two NRTIs as a convenient regimen in HIV-positive people with a viral load less than 50 copies/mL. Agenerase and likely indinavir (studies ongoing) when combined with Norvir also allow for effective treatment of patients with once-daily dosing. The borderline levels of the drug in the bloodstream achieved by the PIs, however, do not allow much room for error in when the pills are taken. In addition, some of these once-daily PI regimens have a hefty pill burden — up to 10 pills at a time (lower case).

Posters at the Ninth Retrovirus Conference supplied data in support of once-daily dosing for a new formulation of Zert (d4T) (Abstracts 411 and 416), additional support of once-daily Fortovase/Norvir (Abstract 441), and new data on once-daily dosing of Kaletra (Abstract 409). There were also several studies using newer, not yet approved, antiretrovirals such as atazanavir (a PI) and DPC 083 (an investigational NNRTI) as part of a once-daily HAART regimen. Bristol-Myers Squibb just submitted its application for approval of atazanavir in Europe.

A large, Phase II, placebo-controlled, prospective study of 783 people com-

pared an extended-release formulation of Zerit (d4T XR) dosed at 100 mg once daily to the currently available formulation of immediate-release Zerit (Zerit IR) dosed at 40 mg twice daily (Abstract 411). The Zerit was used as part of a HAART regimen of Efavirenz (150 mg twice daily) and Sustiva (600 mg once daily). At the start of the study, it was determined that Zerit XR blood levels were just as high as those seen with Zerit IR (Abstract 416). A 24-week interim analysis of the planned 48-week study was reported at the Retrovirus Conference. Virologic and immunologic responses were nearly identical in the Zerit XR and IR groups. The safety, tolerability and efficacy profiles of Zerit XR also appear comparable to that of Zerit IR. Since the results were maintained at the 48-week analysis, this data will likely result in the approval of once-daily Zerit XR in late 2002.

Once-daily regimens using the combination of Fortovase and Norvir (at 1600 mg and 100 mg) have been previously studied with promising results. However, the combination of Fortovase with Sustiva once daily is discouraged because of the increased metabolism of

Fortovase resulting in lower drug levels. L. López-Cortéz studied the safety, efficacy and blood levels of Fortovase (1200 mg) with Sustiva (600 mg) with the addition of Norvir (100 mg) to see if a once-daily NRTI-sparing regimen, using these drugs, was feasible in people in whom NRTIs were withdrawn because of adverse events (Abstract 441). All people were NRTI and PI experienced. All 22 people who entered the study with an undetectable viral load remained undetectable, and 13 of the 20 people with a high viral load became undetectable. At 52 weeks, a total of 71 percent of the people had a viral load below 50 copies/mL with a median CD4 cell count increase of 215 cells. Treatment had to be withdrawn in only one case, due to hepatitis. This regimen may be an effective once-daily alternative for people for whom NRTIs are no longer a good option.

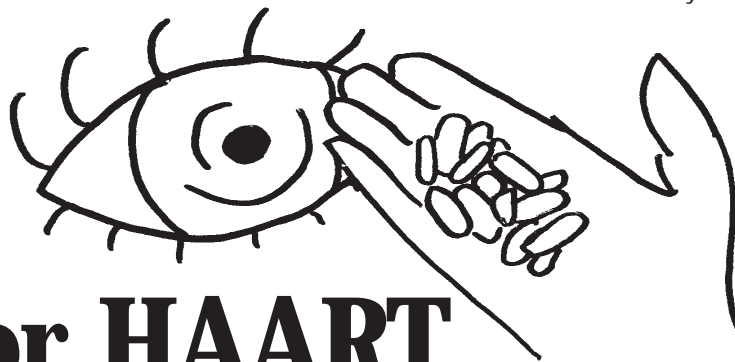
Although once-daily regimens have been shown to be effective for the Fortovase-with-Norvir and Agenerase-with-Norvir combinations, additional once-daily PI regimens are needed. Kaletra (Lopinavir 133 mg / Norvir 33 mg)

is currently being prescribed at a dose of 400 mg / 100 mg (3 pills) twice daily. In a pilot study of 38 people, a once-daily Kaletra dose of 800 mg / 200 mg (6 pills) was compared with the standard twice-daily dose as part of a HAART regimen with Zerit and Efavirenz (Abstract 409). Comparable virologic responses were achieved in the once-daily and twice-daily arms and there were similar CD4+ cell count increases of approximately 240 cells, as well. Although the efficacy and safety results were similar in both groups, there were less consistent Kaletra drug levels with once-daily dosing (Abstract 126). Larger studies are needed before this once-daily regimen is accepted.

One major concern about once-a-day dosing is that if a person skips a dose, they go a whole day without sufficient drugs in the blood to suppress HIV replication, whereas if they miss one dose of a twice-a-day regimen, they go only 12 hours before the next dose. Additional data is needed to determine if missing one dose of a once-daily HAART regimen will allow HIV replication and more frequent failure rates. ✎

Drug	Original Dosing	Once-Daily Dosing
Videx	200 mg (1 pill) twice a day	400 mg (1 pill) once a day
Epivir	150 mg (1 pill) twice a day	300 mg (2 pills) once a day
Zerit 40 mg	1 pill; Zerit IR twice a day	100 mg (1 pill; Zerit XR) once a day*
Viread	300 mg (1 pill) once a day	
Viramune	200 mg (1 pill) twice a day	400 mg (2 pills) once a day
Sustiva	600 mg (3 pills) once a day	600 mg (1 pill) once a day
Fortovase	1200 mg (6 pills) 3 times a day	1600 mg with 100 mg Norvir (9 pills) once a day
Agenerase	1200 mg (8 pills) twice a day	1200 mg with 200 mg Norvir (10 pills) once a day
Kaletra (Lopinavir/Ritonavir)	400 mg/100 mg (3 pills) twice a day	800 mg/200 mg (6 pills) once a day
Atazanavir*	400 mg (2 pills) once a day	

*Zerit XR and atazanavir are not yet FDA approved, but likely will be in the near future.



DOT for HAART

DIRECTLY OBSERVED THERAPY

Directly observed therapy (DOT) refers to the taking of medications in the presence of a medical provider, either in the provider's office or at the patient's home, so the provider can actually watch the pills being swallowed. To date, the use of DOT has been used mainly to help control the tuberculosis (TB) epidemic. DOT programs are an effort to increase medication compliance to achieve better treatment successes. High treatment completion rates, substantial increases in cure rates, and improved survival associated with TB DOT have been documented in the United States. DOT programs have also made great strides decreasing the TB burden in many developing countries. A growing number of projects in Asia, South America, and Africa demonstrate that population-based DOT is feasible in countries without an otherwise well developed public health infrastructure.

The strategy of the World Health Organization (WHO) for TB includes DOT as one of its components. Given the difficulty in predicting which patients will adhere to the anti-TB regimen prescribed, the WHO supports "universal" DOT for TB. DOT programs frequently consist of more than just observed therapy. They include various additional interventions to increase compliance through incentives, aggressive outreach methods to re-engage persons, medication reminders, motivated and supportive staff, improved access to health services, and additional external funds. It is

likely that it is the range of interventions associated with DOT that makes it so successful; DOT may simply be a marker of a more intensive effort towards TB control. Participants identified the access to good medical care and staff as the most important aspects of the DOT strategy. DOT alone without other supportive interventions is unlikely to be effective. This is corroborated by a study that found no difference in the treatment success rates between self-observed therapy (SOT) and DOT when other supportive measures were not used. However, when combined with these other interventions to improve adherence, DOT has increased the success rate of TB treatment when other non-DOT strategies have failed. Acceptance of DOT by both pill takers and providers has generally been high, particularly when DOT is addressing a medical concern, such as TB control. Lastly, in resource-poor settings, DOT overall has been shown to be more cost efficient than SOT for TB.

Since DOT for TB has been largely successful in many settings worldwide, and since similarities exist between HIV and TB, it is reasonable to consider using the DOT strategy for highly active antiretroviral therapy (HAART). TB and HIV are similar in the development of multi-drug resistance due to exposure to inadequate or intermittent treatment. They are both global health threats and have complex treatment regimens with multiple toxicities. Sev-

eral pilot programs have had some preliminary success using DOT and modified DOT to increase adherence to HAART, but a large randomized controlled trial has yet to be done. (For people who take medications multiple times a day, only the pills that are taken in the morning are observed in "modified DOT.") Plus, most studies to date have concentrated on special populations of people with HIV, such as prisoners, people in methadone maintenance programs, children, people with TB, and people with a past record of poor adherence.

DOT has been used to increase adherence with HIV medications in the prison setting. In Italy, 37 prisoners who received DOT were compared to 47 prisoners who were given their daily medications and not observed. After a mean of 8.7 months, an undetectable viral load was achieved in 62 percent of prisoners receiving DOT versus 34 percent of prisoners doing SOT. Within the DOT group, there were also significant increases in the CD4 count. In another study, DOT was administered to 42 HIV-positive women in a correctional center in Buenos Aires, Argentina. Eighty-four percent of women had a rapid decrease in their viral load. Two studies compared DOT in prisoners to SOT in an outpatient population. The first was an open pilot study that found that viral suppression was significantly greater with DOT, but that there was no significant difference in the increase in the CD4+ cell count between the two study groups. The second was

a non-controlled, retrospective analysis of 100 treatment-naïve subjects that also showed that DOT had a greater virologic success than SOT.

Rather than enrolling prisoners, S. L. Hader enrolled 148 people admitted to two residential AIDS treatment facilities in New York. In an antiretroviral-experienced population, although DOT achieved an impressive 99 percent adherence rate, only two-thirds of the residents achieved an undetectable viral load and 41 percent had a treatment failure at least once, regardless of their regimen.

Modified DOT has been easily incorporated into methadone maintenance and TB treatment programs, since the patients are already observed swallowing their morning medications during the week. B. Conway found that after a median follow-up of 11 months, 9 of 13 people on a once-a-day HAART regimen and 8 of 12 on a twice-a-day regimen had a viral load below 400 copies/mL. During an 8-week intervention at a methadone maintenance program in San Francisco, participants receiving modified DOT showed slightly better adherence rates on all outcome measures when compared to usual care participants, but there were no significant group differences in any measures at the 1-month follow-up. In HIV-positive people with TB, it was found that supervision of the morning dose of HAART led to better adherence with evening medications and more awareness of potential side effects of the medication regimen.

Research using DOT has also focused on populations with documented or anticipated non-adherence. M. S. Stenzel was referred 49 high-risk people, of whom 37 agreed to participate. Of the 12 who refused to participate, 5 reported the ability to take their own medications without assistance, 4 felt the regular home visits were intrusive, 2 were homeless and unable to arrange regular contact, and 1 was unwilling to initiate HAART. Modified DOT for HAART was given at the patient's home every morning during the week and prepackaged

medication was given for the afternoon and weekend doses. Six participants (16 percent) missed visits for 2 weeks and were disenrolled, 3 (8 percent) discontinued HAART, 5 (14 percent) opted to take medications without modified DOT because they didn't like home visits, and 17 (46 percent) completed 12 months of modified DOT. There was a significant virologic response on DOT, but there was no control group as a comparison. At enrollment, 4 of 37 people (11 percent) had a viral load below 400 copies/mL; at 3 months, 14 of 30 (47 percent) people had achieved that level; and at 12 months, 10 out of 18 (56 percent) had. There was also an immunologic advantage to DOT. The mean CD4+ cell count increased to 245 cells ug/L at 3 months and 339 cells ug/L at 12 months.

DOT for HAART may be more cost-effective and ultimately more successful in resource-poor settings where the cost of antiretrovirals is relatively high, especially when compared to the cost of personnel. Since 1998 in Haiti, one of the poorest countries in the world, Dr. Paul Farmer has been conducting a preliminary demonstration project of DOT for HAART. The program is modeled after the existing TB-control program in the country and involves a community health worker observing the ingestion of pills and providing support and assistance with social services. An initial cohort of 60 people has been enrolled and although outcomes have not been systematically analyzed, 18 of 20 had undetectable viral load after 4 to 30 months of follow-up.

Unlike TB, however, HIV requires long-term, potentially life-long, therapy. The goal of DOT programs for HAART is to improve education and foster medication self-administration over a limited time period, leading to long-term improvement in medication compliance. However, the data on long-term results associated with DOT is very limited. In the study by M. Fischl, HIV-positive individuals who received DOT had both greater short- and long-term virologic responses compared with those that received SOT. After 80 weeks, the num-

ber of patients with an HIV viral load below 400 copies/mL was 95 percent for those receiving DOT and 75 percent for those receiving SOT. M. S. Stenzel found that 47 percent of people understood how to take their medications at baseline and 80 percent understood at 3 months. At 12 months, most people felt prepared to take their HAART with minimal assistance. J. L. Sorenson, on the other hand, found that although modified DOT distributed at a methadone maintenance program enhanced medication adherence, it did not produce effects enduring beyond the time of the intervention.

It is still too early to judge long-term adherence following completion of DOT. The optimal duration of DOT for HAART, the most appropriate candidates to target and its cost effectiveness are all questions that still need to be answered. The AIDS Clinical Trial Group has begun a study to compare DOT to standard, self-administered medications. This study is discussed in more detail in this issue of the *STEP Perspective*. ❧

Mitochondrial Damage

The topic of mitochondrial damage is gaining more and more press as a potential side effect of anti-HIV medication. Simply put, the mitochondria are the “energy factories” of the cell — the tiny, rod-shaped structures, or “organelles,” within each cell responsible for producing roughly 90 percent of all the energy that cell needs in order to survive. The number of mitochondria in a particular cell is based upon the energy needs of that cell and can range from 200 to 2,000.

About 80 percent of the energy generated by mitochondria is created through a cellular aerobic (meaning requiring oxygen) process called oxidative phosphorylation, which creates adenosine triphosphate, or ATP. Creating ATP includes an intricate series of steps that involve five multi-subunit enzymes or complexes. Each complex has a different nutritional and chemical need in order to function properly. This is important to remember when exploring the nature of treatment for mitochondrial damage.

As mitochondria produce ATP, they simultaneously yield reactive oxygen species (ROS), which are harmful free radicals that circulate throughout the cell, the mitochondria, and the body, causing more damage. The circulation of ROS leads to the activation of reactive nitrogen compounds, which in turn induce, or activate, genes in the DNA that are associated with many degenerative diseases such as Alzheimer’s, Parkinson’s, strokes, and multiple sclerosis. The term “mitochondrial toxicity,” therefore, is a misnomer and actually refers to the process of mitochondrial

damage.

The DNA for each mitochondrion (mtDNA) remains unprotected within the membrane of the mitochondrion itself. In comparison to the DNA in the nucleus of the cell (nDNA), mtDNA is easily damaged by free radicals and the ROS that they produce. Freely floating mtDNA lacks protective measures associated with nDNA, and therefore mtDNA suffers from multiple mutations. It has been estimated that this lack of protective measures results in mutations to mtDNA occurring 10 to 20 times more frequently than mutations to nDNA. The mitochondria that are produced have decreased ability to function, resulting in the inability to utilize fatty acids for energy production, and therefore a decreased ability to store fat in muscle tissue.

In order for mitochondria to reproduce themselves, a specific enzyme called gamma-DNA-polymerase, or “pol gamma” is required. Many medications have been found to interrupt pol gamma. Studies suggest that virtually all the nucleoside analog reverse transcriptase inhibitors (NRTIs) — such as AZT, 3TC, ddI, ddC, d4T, and abacavir — interrupt pol gamma to some extent. This disruption prevents the transport of long-chain fatty acids from being transported the membrane wall into the mitochondria, where they are used as primary fuel and energy sources. As a result, fatty acids are dysfunctionally deposited and accumulated in muscle tissue. Without the cell’s main source of energy, the number of newly formed mitochondria drops, and therefore, cell function decreases, and possibly even cells die (or apoptosis).

Symptoms developed by an individual would depend upon the type of cell affected. However, the most common symptom is generalized, overall fatigue.

Test tube (“*in vitro*”) studies have demonstrated that ddC, ddI, and d4T are the most potent inhibitors of pol gamma, although the other NRTIs exert some influence as well. To date, researchers have not studied the extent of mitochondrial damage when anti-HIV medications are combined, which is standard practice for most individuals currently on anti-HIV therapy. Moreover, the effect of combining NRTIs with other anti-HIV medications, such as protease inhibitors, is not known. However, one study demonstrated a reduction in number of mitochondria produced in a cell in people taking d4T. Data from yet another small study suggested that HIV-positive individuals taking any of the NRTIs had up to 44 percent fewer mitochondria per cell than those individuals who are either not taking NRTIs or are HIV-negative. One study demonstrated that those taking AZT had significant depletion of mitochondrial DNA in muscle tissue.

In a study examining the number of mitochondria per cell, participants were separated into four groups: (1) HIV-positive individuals who were on medications and had fat loss/wasting, (2) HIV-positive individuals on medications without signs of fat redistribution, (3) HIV-positive individuals who had not taken anti-HIV drugs and (4) individuals who were HIV-negative. The group with the greatest decrease in mitochondria in cells was the group with fat loss/wasting, followed by the HIV-positive group

on medications yet without signs of lipodystrophy. The latter two groups showed no difference in the number of mitochondria. **The conclusion drawn is that anti-HIV medications do interfere with the production and lifecycle of mitochondria.**

It has been postulated that mitochondrial damage is always present, but the question is to what extent. Mitochondrial damage is poorly diagnosed, and when symptoms do occur, they can run the range from mild, to severe, to life-threatening. For instance, common symptoms include fatigue, muscle weakness (myopathy), peripheral neuropathy, and pancreatitis. However, some researchers suggest that regardless of HIV serostatus, damage to mitochondria can be a possible factor in low platelet count (thrombocytopenia), anemia, and low neutrophil count (neutropenia). Furthermore, there is a significant link between damaged and dysfunctional mitochondria and the development of Type II diabetes in adults, again, regardless of HIV serostatus.

With early enough detection, many of these symptoms and conditions are reversible by altering therapy. This may include stopping medication, or significantly reducing dose. However, people considering such a course of action should first consult with their healthcare provider to identify the specific cause for the symptom.

How can mitochondrial damage be detected? The easiest way is through a blood test that measures lactate levels in the blood. Lactate is a natural by-product from the breakdown of glucose and fat in the mitochondria. The sore and tired feeling in the muscles following rigorous exercise is a result of the body shifting to "anaerobic respiration" that leads to a buildup of lactic acid. When the mitochondria are damaged, lactate levels rise in the bloodstream and lead to lactic acidosis. This increase in the acidity in the blood is life threaten-

ing and must be dealt with immediately. Lactic acid level in the blood should be measured (without a tourniquet, if possible) after a person has been resting for at least 5 minutes, and has refrained from vigorous activity and alcohol consumption for 24 hours.

Early symptoms of lactic acidosis are severe fatigue, nausea, vomiting, shortness of breath, abdominal pain, rapid weight loss, muscle cramps and aches, muscle numbness and tingling, and rapid and progressive muscle weakness. As the severity increases and lactate levels rise over 5mmol/liter (the normal value is less than 2), mitochondria lose their ability to produce energy, leading to potentially irreversible organ damage and death.

At present, there are no comprehensive studies presenting clear treatment strategies for dealing with mitochon-

Supplementation with L-carnitine has been successfully used in the treatment of mitochondria-induced muscle weakness and degeneration.

drial damage associated with HIV. Extrapolation can, however, be made from the knowledge available about treatment of mitochondrial damage associated with other diseases. First and foremost is to identify and treat the cause. For many, however, this option may be limited. If it is true that the main associated factors are the NARTIs, then switching to another therapy might be suggested. Eliminating this entire class of HIV medication from treatment options leads to a whole host of medical and health-related issues. It does seem, at this time, that ddI, ddC, and d4T are the most potent inhibitors of pol gamma. This should be considered for those suffering from mitochondrial damage. The availability of Viread (tenofovir) has provided a good alternative to other NRTIs for many people, and Viread does not appear to affect mitochondrial function.

Finally, several nutrients have been studied for their ability to decrease damage to the mitochondria. In the current literature regarding mitochondrial dam-

age and HIV therapies, some mention has been made about carnitine, coenzyme Q10, and riboflavin (B2). Most of these are being studied in isolation and not in conjunction with one another. Although the approach is to determine whether or not each particular nutrient is beneficial in the treatment of mitochondrial damage, the flaw in this approach stems from the fact that each of the five complexes in the oxidative phosphorylation process requires different and varying nutrients *simultaneously*. Other nutrients that support mitochondrial function are alpha lipoic acid, NAC (N-acetyl-cysteine), vitamin E, and essential fatty acids, to name a few.

Carnitine is a natural substance found in food, mainly meat and dairy products, that can be quickly absorbed in the small intestines. The standard American diet contains roughly between 10 to 100 milligrams of carnitine. The body can

synthesize carnitine from the essential amino acid, lysine, with vitamin C, niacin, vitamin B6, iron,

and the amino acid methionine as necessary cofactors. Carnitine is vital to the life of the cell since it is required for the transport of long-chain fatty acids into the mitochondria. Regarding supplementation, two forms of carnitine have been used, either L-carnitine or acetylcarnitine. Studies show that supplementation with L-carnitine decreases the percentage of both CD4 and CD8 cells undergoing cell death (apoptosis.) Furthermore, supplementation with L-carnitine has been successfully used in the treatment of mitochondria-induced muscle weakness and degeneration. Studies with patients taking AZT reveal low levels of carnitine found in their muscle tissues. Several studies explored the use of 6 grams of L-carnitine daily intravenously. The results revealed a reduction in serum triglyceride levels, an increase in peripheral blood mononuclear cell-associated ceramide (an intercellular messenger of apoptosis), and a decrease in tumor necrosis factor

continued, next page

Mitochondrial Damage

(a cytokine that is produced as a result of infection, which intensifies viral replication). Another study, in which HIV-positive patients with severe neuropathy were given daily intramuscular injections of 1 gram of acetyl-carnitine (the form of carnitine more easily absorbed in the intestines), showed decrease in patient report of pain and improved movement and mobility. Overall, carnitine is necessary to keep mitochondria alive and functioning well, thereby resulting in proper nerve and muscle function, fatty-acid synthesis, and energy production.

synthesized in the cells of every living organism in nature. The body produces CoQ10 in a 17-step process that requires riboflavin (B2), niacinamide (B3), pantothenic acid (B5), pyridoxine (B6), cobalamin (B12), folic acid, vitamin C, and other trace minerals. Due to its complex and intricate requirements, nutritional deficiencies with any one of these vitamins can disrupt mitochondrial energy production. Generally, symptoms of CoQ10 deficiency affect cardiovascular health in the form of congestive heart failure, stroke, arrhythmias, high blood

diarrhea, weight loss, and lymphadenopathy.

Again, no RDA has been established for CoQ10; yet, current recommendations range from 30 to 120 mg per day, depending upon the severity of symptoms and health status. No side effects have been reported for CoQ10.

Riboflavin or B2, is a water-soluble vitamin, that, like other B vitamins, is not stored well in the body so must be ingested daily. Riboflavin belongs to a category of yellow colored pigments called flavins (the reason urine changes color when taking B vitamin supplements). When riboflavin interacts with phosphoric acid it becomes a part of two essential enzymes. These enzymes are necessary for the conversion of carbohydrates to

Mitochondrial damage is poorly diagnosed, and when symptoms do occur, they can run the range from mild, to severe, to life-threatening. For instance, common symptoms include fatigue, muscle weakness (myopathy), peripheral neuropathy, and pancreatitis.

No RDA (recommended daily allowance) has been established for carnitine. Studies range in the amounts used for mitochondrial and neurological benefits. No side effects have been reported, but this author has had patients report slight gastrointestinal pain within a half hour of taking carnitine orally. Current trends recommend between 1,000 to 4,000 mg of L-carnitine or acetyl carnitine in divided doses daily. Because carnitine is an amino acid, it is best absorbed on an empty stomach.

Carnitine works synergistically with another nutrient, the fat-soluble vitamin-like compound called coenzyme Q10 (CoQ10), also known as ubiquinone. CoQ10 is an essential factor in the electron transport chain, the pathway from which ATP and metabolic energy is derived, which occurs within the mitochondria. CoQ10 is a strong antioxidant that resides in the lipid membrane surrounding the mitochondria and protects it against free radical damage. Although the body can generate its own CoQ10, supplementation has been shown to be warranted in persons with HIV. CoQ10 is

pressure, mitral valve prolapse, and cardiomyopathy. Additionally, lack of energy, gingivitis, and overall weakened immunity are symptoms of CoQ10 deficiency.

Many medications directly deplete the body of CoQ10. While antiretrovirals have not been studied for their effect on CoQ10 levels, both antiretrovirals and antibiotics, such as Bactrim and Dapson, deplete the body of the B-vitamin family. Other medications, specifically cholesterol-lowering medications, anti-hypertensive medications like beta-blockers, and some tricyclic antidepressants like amitriptyline (at times used for treatment of neuropathy) all directly deplete the body of CoQ10, and thereby negatively impact the mitochondria. Studies of HIV-positive individuals who are either on antiretroviral medications or are drug naïve reveal CoQ10 deficiencies. Supplementation with CoQ10 has shown decreased incidence of opportunistic infections and improved immune parameters, measured by a reduction in symptoms such as night sweats, fever,

energy in the form of ATP within the mitochondria of the cell. Furthermore, deficiencies in riboflavin will exacerbate CoQ10 deficiencies. For these reasons, riboflavin supplementation has been considered in the treatment of mitochondrial damage. Many medications, such as antiretrovirals, antibiotics, oral contraceptives, and the tricyclic antidepressant nortriptyline result in direct riboflavin deficiencies. No major studies have demonstrated a direct improvement in mitochondrial health with supplement of riboflavin. However, since multiple cofactors are required in energy production in the mitochondria, studies of riboflavin alone may be misguided.

Typical symptoms of frank riboflavin deficiencies are inflamed mucous membranes, chelosis (cracks in the corners of the mouth), soreness and burning of lips, tongue, and mouth, burning, itching and tearing eyes, eczema of skin and genitals, light sensitivity, dry and itching scalp, nerve damage, depression and hysteria.

RDA for riboflavin is approximately

1.7 mg per day. For pregnant women, nursing mothers and heavy exercisers, higher doses are recommended. Several studies have used dosages in the range of 2 to 100 mg per day.

Several other nutrients, which are beneficial to the health of the mitochondria and immune system, need mention here. The first, alpha lipoic acid, is a powerful antioxidant. Alpha lipoic acid is found in highest concentration within the mitochondria, and helps protect against damage to the cell's membranes. In vitro, alpha lipoic acid has been demonstrated to inhibit tumor necrosis factor, NF-kappa B, the on-off switch for activation of HIV, and tat gene activity. In Europe, alpha lipoic acid has been used successfully for the treatment of diabetic neuropathy, leading to its study in the efficacy of treatment for HIV-related neuropathy either as a result of medication or the virus itself. Because of its ability to cross the blood brain barrier, alpha lipoic acid has been recommended as a potential treatment for cognitive disorders as well. Alpha lipoic acid has been shown to heal liver cells, decrease elevated liver enzymes, and lower high blood glucose. An added benefit of alpha lipoic acid is its ability to recycle vitamin C and vitamin E, and to increase blood levels of glutathione. No RDA exists for alpha lipoic acid, but use ranges between 100 to 1,200 mg per day. However, one study postulated that high doses (above 1,200 mg daily) may result in thrombocytopenia, decrease in platelet counts, but this has not been replicated. Standard practice often recommends 200 mg twice a day.

One of the most significant benefits of N-acetyl-cysteine (NAC), the sulfur-containing amino acid, is its reported ability to raise glutathione levels. Glutathione is the primary antioxidant system within the body, thus aiding the body against free radical damage. While the literature is still unclear as to whether or not supplementation with oral glutathione will in fact raise tissue stores of glutathione, the majority of studies do conclude that NAC supplementation will raise glutathione levels. Many medications and substances deplete glutathione, such as

acetaminophen, sulphamethoxazole (Bactrim), and alcohol, and protease inhibitors deplete liver stores of glutathione, thus the recommendation that those with HIV infection refrain from using large amounts of acetaminophen. Additionally, NAC supplementation leads to a "relative" increase in CD4 cells and a reduction in HIV-1 replication in stimulated CD4 cells. Dosage suggestions vary considerably with ranges between 1,000 mg to 8,000 mg per day having been studied. Side effects of higher dosages include gastrointestinal distress that can be alleviated by taking NAC with food. Standard protocols suggest between 1,000 mg and 3,000 mg per day in divided doses.

Finally, dietary fat has a major impact on the health of mitochondria. Trans-fatty acids, fat sources from hydrogenated and partially hydrogenated vegetable oils directly affect the membranes through which fats must be shuttled to be used by the mitochondria for energy. The greater the amounts of trans-fatty acids in the diet, the less fluid can easily pass through. As mentioned earlier, the production of ATP involves five multi-subunit complexes. Studies suggest that trans-fatty acids might inhibit ATP production by inhibiting complex V in the process. Therefore, diets high in saturated fats and trans-fatty acids are to be avoided in order to prevent damage to or improve the function of mitochondria. Rather, essential fatty acids such as flaxseed oil and fish oils should be recommended to ensure healthy membranes surrounding mitochondria.

Mitochondria are sensitive organelles whose function and health can be easily disrupted. In searching for "treatments" for mitochondrial damage, many researchers continually focus on one nutrient or one substance to restore balance. Since the ATP system is complex and requires a large number of nutrients, such a singular search will often fail to yield a significant result. For this reason, a series or group of nutrients needs to be explored. L-carnitine (acetyl-carnitine), CoQ10, and B vitamins would be an excellent starting point for

someone suffering with mitochondrial damage. Since all nutrients have multiple benefits, those interested in expanding their protocol should consult about any supplementation program with a qualified healthcare provider well versed in HIV medications as well as diet and nutrition. ✦

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Therapeutic Drug Monitoring

The Next Best Thing in HIV Treatment?

Therapeutic drug monitoring (TDM) uses blood levels of a drug to adjust its dose to achieve the maximal benefit and/or to achieve the minimal toxicity. This approach to customizing drug dosing has great appeal for the treatment of HIV. The promise of TDM is that it could increase HIV suppression and possibly lower drug side effects. The problem with TDM is that the studies are difficult to conduct, and there have not been adequate TDM trials to support its routine use in the clinic. Several studies have shown better HIV suppression with the use of TDM. However, it is difficult to separate the effect of TDM in increasing adherence compared to its effect in increasing the blood levels of drugs. Several studies are now under way by the AIDS Clinical Trials Group (ACTG) and others, evaluating TDM.

TDM is not routinely used in most areas of medicine, so this approach needs to be tested. However, the rationale for TDM is supported by retrospective data showing that there are great variations from person to person in blood levels of some anti-HIV drugs, particularly the protease inhibitors (PIs). It has been shown that the people with the higher blood levels have greater HIV suppression.

Many factors are responsible for the different blood levels in different people. These include known and unknown genetic variations, different absorption rates, different rates of removal of the drug once it reaches the blood, and different rates of protein binding, which

can make a drug unavailable. Also, since people vary greatly by body fat and lean muscle composition, it may be beneficial to customize the dose. Some drugs are stored in body fat and may last longer in the body of people with greater body fat.

What needs to be shown in large trials is that by adjusting the dose in individual people, the outcome of treatment will be enhanced. Data similar to that obtained for PIs is harder to come by for the nucleoside reverse transcriptase inhibitors (NRTIs) because they are activated inside the cell and the blood level does not necessarily correlate with the level of the activated nucleoside inside the cell.

The basic approach of TDM is to measure the level of the drug in the blood when it is near its lowest, just prior to the next scheduled dose. **This is called the trough level.** The trough level should be high enough to suppress HIV replication. In the past, another obstacle to TDM trials has been that the ideal trough level for the individual person was not known. However, the phenotype resistance test allows determination of what the minimally effective blood level of a drug should be, at least for the PIs.

The general design of the current, long-awaited, TDM trials is a comparison, by randomization, between a group of people on standard dosing and a group receiving active monitoring and adjustments in the blood level of the PI. TDM trials can be challenging because a

person needs to come to the clinic at precise times related to their dosing schedule to obtain accurate trough levels, and then return after an adjustment to determine if the adjustment has had the desired effect. Also, there is a concern about additional side effects when people are given drugs at higher doses than those usually prescribed. It may be that some side effects are not directly related to the blood level of the drug.

Most TDM trials are focusing on people with evidence of some degree of HIV drug resistance because this is where the greatest effect of customizing drug dosing may be observed. If the HIV virus is very sensitive, the difference in drug levels from person to person may not make much difference. But when only higher drug levels suppress HIV, TDM may make the difference between total versus partial HIV suppression.

Another potential benefit of TDM could be lowering the dose in people with higher than necessary levels, to reduce side effects. Studies are currently being conducted to examine the blood level of drugs to see if they correlate with side effects, such as the altered thought processes that some people experience from Sustiva. Do those people have higher blood levels than people not experiencing those side effects?

Hopefully the results of the current TDM studies will determine if this approach should be used in all people receiving HIV treatment. ✎

Viread-Videx EC Drug Interactions —

What's a Person To Do?

A few months ago, Bristol-Meyers Squibb released data from a study of the interaction of Viread (tenofovir) with Videx EC (enteric-coated ddI). The results were also recently presented at the XIV International AIDS Conference. Viread needs to be taken with food once a day for optimal blood levels, while Videx EC needs to be taken on an empty stomach once a day. Since it was known that Viread caused some increase in blood levels of ddI, it was hoped that by taking Viread and Videx EC together, with food, adequate levels of both drugs would be achieved with once-daily dosing.

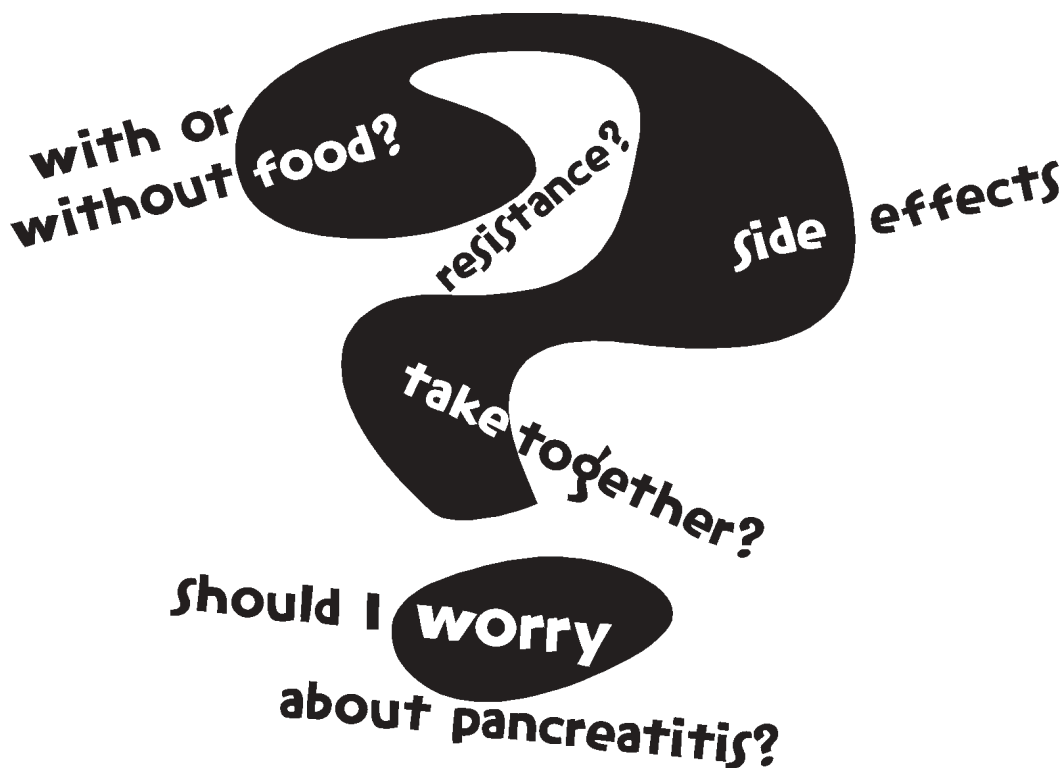
Unfortunately the drug interaction of Viread with Videx EC is greater than expected. So the concern is that whether the two drugs are taken together or apart, the blood levels of ddI may be too high. The levels of ddI increased from 48 to 64 percent, both when Videx and Viread were taken together and when they were taken 2 hours apart. (This study was performed on a small number of HIV-negative people. Multiple studies have shown that drug levels in HIV-positive people can be very different than in HIV-negative people for completely unknown reasons.) Because ddI may cause inflammation of the pancreas (pancreatitis), which can be fatal even after the drug is stopped (although this is rare), this interaction is of significant concern.

Bristol-Meyers Squibb has sent a letter to all healthcare providers informing them of this interaction and advising them to monitor their patients closely. But is this enough? Unfortunately, the next lower dose of ddI available, at 250 mg, is the old formulation, which is not as well tolerated as Videx EC. Also, that formulation is not approved for once-

Decreasing the dose of ddI means switching to a less well-tolerated formulation, and possibly a suboptimal dose of ddI. Staying with the 400 mg dose Videx EC combined with Viread risks a rare but potentially fatal case of pancreatitis. Patients on this combination should definitely discuss these concerns with their healthcare providers. Patients with another treatment option and those who can discontinue one of the two drugs may have the safest choices. However, many people on this combination do not have other good options. Certainly, people who develop significant abdominal pain, back pain, nausea, or vomiting should contact their healthcare provider immediately, as

these could be symptoms of pancreatitis.

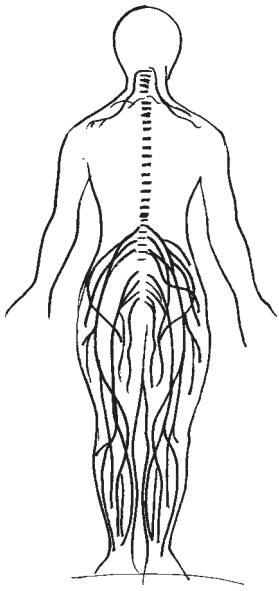
The *E-Zine* (STEP's electronic newsletter) will carry updates about any new information or recommendations as they become available. ✎



daily dosing as the Videx EC formulation is, and the same drug interaction study with Viread has not been conducted. Adding to this challenge, many people on the combination of Viread and Videx EC are on that combination because of resistance to other agents, so they have limited options for discontinuing or switching to other drugs.

In view of this drug interaction, Bristol-Meyers Squibb, people living with HIV, healthcare providers, government regulators, and large clinical trials groups are all struggling with recommendations.

The Central Nervous System and HIV



The role of the central nervous system (CNS) (brain and spinal cord) in HIV disease can be divided into two areas: diseases of the CNS caused by invading pathogens or tumors and psychological/psychiatric disease.

Infectious diseases of the CNS such as toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy (PML), cytomegalovirus (CMV) and herpes have greatly diminished since the era of highly active antiretroviral therapy (HAART) began in 1996; so too has the incidence of tumors such as lymphoma.

These opportunistic diseases (OIs) were the result of uncontrolled HIV virus causing severe immune suppression and low T-cell counts. Effective treatment with HAART can lead to an undetectable viral load, and the immune system can and does recover.

Even when the viral load is not completely suppressed, HAART can often prevent these diseases by making the HIV virus less fit. Only by selecting a number of mutations can the virus survive in the presence of HAART and these mutant forms are not as robust as the original 'wild' type. A weakened virus results in less immune suppression and fewer OIs.

HIV itself can infect the CNS, causing a brain infection called AIDS dementia

that is directly related to the amount of virus in the CNS. While most kinds of HAART will reduce level of the virus in the CNS, only a few of the drugs actually get into the CNS. These are AZT, Zerit, Ziagen, Viramune and Crixivan and they are the best choices to actually treat AIDS dementia. More subtle impairment of brain function (often overlooked) may also result from infection with HIV.

Psychological disease is very common in people with HIV. The HIV Service and Cost Utilization Study (HSCUS) enrolled 2,864 people with HIV in 1996 at 50 sites in the United States. An analysis in 1999 showed that 50 percent of participants had a psychiatric disorder, 40 percent used an illicit drug other than marijuana, and 12 percent were drug dependent.

Compared to the general population studied with the same methods, depression was five times more common in people enrolled in the HSCUS study, anxiety was eight times more common, panic was four times more common, and substance abuse was also much higher. In a study published by Bing et al. in the *Archives of Psychiatry* in 2001, the incidence of depression was 36 percent in the HIV population compared to 14 percent in the general population.

Depression is a major predictor of disease progression and death in HIV, as it is in other disease states. This may be because depression directly affects the immune system, but it is more probable that it is because people who are depressed are more likely to stop taking their drugs or to be less adherent to their regimen. Substance abuse and drug dependence can also reduce adherence to HAART. All of these common problems present a challenge when

healthcare provider and patient consider how to control HIV.

Some of the drugs commonly used to treat HIV have a direct toxic effect on the central and the peripheral nervous systems. The "D" drugs — D4T, DDI and DDC — may cause a numbness and burning pain in the feet, legs, or hands, which is often difficult to treat.

Efavirenz (Sustiva) is a commonly used antiviral drug that affects the CNS and often causes dizziness, abnormal dreams, poor concentration, anxiety, and even hallucinations. These are worse in the first 4 weeks of therapy and then usually improve. Studies have shown that psychological symptoms from Efavirenz often persist for 6 months or more (ICAAC 2001). A recent study presented in Barcelona showed that people with a prior psychological illness tend to have greater and more sustained CNS side effects from Efavirenz.

Unless there is an urgent and critical need to start HIV therapy right away, evaluation and treatment of both mental illness and substance abuse should occur before HAART is begun. This should be done both initially and at periodic intervals to make sure old illness is managed and that no new issues are occurring. However, continued use of injectable drugs is not necessarily a bar to effective HAART. Two individual histories illustrate the interactions between HIV and disorders affecting the CNS.

In one case, a 35-year-old Native American was seen for a stroke that had left his left side paralyzed. A CAT scan of his brain showed a lesion that was diagnosed as being caused by toxoplasmosis. He was a long-time alcoholic and had a CD4 count of 10 and a viral load over

New Expanded Access Program for T-20

100,000 copies per mL of blood. He was treated with antibiotics for the toxoplasmosis, received physical therapy for his paralysis, was treated for alcoholism (with significant input from his family), treated with antidepressants for an underlying and untreated depression — and treated with HAART (two nucleosides and a protease inhibitor) for HIV. He has completely recovered from the stroke, has been sober for 4 years, has an undetectable viral load, and a CD4 count above 500.

In a second case, a 42-year-old white gay male scientist began therapy for his HIV disease with two nucleosides and Sustiva. He had a history of alcohol abuse and depression, both in remission. His viral load became undetectable and his CD4 count rose. However, he became severely depressed, began to drink, and became suicidal. When his medication was changed from Sustiva to Viamune, he quickly recovered from his depression with continued good control of his viral load.

Effective treatment of HIV should consider not only the choice of HAART regimen but the underlying health of the CNS. ✎

Trevor Hawkins, MD is the Medical Director of Southwest CARE Center and the Associate Clinical Professor at the University of New Mexico.

The Expanded Access Program for the first entry inhibitor T-20 aka (Fuzeon) has begun.

The brand name for this product will be Fuzeon, and the generic name enfuvirtide. The manufacturer, Trimeris, has had problems in making large volumes of this compound for distribution. Slowly, however the supply of this first entry inhibitor has started to increase. T-20 is a protein chain of 36 amino acids. It is not absorbed in the stomach and must be injected under the skin twice a day. In August, 2002, an "Early Access Program" began for Fuzeon. Physicians can register to participate in the program at the following web site: www.T20EAP.com. It is anticipated that the drug for this program will be available in October. Health care providers at major hospitals and universities may also have to get approval from their local institutional review board (IRB) a process which can take up to several months.

The criteria or eligibility for this program is as follows: age 16 or older; HIV RNA viral load above 10,000 copies/ml; and CD4 T cell count under 100 cells/mm while on a HAART regimen. Individuals must also have limited treatment options in the judgment of their health care provider. Initially, each registered health care provider will be allowed to enroll a maximum of 5 people. Hopefully, as drug supply increases, this limit will be increased.

Reported trials of Fuzeon have shown that it can add additional viral suppression when added to a current "failing" regimen. Difficulties can arise with the issue of twice a day injections (like insulin) and tender nodules can become

present at the injection sites. However, in early trials the discontinuation rates were very low. Also, resistance to Fuzeon develops in some people over time. The next entry inhibitor in development by Trimeris is T-1249. This inhibitor will need only a once a day injection, and appears to be effective even if resistance to T-20 develops. Schering also has a compound in development which is an entry inhibitor, Schering-C, which can be taken by mouth. Both T-1249 and Schering C are still fairly early in development. It is not known when, or if, there will be an expanded access program available for these compounds. ✎



Ask Dr. Jeff

by Dr Jeff Schouten

Q:

Some of my friends have had surgery to correct body shape changes caused by the HIV drugs. What is your opinion of this option?

A:

The two major body shape changes that may be modified with plastic surgery are facial fat loss, and the so-called buffalo hump, or a fat pad on the back of the neck. Some people with loss of facial fat have had surgical implants or injections to fill out their cheeks. The results of the implant surgery can be quite good. The silicon implants are permanent. Also, some surgeons will suction fat from other areas of the body and use it to fill facial areas. However, most people with significant fat loss in the face also have lost most of the fat under the skin of their arms and legs, so there is not too much fat available from other areas.

There is a new product which is a synthetic poly-lactic acid, called New-Fill. It is an injectable substance used to fill in areas of fat loss. However, the FDA has put a hold on the use of the substance in the U.S. For a full discussion of New-Fill see the excellent article from Positively Aware at: http://www.thebody.com/tpan/janfeb_02/newfill_t20.html.

The use of liposuction for removal of a buffalo hump can be very successful. A few years ago there was concern that the fat would quickly reform following liposuction. However, the people I know who have had liposuction have not experienced this problem.

The increased fat in the abdominal cavity that some people develop cannot be corrected with liposuction. This is because liposuction can remove fat from only under the skin. In people who develop the "protease paunch," the fat surrounds the internal organs, and is not under the skin.

The biggest challenge in seeking out plastic surgery to correct

body shape changes caused by HIV treatment is paying for it. Almost all healthcare plans consider the above procedures to be cosmetic, meaning they will not pay for it. Some people have convinced their healthcare plan to pay for liposuction to remove a buffalo hump. The more documentation that the patient can produce showing that the fat deposit at the back of the neck is causing pain, sleeping problems, or other symptoms, the greater the chance of convincing a healthcare plan to pay for the procedure. However, I know people with large buffalo humps and significant pain and discomfort who have been unable to convince their healthcare plan to pay for the liposuction.

In general, I think that not as many people on treatment for HIV are developing major body shape changes as was once feared, although some definitely are. However, the disappointing results of trials that test switching from drugs thought to cause these problems, and the lack of encouraging results from early studies of insulin-sensitizing drugs means that, for some people, surgery will continue to be their best chance of reversing some of the fat loss or gain caused by their HIV treatment. ✕



Dr Jeff Schouten is a former general surgeon who has been living with HIV for over 10 years. He is chair of STEP's Publications Advisory Committee and contributes regularly to the *STEP Perspective*. He has also earned a law degree from the University of Washington, so HIV-related legal questions, as well as medical, will be accepted.

Ask Dr. Jeff or Dr. Brad your question!

Mail in your question or e-mail us at

dr@stepproject.org

We will answer all questions and print those that space allows.

Ask Dr. Brad

by Dr Brad Lichtenstein



Q: Looking at my tongue lately, it has a white coat to it. Could this be thrush? If so, what can I do about it?

A: Thrush, the common term for *Candida albicans* in the mouth, is a fungus that presents when our immune system is weakened. When healthy, we have approximately 400 different kinds of bacteria living in balance in the digestive tract. When this balance is disrupted, one or several organisms, such as *Candida*, will increase (overgrow) and symptoms will develop. Typically, thrush presents as white, cottage-cheese-looking patches on the tongue, sides of the mouth, or the back of the throat. A simple white coat to the tongue is not necessarily thrush, so contact your doctor before seeking treatment.

As the immune system continues to weaken and CD4 cell counts drop, many patients take antibiotics to prevent opportunistic infections. Both Bactrim and Dapsone, taken to prevent pneumocystis pneumonia (PCP), can disrupt the normal bacteria balance in the digestive tract. When this happens, *Candida* overpopulates not only in the mouth, but in the intestines as well. Fortunately, multiple options for the treatment of the thrush exist, with the most fundamental being dietary.

The first and foremost nutritional suggestion is the complete avoidance of sugar and alcohol. *Candida's* main source of food is sugar, and alcohol contains a great deal of simple sugars. While some naturopaths stress the avoidance of all forms of fruit in the sugar-free diet, I reserve that strict recommendation for cases of severe thrush. Eating the entire fruit or vegetable provides you with fiber that can minimize sugar's effect on *Candida*. For those with severe thrush, for instance, when it spreads into esophagus, all fruit and vegetables should be avoided.

For most cases, however, I recommend avoiding the following: fruit and vegetable juices, jellies and preserves, sodas, honey, molasses, or brown rice

and maple syrup. Concentrate your diet on whole, unrefined, and unprocessed food sources of protein and complex carbohydrates. The protein category includes lean meats (beef, lamb, venison), poultry (chicken and turkey), fish, eggs, tofu, beans and legumes. Since the majority of my HIV-positive patients on anti-retrovirals tend to be allergic to milk products, I suggest people avoid dairy, especially because milk, yogurts, and cheeses contain sugars that are fuel for *Candida*. Acceptable forms of complex carbohydrates are whole grains, again an issue over which doctors will dispute. Since carbohydrates are broken down in the gut into sugar, several physicians and nutritionists suggest avoiding these as well. Clinically, I have seen improvement in thrush even when patients consume whole, cooked grains, such as rice, millet, or quinoa, and avoid processed carbohydrates, such as breads, pastas, crackers or cereals. Whole, cooked vegetables are also included in the complex carbohydrate category. Once more, I reserve the suggestion of total avoidance of complex carbohydrates for severe *Candidial* infection.

The best food item you can consume if you suffer from thrush is garlic (for issues regarding garlic and anti-

Brad S. Lichtenstein, ND is licensed naturopathic physician, personal trainer, and yoga and meditation teacher. In private practice, he specializes in HIV care, counseling, and yoga therapy. Brad works with people interested in taking an active role in their lives and looking beyond their diagnosis and illness in order to create meaning purpose in their lives. Brad continues to offer meditation, yoga and movement classes as well as offering workshops on naturopathic approaches to living well with HIV and AIDS. He can be reached at (206)545-7133 or at his website at www.naturopathiclifecoach.com

retroviral medications see Ask Dr. Brad column in the previous issue of the *STEP Perspective*). One of garlic's many healing properties is its ability to kill funguses, bacteria, and other microorganisms. The best form is raw garlic. The active part of garlic is the allicin, or the odor-producing portion. Unfortunately, garlic must be macerated or chopped in order for it to be active, so swallowing a clove of garlic whole provides little benefit. Furthermore, cooking garlic causes allicin become less potent. I recommend one clove of crushed

continued next page

“POZ in the City”



STEP, POZ Seattle and **the Lifelong AIDS Alliance** invite you to a community meeting with featured speaker Nelson Vergel , Executive Director of the Program for Wellness Restoration, **PoWeR**. Nelson is a long- term survivor and co-author of the book “ Built to Survive”. Nelson will give a presentation on strategies on how to meet the challenges of Lipodystrophy, facial wasting and disclosure.

WHEN Oct 17th 2002 **6:30-9pm**
WHERE Miller Community Center, Seattle
330 19th Ave East

For more information or directions to this event please e-mail us at [Step100 @stepproject.org](mailto:Step100@stepproject.org) or call us at 206-329-0064 ext 105.

continued from Dr. Brad

garlic mixed with a tablespoon of an essential fatty acid, such as flax seed oil, one to two times a day. If swallowing raw garlic with olive or flax seed oil alone is not palatable, try making a salad dressing with oil, vinegar, and one clove of crushed garlic. Or try adding one clove of crushed garlic for taste to your vegetables, grains, or protein after they are done cooking.

Since thrush develops from an unbalanced bacteria ratio, supplementing with healthy microorganisms is beneficial. The *Lactobacillus* species (*L. acidophilus*, found primarily in the small intestines, and *L. bacillus*, found primarily in the colon) facilitate digestion of carbohydrates in the gut, and as a by-product of this process, they produce lactic acid. Lactic acid is unfavorable to many forms of yeast and bacteria like *Candida albicans*. *Lactobacillus* species also help keep the balance of organisms in the gut in check through the production of antibiotics (acidophilin, lactocidin, and acidolin) that prevent toxic bacterial organisms (*E. coli*, *Helicobacter pylori*, and *clostridia*, etc.) from seeding the gastrointestinal tract. In addition to these properties, *Lactoba-*

cillus helps synthesize B vitamins and butyric acid (an essential fuel source and healer for the cells that line the colon), improves lactose digestion and absorption, and helps maintain normal bowel functioning by reducing diarrhea, constipation, gas, bloating, etc.

Regarding supplementing with *Lactobacillus*, I always recommend a dairy-free (avoid *acidophilus*-enriched milk), wheat-free, refrigerated, powdered or liquid form of *acidophilus* to be mixed with water (no juice due to the sugar content) and taken on an empty stomach 1 hour before eating or 2 hours after eating.

Another organism that has been used for the treatment of thrush is the yeast called *Sacchromyces boulardii*. Unlike *Candida*, *Sacchromyces* is a non-pathogenic (friendly) yeast. Like *Lactobacillus*, it, too, helps rebalance the organisms in the gut flora, but is not destroyed by antibiotics as *Lactobacillus* will be. *Sacchromyces* comes in capsule forms and should be taken like acidophilus, on an empty stomach. If you are currently on antibiotics, the recommendation is

to take either or both *Lactobacillus* or *Sacchromyces* daily. If you are suffering from thrush and aren't taking antibiotics, continue with supplementation for at least a month after the thrush clears. I recommend that patients with recurrent thrush continue preventive treatment with *Lactobacillus* or *Sacchromyces* at least three times a week as a precautionary measure.

Finally, oregano oil has been found to kill many pathogenic yeasts like *Candida*. Encapsulated oregano oil taken three times daily has been quite successful in the treatment of mild to severe thrush when taken in conjunction with the above measure. ✕