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Update on Structured Treatment Interruptions

Structured Treatment Interruptions, or STIs, were the subject of a lively session at this year's Conference on Retroviruses and Opportunistic Infections (CROI). Spurred in part by the early closure of enrollment for the SMART study (see below), interest in STIs is higher than in many years. This article reviews the studies presented at CROI and summarizes the state of current understanding on this important subject.

In order to better understand the results of these studies, it is helpful to review the focus of STI research and what previous studies have shown. Interest in STI research is driven by four different and sometimes overlapping goals:

- ☞ Reinvigorating the immune response,
- ☞ Helping people with treatment fatigue,
- ☞ Helping reduce the costs of treatment, and
- ☞ Helping reduce long-term side effects of treatment.

The following is a brief overview of the rationale for each goal and what research to date has shown.

Reinvigorating the immune response

This strategy came from observations that HIV disease progression may be linked to the loss of a type of immune cell, called an HIV-specific cytotoxic lymphocyte (CTL). These cells seek out and destroy HIV-infected cells. Some, but not all, research indicates that some long-term non-progressors—those who stay well for many years despite HIV and without therapy—maintain robust levels of potent HIV-specific CTLs while people who progress more rapidly do not.

The goal of one STI approach is to preserve and enhance the body's natural immune responses against HIV infection. In theory, this would help a person's immune system better control HIV on its own for longer, perhaps indefinitely, without therapy. In this context, anti-HIV therapy curbs the destruction of cells by HIV while treatment interruptions are employed to modify the immune response. By starting and stopping therapy periodically, it was hoped that with each successive treat

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Note to the Reader:

The numbering of the pages for the July issue was incorrect. Instead of the first two pages being "1" and "2" they were listed as "3" and "4." Therefore, the Table of Contents did not match the listed page numbers. The actual content (the articles), however, was complete. We apologize for the error and the confusion it may have caused you, the readers.

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41st EASL Coverage

Liz Highleyman

The 41st annual European Association for the Study of the Liver (EASL) meeting took place April 26-30 in Vienna, Austria. The hepatitis C abstracts that generated the most interest were mainly in two areas: refinements of standard therapy and novel experimental agents.

Treatment Refinement

J.G. McHutchison and colleagues (abstract 744) reported that patients who achieve sustained virological response (SVR) – undetectable HCV viral load six months after the end of treatment – are very unlikely to relapse in the future. After five years of follow-up, 98% of nearly 500 patients in six clinical trials who achieved SVR with interferon (with or without ribavirin) still had undetectable HCV RNA. The authors concluded that SVR at six months “is an excellent predictor of long-term clearance of the virus” – further evidence that a “cure” for hepatitis C is possible.

In an attempt to reduce the side effects and costs associated with hepatitis C therapy, researchers have increasingly focused on individualized regimens using lower doses or shorter courses of therapy. Long-term data from the WIN-R study, presented by R. Brown and colleagues (abstract 41), confirmed that a 24-week course of therapy is adequate for patients with genotypes 2 or 3 HCV. In this study, more than 1800 participants with these genotypes were randomly assigned to receive pegylated interferon-alpha 2b (Peg-Intron) plus either fixed-dose or weight-based ribavirin for 24 or 48 weeks. Among patients who achieved an end-of-treatment response, 6-10% in the 24-week arm relapsed during the post-treatment follow-up period, similar to the 5-12% seen in patients treated for 48 weeks; discontinuation rates were also similar.

But further shortening treatment to 16 weeks is not advisable, according to data from the 1469-person ACCELERATE trial, presented by M. Shiffman and colleagues (abstract 734). In this study, 24 weeks of pegylated interferon-alpha 2a (Pegasys) plus ribavirin was more effective than 16 weeks for patients with HCV genotypes 2 or 3. While both groups responded well at the end of treatment, the extra eight weeks reduced the risk of relapse: 76% in the 24-week arm achieved SVR, compared with 65% in the 16-week arm. “This study shows that genotypes 2 and 3 patients really do need 24 weeks of treatment for optimal results,” Shiffman said.

Research has consistently shown that early response predicts ultimate treatment success. P. Ferenci and colleagues (abstract 8) reported that shorter therapy may

be effective for so-called “super-responders” who achieve undetectable HCV viral load by week 4. In this study, 106 “super-responders” out of more than 400 total participants with “hard to treat” genotype 1 or 4 HCV were randomly assigned to receive standard-dose Pegasys plus ribavirin for 24 weeks (rather than the usual 48 weeks for these genotypes). Using an intent-to-treat analysis, 75% achieved SVR at the end of follow-up – higher than the overall SVR rate for all genotype 1 patients observed in most studies using 48 weeks of therapy.

Lowering the dose of ribavirin is another approach that has been proposed for reducing side effects. Ferenci and colleagues (abstract 82) also reported that reduced doses of ribavirin produced similar SVR rates, while improving tolerability in patients with genotype 2 or 3 HCV. More than 200 patients (most with genotype 3) were randomly assigned to receive either 800 or 400 mg daily ribavirin plus standard-dose Pegasys for 24 weeks. At the end of follow-up, 74% and 80%, respectively, achieved SVR. Hemoglobin levels (a measure of anemia, a common side effect of ribavirin) remained higher in the patients who received the lower ribavirin dose, leading the authors to conclude that reduced dosing provides “tolerability benefits.”

Treatment of Non-Responders

Another important area of research is management of individuals who did not respond to their first course of therapy. P. Marcellin and colleagues (abstract 11) reported data from the REPEAT trial, in which 950 participants who did not respond to prior treatment with Peg-Intron plus ribavirin were retreated with either a standard dose (180 mcg) or a higher induction dose (360 mcg) of Pegasys plus weight-based ribavirin. After 12 weeks, 45% in the standard-dose arm achieved early virological response (at least a 2 log decrease in HCV RNA), compared with 62% in the induction arm. In a separate presentation, D. Jensen and colleagues (abstract 583) reported that while the rate of side effects was similar in both arms, more patients in the induction arm required dose reduction.

In promising news for non-responders, S. Kaiser and colleagues (abstract 584) presented further data showing that long-term maintenance therapy with low-dose Peg-Intron can improve liver histology. In this study of 240 previous non-responders with advanced fibrosis or cirrhosis, those receiving the maintenance regimen (0.5 mg/kg weekly for 36 months) were significantly more

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likely than untreated control subjects to experience reduced liver fibrosis and decreased necroinflammatory score, although the latter was temporary and rose again after maintenance therapy was discontinued. No adverse side effects were reported, leading the researchers to conclude that interferon maintenance may be used as "salvage therapy."

Side Effects

Traditionally, healthcare providers have discouraged hepatitis C treatment for patients with pre-existing psychiatric conditions due to the higher risk of side effects. J. Lang and colleagues (abstract 591) reported data from a study of nearly 2000 French patients, 22% of whom had a history of psychiatric disorders including depression, suicide attempts, or psychiatric hospitalization. Patients with a psychiatric history were four times more likely to stop treatment (16% vs 4%); however, the overall rate of treatment discontinuation for any reason was similar in patients with and without a psychiatric diagnosis (36% vs 30%). These results suggest that such patients should not automatically be excluded from treatment, since a majority can tolerate therapy.

Thrombocytopenia – a low level of platelets in the blood, which can lead to easy bruising and bleeding – is common in patients with hepatitis C, and is a potential side effect of interferon. McHutchison and colleagues (abstract 745) reported that a new medication called eltrombopag is a safe and effective treatment for this condition. Eltrombopag stimulates the proliferation and maturation of platelet precursor cells called megakaryocytes. In this interim analysis of data from a Phase II placebo-controlled trial, eltrombopag increased platelet counts in 67-90% of 28 patients; response rates increased with higher doses (30, 50, or 75 mg daily). There were no serious side effects, and platelet counts increased enough to allow all treated patients to start interferon.

Experimental Therapies

The latest trial data for several new hepatitis C agents was presented at EASL. Valeant Pharmaceuticals' virmidine is a pro-drug of ribavirin that works primarily in the liver, and thus is less likely to cause anemia. Y. Benhamou and colleagues (abstract 751) reported data from the Phase III VISER1 trial comparing fixed-dose virmidine (9600 mg twice daily) to weight-based ribavirin (500-600 mg twice daily), both with Peg-Intron. In this study, which included 970 treatment-naïve patients, anemia rates were significantly lower in the virmidine arm compared with the ribavirin arm (5% vs 24%). However, in an intent-to-treat analysis, vira-

midine was not shown to be "non-inferior" to ribavirin, with SVR rates of 38% vs 52%, respectively. Virmidine did work as well as ribavirin in younger patients (under 45 years) and lighter-weight individuals, suggesting that weight-based dosing may be preferable.

One of the novel anti-HCV agents furthest along in the development pipeline is the oral polymerase inhibitor valopicitabine (NM238) from Idenix Pharmaceuticals. N. Afdhal and colleagues (abstract 483) presented interim results from a Phase IIb study that included 190 previous non-responders with genotype 1 HCV. Participants were assigned to one of five arms: 800 mg daily valopicitabine monotherapy, Pegasys plus one of three doses of valopicitabine (400 mg daily, 800 mg daily, or escalating doses from 400 to 800 mg), or continued standard therapy. After 24 weeks, those in the two higher-dose valopicitabine/Pegasys arms responded significantly better (2.99-3.29 log IU/L decrease in HCV RNA) than subjects receiving valopicitabine monotherapy (.046 log IU/L decrease) or standard therapy (2.27 log IU/L decrease). In the combination valopicitabine arms, 12-24% achieved undetectable HCV RNA, compared to 18% in the standard treatment arm and none in the valopicitabine monotherapy arm. Valopicitabine was generally well-tolerated, although mild-to-moderate gastrointestinal (GI) side effects were common, and four patients (3%) discontinued for this reason. Response rates were higher in treatment-naïve patients. D. Dieterich and colleagues (abstract 736) presented data from another study in which 173 previously untreated genotype 1 patients were randomly assigned to receive Pegasys plus valopicitabine at doses of 200 mg daily, 800 mg daily, or escalating doses from 400 to 800 mg, or else Pegasys monotherapy. In the combination arms, at least 80% achieved early virological response, 45-67% had undetectable HCV RNA at 12 weeks, and median viral load reductions were about 3.9-4.5 log IU/L. Similar early results were seen in the Pegasys monotherapy arm, however, and the question remains whether valopicitabine will produce a more durable response after treatment is completed.

Joining valopicitabine, S. Roberts and colleagues (abstract 731) reported the first data from a Phase I study of another HCV polymerase inhibitor, Roche's R1626. Eighteen treatment-naïve patients with genotype 1 HCV were randomly assigned to receive either 1500 mg or 500 mg twice daily R1626 monotherapy or placebo for 14 days. After 14 days of follow-up, those who received the 1500 mg dose experienced a median 1.2 log IU/L (range 0.5 to 2.5) reduction in HCV RNA. R1626 was well-tolerated, with no serious adverse events or early withdrawals.

S. Zeuzem and colleagues (abstract 78) presented data from a study of SCH503034, an HCV protease inhibitor

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Alcohol and the Liver

Alan Franciscus, Editor-in-Chief

One of the best strategies to keep the liver healthy for people living with hepatitis C is to stop drinking alcohol or to greatly reduce the amount of alcohol consumed. In addition to the harmful effects alcohol has on the liver, alcohol also poses other problems for people with hepatitis C. Consuming alcohol (especially in large quantities) can:

- Lower the immune response in people with hepatitis C
- Help the hepatitis C virus replicate or make more copies of itself
- Lower HCV treatment response
- Add to the emergence of HCV quasi-species
- Increase the level of iron stored in the liver
- Increase fat accumulation in liver cells

When all of these factors are considered, it is no wonder that people are advised to abstain from alcohol. But how is alcohol actually metabolized by the body? This article will focus on how alcohol is absorbed and metabolized throughout the body and also on some of the effects of prolonged alcohol use.

When alcohol is consumed it reaches the stomach then the small intestine where it passes into the blood stream. About 20% is absorbed through the stomach and about 80% is absorbed through the small intestines. Once the alcohol enters the blood stream it is sent to and processed by the liver. After one drink of alcohol the concentration of alcohol in the blood peaks in about 30 to 45 minutes and drops back to normal in about an hour if no further alcohol is consumed.

The liver is responsible for converting the alcohol into a substance that is safe for the body. There may be a small quantity of alcohol that does not reach the liver – this is excreted in the urine and breath. That's why breath analyzers are able to measure the amount of alcohol someone has consumed.

Liver

There are two liver enzymes that are responsible for converting alcohol into a safe substance: alcohol dehydrogenase (ADH) and cytochrome P450IIE1 (CYP2E1). ADH is the main enzyme responsible for converting alcohol. CYP2E1 is another enzyme that is involved in the process of metabolizing alcohol. In people who are chronic alcohol drinkers the liver will make more CYP2E1 in an effort for the body to compensate for ex-

cess alcohol consumed. Unfortunately, the extra production of CYP2E1 does not stabilize the effects of long term alcohol use or the damage that is caused to the liver.

In people without liver disease, chronic drinking will lead to the deposit of fat in the liver cell, leading to inflammation and cell death. After a time the cell death will cause light scarring of the liver and after years of chronic drinking the liver can develop cirrhosis. If you combine the efforts of alcohol and with another factor such as hepatitis C the time it takes to cause damage is much shorter.

There are differences in what causes intoxication in people. Some factors that influence the degree of absorption and, therefore, intoxication include:

The amount of alcohol consumed – the liver can only metabolize a certain amount of alcohol per hour

The rate of metabolism differs depending on the amount of ADH enzyme in the liver and this differs by gender.

Food can affect the amount of alcohol absorbed by the body. If there is food in the stomach it can slow down the absorption of alcohol. Foods high in carbohydrates and fat help to slow down the process of the stomach pushing the food (and alcohol absorbed) into the small intestine. Mixing alcohol with beverages can also affect the absorption of alcohol – alcohol mixed with fruit juice or water is absorbed more slowly than alcohol mixed with carbonated beverages.

Muscle tissue contains more water than fat tissue so the more muscle tissue a person has the more diluted the alcohol will be.

Gender Differences

There are differences in the way alcohol affects men and women. The amount of body water affects the rate at which alcohol is absorbed. The more body water a person has the less the amount of alcohol that is absorbed. In general, women have higher body fat composition (less body water); men have a higher body composition of muscle (more body water). For this reason women will achieve higher concentrations of alcohol in their bodies than men who consume equal amounts of alcohol. In addition to gender differences, total body water composition decreases as people age

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Anti-HIV Therapy Update

Prediction is, at best, an imprecise exercise. This is certainly true of anti-HIV drug development. Many factors affect the pace of drug development and research. Drugs do not move through these processes at an even or entirely predictable pace. Economic, scientific and human factors can have a profound affect on the speed with which a drug or other product moves from the laboratory shelf (or increasingly a computer model) to a product available in pharmacies or drug stores. Nonetheless, it's important for people to know what is coming through the development pipeline—as the treatment decisions made today may affect one's options available later and can, in turn, be affected by what we think will become available. This article looks at some of the developments we expect over the next year or so, knowing that these are only our best guesses based on the information we have at this time.

The next new anti-HIV drug to be approved by the Food and Drug Administration (FDA) is likely to be darunavir (previously known as TMC-114 and soon to have the trade name Prezista). This protease inhibitor (PI), developed by Tibotec Therapeutics, is designed to work for people whose virus has developed resistance to any of the currently approved PIs. Tibotec has submitted data from phase II studies to the FDA, which is expected to rule on it in late June 2006.

Based on promising results of earlier studies (called POWER 1 and 2), there is little doubt that the FDA will approve this drug. The drug will initially be approved only for people with PI resistance, like another PI called Aptivus (tipranavir). The manufacturer is expected to quickly complete other studies in people just beginning therapy, thus widening the drug's approval.

Based on its high potency, its strong barrier against development of resistance, and its low level of toxicity seen so far, there seems little doubt that the drug will succeed as first line therapy. This might make it one of the most important drugs in the anti-HIV arsenal. Although completing studies to prove its value in first line therapy will take at least another year, once it's approved for any group of patients, doctors are free to prescribe it for anyone they wish.

It is less clear, though, whether insurance companies and other payers will be as quick to offer reimbursement until these other studies are completed. However, if darunavir offers all the advantages people are hoping for, even payers may see it as a real advance and move quickly to offer reimbursement. The price charged for the drug may play an important role in how supportive payers will be.

Another new drug from Tibotec should enter expanded access in late 2006 or early 2007. Etravirine (TMC-125) is an experimental non-nucleoside reverse transcriptase inhibitor (NNRTI). It is designed to work on viruses that are resistant to other NNRTIs, like Sustiva (efavirenz) and Viramune (nevirapine). This is a potentially important development, as all of the current drugs in this class are highly cross-resistant—meaning that HIV that develops resistance to one is likely to be resistant to the others. Between etravirine and a second and possibly more potent NNRTI in development at Tibotec (TMC-278), the curse of cross resistance may be conquered for this class of drugs.

Tibotec is also responsible for a unique advance in HIV research beginning in the spring 2006. It is the first study that combines two experimental anti-HIV drugs at the same time. The trial, called DUET, will study darunavir + etravirine vs. darunavir alone in people with resistant virus—with both groups taking optimized background therapy in addition to the experimental therapy. This study is enrolling now, and data should start coming out in 2007. Tibotec deserves recognition for this innovative approach. For years researchers and companies have urged patients with resistant virus always to start two new drugs at the same time, but this is the first time a company has made it possible for those with the most serious resistance problems.

2006 will see two important milestones for an entirely new class of drugs called integrase inhibitors, represented by Merck's MK-0518. Large, pivotal Phase III trials of MK-0518 began enrolling in spring 2006 and the company will open an expanded access program no later than fall 2006. (Expanded access programs provide some people early access to experimental drugs prior to approval.) For a more detailed discussion of MK-0518, read the article Drug Pipeline Offers Diverse New Therapies and Hope. Early indications are very positive for this class of drugs and for MK-0518 in particular, which is the farthest advanced in development. FDA approval is likely in 2007.

Two other major advancements expected in the near future aren't new drugs, but hopefully better ways to use existing drugs. The first is a needleless injection system for the entry inhibitor (EI) Fuzeon (enfuvirtide, T20). The device, called a Biojector, uses high pressure carbon dioxide to inject the drug under the skin, rather than through a metal needle. The hope is that this new system will result in fewer injection site reactions and be easier to use. There is no firm timetable

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HealthWise: Healthy Living with HCV Series *Part 2:* *Physical Fitness*

Lucinda K. Porter, RN

Anyone over the age of 50 might remember one of my favorite weight loss commercials. The ad featured a vibrating belt, strapped around the user's hips. The hype professed that fat could be jiggled off without any exercise. The notion was ridiculous, but the device sold well.

Here we are, more than half way through the first decade of the new millennium and guess what? Vibrating weight loss belts are popular again. Does this mean they work? Absolutely not. Think about this: if we could vibrate off unwanted pounds, then anyone who uses a jackhammer or rides the New York subway would be thin. Models and movie stars would be trading personal trainers for personal tremblers.

Yet in spite of the quackery, people are buying vibrating belts. This is probably because exercise involves effort, commitment and time. For those who do not like it, exercise is especially hard work. Having our fat pulsed off sounds appealing, especially if it involves minimal effort.

However, exercise is more than a weight management technique – much more. Physical activity helps fight fatigue and depression. It is the cornerstone for managing high blood pressure, high cholesterol and diabetes. There is evidence that physical activity reduces the risk of cancer and may boost the immune system. Experts recommend exercise to reduce the risk of stroke and heart attack. Movement can reduce the symptoms of back pain, arthritis and other muscle and joint aches. It may lower the risk of osteoporosis and dementia.

Insurance companies and employers promote physical fitness because ultimately it is good for business. Fitness programs can improve flexibility, balance, tone, strength and stamina. Exercise can clear the head and body of worry and anxiety. Being physically active may improve sleep, reduce food cravings, and help us feel more energetic.

The following recommendations for minimum fitness goals are from the Centers for Disease Control (CDC):

*Adults should engage in **moderate-intensity** physical activities for at least 30 minutes on 5 or more days of the week. Moderate intensity exercise is defined as an increase in breathing or heart rate; the effort a healthy individual might use while walking briskly, mowing the lawn, dancing, swimming, or bicycling on level ground; any activity that burns 3.5 to 7 calories per minute*

(kcal/min)

–American College of Sports Medicine

OR

*Adults should engage in **vigorous-intensity** physical activity 3 or more days per week for 20 or more minutes per occasion. Vigorous-intensity physical activity may be intense enough to represent a substantial challenge to an individual and refers to a level of effort in which a person should experience: large increase in breathing or heart rate; the effort a healthy individual might expend while jogging, mowing the lawn with a nonmotorized pushmower, participating in high-impact aerobic dancing, swimming continuous laps, or bicycling uphill, carrying more than 25 lbs up a flight of stairs, standing or walking with more than 50 lbs; any activity that burns more than 7 kcal/ min*

– Healthy People 2010

Many of us already engage in moderately intense activities. Examples are most household and home repair chores, grocery shopping, gardening, and waxing a car. The rule of thumb for vigorous activity is you should be able to talk but not sing during the activity. I tried this yesterday and attracted a lot of attention. I do not know if this was due to my singing or my running style.

Most of us know that we are supposed to exercise, but there can be a huge gap between what we do and what we wish we could do. People living with hepatitis C (HCV) know this more than most. People with HCV report fatigue, muscle and joint aches. Depression, weight gain, and mental “fogginess” can also create obstacles. Exercise is still harder for those undergoing HCV treatment. For them, climbing the stairs may feel like climbing Mt Everest.

If this is true, then how do we get moving? The key may be the way we perceive exercise. If we view exercise as a chore or something that creates pain, then physical activity may feel like an obstacle. Perhaps the first step is as simple as replacing the words “exercise” and “fitness” with “play” and “fun.” When exercise is an act of recreation or play, we are more willing to engage in it.

Willingness to act is a good first step, but then what?

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Consult your medical provider. There may be medical reasons to limit or modify a fitness program. This is especially true if you are older or live with disabilities. A physical fitness plan should be safe and fit your needs. Identify what you need most. Is it strength, flexibility, balance, aerobic endurance or a combination of these? What type of program does your provider recommend?

For those new to exercise, a reasonable beginning regimen might be to walk a few minutes, stretch, and stop for the day. Always allow a day of rest between weight training workouts. Some fitness trainers recommend a day of active rest every week. Active rest means taking a break from a regular fitness regimen but does not mean spending it on the couch.

Start small and gradually work up to a goal. If the long-term goal is to walk 30 minutes five days a week, then start with 5 minute walks 3 days a week until you can do this effortlessly. Do not overdo it. Too much exercise may lower your immune function.

Be sensible about exercise. Remember to drink water, apply sunscreen and avoid injuries. Pain is NOT gain. However, sore muscles may occur. Heat, cold packs, and stretching may be beneficial. Remember to consult a doctor for injuries and discuss a back-up fitness plan for common injuries. Avoid exercise when ill.

Sometimes a successful fitness program is just a matter of finding the right one. Fortunately, there are many from which to choose. Walking, hiking, swimming, dancing, bicycling and weightlifting are some common recreational activities. Yoga, Tai Chi, Pilates, gardening and playing with children are forms of exercise.

Physical fitness is more likely to be successful if it is portable, not dependent on the weather, and fits any budget. Water bottles are good hand weights. Put the radio on your favorite oldies station and dance to your heart's content. Take a walk in a park.

Staying fit does not have to be an all or nothing proposition and can fit into the busiest schedules. Some ways to do this include gardening, using the stairs, choosing a parking spot on the outskirts of the lot, getting off the bus before the scheduled stop and walking the rest of the way, window shopping, sweeping the floor, and mowing the lawn. Replace power tools with manual tools. Trade a motorized lawnmower for a nonmotorized one. Walk rather than drive. Do not use the remote control when watching TV. Stretch, do leg

exercises or lift light weights while talking on the phone or watching television. Any opportunity to be active helps us to stay in shape.

Make sure you reward yourself. Reward efforts, not results. Choose healthy rewards, such as new exercise clothes, like socks or a warm-up jacket; exercise gadgets such as a pedometer, heart rate monitor; and additional time for relaxation or engaging in a favorite activity.

Just as in life, variety is an important aspect of exercise. If you walk, add activities at various intervals that increase your heart rate and use other muscles. Examples of this: Every 5 minutes of walking, try skipping for a minute, or do 4 lunges, or 2 minutes of speed walking. If you use weights for toning, try a session using light weights with 20 to 30 repetitions, and another session using heavy weights and perhaps only 5 or 6 repetitions. You can also vary the speed of your workout. Lifting weights at a very slow rate can be incredibly challenging.

Here are some other suggestions, especially when it is hard to maintain a fitness program:

- Schedule your exercise. Mark it on a calendar. Stick to your schedule.
- Make it regular. This is how good habits are formed.
- Suit up and show up. Some people find the act of putting on sneakers and starting the activity helps overcome mental resistance.
- Find a fitness buddy. We are less likely to cancel out on a friend than we are on ourselves.
- Join a group or class.
- Keep a log. Watch your progress.
- Use the Internet and other motivation tools. (See *Resources* for more information.)
- Get a good coach. We have unlimited access to one – the coach we carry with us. Be a supportive coach. Skip the criticism. Show up, suit up and keep a positive attitude. The effort is worth it, especially when fitness becomes fun.

Resources

Note: These websites are recommended for the quality of information. Although some sites have advertising, these products and services are not endorsed by HCSP or the author.

Aetna Intellihealth – www.intelihealth.com
 American College of Sports Medicine – www.acsm.org/AM/Template.cfm?Section=General_Public

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HIV-1 Infection of CD4+ T Cells in the Gut

By Megan Wind-Rotolo Ph.D, and Joel N. Blankson M.D., Ph.D.

Clinicians and researchers have used peripheral blood as a convenient way of obtaining information on CD4 cell counts and the extent of viral replication in HIV-infected individuals. However, it should be noted that only 2% of the total body store of lymphocytes circulate in the peripheral blood; the other 98% reside in lymphatic tissue scattered throughout the body. Gut-associated lymphatic tissue (GALT) represents the single largest pool of lymphocytes, and as such, it is not surprising that it is a major target for HIV infection. In the past few years several major observations have been made regarding GALT. First, there is a massive depletion of GALT CD4 cells during primary infection. These cells are affected to a much higher degree than CD4 cells in the peripheral blood [Veazey R, et al. *Science* 1998;280:427-431, Brenchley JM, et al. *J Exp Med* 2004;200:749-759]. Furthermore, there is little or no reconstitution of these cells after the initiation of HAART in chronically infected patients [Guadalupe M, et al. *J Virol* 2003;77:11708, Mehandru S, et al. *J Exp Med* 2004;200:761-770]. Finally, HIV-1 DNA and RNA can be detected in rectal biopsies from patients on HAART with undetectable plasma viral loads, suggesting that GALT CD4 cells can serve as a reservoir for HIV infection [Anton PA, et al. *AIDS* 2003;17:53-63]. At this year's CROI there were numerous oral presentations regarding this interesting topic.

Brenchley and colleagues determined the frequency of HIV-infected CD4 cells in the gut of HIV-infected patients who had been on HAART for up to 3 years [Abstract 38]. They found that on average the frequency of infection of GALT CD4 cells was 10 times higher than that of CD4 cells from blood. Memory CD4 cells from the gut were also shown to be capable of producing virus, and while there was no direct evidence of active replication, it was concluded that gut depletion is likely caused by ongoing infection of local CD4 cells. In addition, few HIV-specific CD8 cells were found in the gut compared to the blood, indicating that the proposed ongoing viral replication in GALT is associated with a lack of local HIV-specific immunity.

Baker and colleagues also measured the frequency of CD4 cells in GALT and showed that the percentage of CD4 cells in this region is 50% lower in HIV-infected patients compared to non-infected controls [Abstract 41]. Interestingly, while there was a significant increase in peripheral CD4 cell counts after 6 months of HAART, there was no increase in the percentage of GALT CD4 cells. This is more evidence that CD4 cell depletion in the gut may not be reversible in chronically infected patients. The effect of depletion of gut CD4 cells is unknown, but there was an incidental finding of intestinal

polyps in 6/31 relatively young HIV-infected patients, including 1 precancerous lesion and 1 case of cancer.

HIV-infected patients who started HAART within 3 weeks of infection were shown to be able to repopulate memory CD4 cells in the gut [Dandekar, et al. Abstract 39]. The initiation of HAART was also associated with a lower frequency of infection of GALT CD4 cells. The expression of genes in the gut of patients who started HAART early was compared with that of patients who started HAART at later time points. Those who were started HAART early showed lower expression of inflammation and cellular activation genes and increased expression of mucosal repair and regeneration genes. These results led to the conclusion that the disruption of the gut microenvironment causes the depletion of CD4 cells.

Having shown a high frequency of infection of GALT CD4 cells, Douek and colleagues looked at other mucosal sites as well [Abstract 166]. Massive depletion of CD4 cells in the lung has previously been described in pathogenic SIV infection of Rhesus macaques [Picker L, et al. *J Ex Med* 2004;200:1299-1314.] The investigators have begun to study the effect of HIV on CD4 cells of the lung by analyzing cells from bronchoalveolar lavage of HIV-uninfected and HIV-infected patients. Preliminary data indicate that the pattern seen at this site differs markedly from the observed in the GALT. There is no depletion of CD4 cells associated with HIV infection; instead, an increase in the number of both CD4 and CD8 cells is seen. In contrast to the high frequency of infected cells in the GALT, the frequency of infection of lung CD4 cells is relatively low (comparable to the frequency of infection of peripheral blood CD4 cells). In addition, HIV-specific CD8 and CD4 cell responses are preserved at this site, and it was proposed that this local immunity may explain the low cellular viral loads and the preservation of normal CD4 cell counts.

What are the clinical consequences of CD4 cell infection in GALT? While it appears that the poor reconstitution of CD4 cells at this site is not associated with major GI symptoms in most patients on HAART, the relatively high frequency of pathology seen by Baker and colleagues is concerning [Abstract 41]. Confirmatory studies in larger cohorts of patients are needed. If reconstitution of GALT CD4 cells is important, then the work of Dandekar and colleagues [Abstract 39] would suggest that there is a major advantage to early treatment with HAART. The GI tract appears to be the

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HIV-1 Infection of CD4+ T Cells in the Gut (continued from page 9)

major target in primary infection; therefore, it follows that preventative vaccines will need to induce strong mucosal immunity in order to be effective. The high frequency of infected cells in the GALT has been interpreted by some investigators to be evidence of ongoing replication in patients on HAART. If this is correct, it could potentially explain treatment failure in some patients. This issue clearly needs to be definitely addressed, and tissue drug levels at this site should be measured. Finally, investigators working on eradication

of HIV infection have based their models on the rate of decay of latently infected cells in the peripheral blood. Nothing is known about the half-life of infected cells in GALT. As these cells and infected cells from other anatomical reservoirs are studied, major revisions in these models will more likely be needed.

The Hopkins HIV Report, May 2006

“Nef off”

NOTE to the reader: One of our Technical Reviewers drew our attention to an article with the above title that presents a possible explanation for the virulence of HIV. The article appeared in *The Economist*, June 17th 2006, page 87. The following is a summary of that article.

Authors Frank Kirchoff and Michael Schindler of the University of Ulm, in Germany, have published findings in *Cell*, suggesting that HIV virulence results from a change in what is called the “nef” gene. One role of that gene is to remove a protein called TCR-CD3 from the surfaces of the helper T-cells. TCR-CD3 assists in the immune system’s recognition of antigens, resulting in an immune response to destroy any infectious agent.

The article explains how differences between the nef gene in simian immunodeficiency virus (SIV) and HIV result in a fairly inconsequential disease in monkeys, but a serious one in humans. One reason why SIV has little impact on the host’s health is that the viral nef gene removes the TCR-CD3 protein for presentation and examination by an “antigen presenting cell.” This is also true in humans, but in simians the nef is self-limiting, and so regulates the amount of TCR-CD3 proteins that are separated from the virus. In humans, without the nef regulation that monkeys have, TCR-CD3 floods the system, presenting too much of this protein to T-helper cells. The T-helper cells when presented with the TCR-CD3, secrete chemicals that stimulate growth and multiplication of more T-helper cells and T-killer cells. The problem is that the T-killer cells are ineffective and do not suppress the HIV. Meanwhile, the TCR-CD3 “presentation” process, again, unregulated by HIV nef, results in over replication of T-helper cells, which “eventually exhausts the immune system’s capacity to regenerate itself.”

Questions, Questions The Future of HIV Research

By Bob Huff

The Retrovirus Conference is the most important scientific meeting on HIV of the year. This year's conference, the 13th, was held in Denver in early February 2006. Most presentations were aimed at scientists actively working on HIV basic science, clinical science, or drug development. But a group of leading HIV researchers organized a special session designed to acquaint younger scientists with some of the critical unanswered questions about HIV and to entice them into making HIV their career. AIDS research has made amazing strides in the 25 years since it was first described in the medical literature. The disease has gone from being a death sentence to being a mostly manageable condition for those with access to anti-HIV drugs. Still HIV is no picnic, and worldwide, millions of people with AIDS will die this year. It's clear that there is much work to be done in HIV research. It's also clear that it may be 10 or 20 years before some of the most important scientific goals, such as a vaccine or achieving immune control of the virus are accomplished. The quest for a cure may take much longer.

HIV Pathogenesis

John Coffin, National Cancer Institute, Frederick Md.

It may sound hard to believe, but 25 years into the epidemic we still don't know exactly how HIV causes disease. We know that HIV infects immune cells and that after prolonged damage to the immune system people with HIV can get sick and die from one of the illnesses that make up the acquired immune deficiency syndrome (AIDS). But we don't know exactly how this damage to the immune system occurs. Dr. Coffin's talk surveyed this question and several other key mysteries in the basic science of HIV.

Though we don't know enough about how HIV behaves in the body, we do know a great deal about how HIV replicates in cells. For example, to infect a new cell, the virus must bind to a CD4 receptor on a target cell's surface. This is why HIV infection is mostly limited to the CD4-bearing T cells of the immune system.

Most people count T cells in the tens or hundreds, but these are the number of cells found in just a small sample of blood. There are actually 5,000 times that number in the body's total blood supply and many millions more living in tissue, totaling perhaps a billion CD4 T cells—many of them targets for HIV. Most of the CD4 T cells that HIV targets typically have a very short lifespan, and

once infected, most T cells will die within a day or two. Meanwhile, free-floating HIV may survive in the blood only for a few hours, with between 100 million and 10 billion virions formed and removed per day.

In the absence of treatment, an estimated 10 million to 100 million CD4 T cells become infected nearly every day, and the infected cells make enough new HIV to infect all of the next generation of CD4 T cells. This constant daily cycle of CD4 cell infection, production of new virus, and cell death occurs continuously in most infected people who have not suppressed the virus with antiretroviral drugs.

While the production and destruction of virus and CD4 cells proceeds at a near steady state in this furious but silent cycle, over much longer periods of time, the cycle becomes unbalanced and the total CD4 cell count begins to decline.

The biggest single unanswered question about HIV is how this slow loss of CD4 cells occurs. A newly infected person experiences an extremely high spike in viral load within the first few months. This is probably due to the abundant supply of target cells and the lack of any immune control at that early stage. This early phase of high viremia may also be a time when a person is especially likely to pass the virus on to others.

Surprisingly, the body is often able to mount an initially effective immune response to HIV with immune cells that recognize and kill infected CD4 cells. After the sharp initial rise in viral load and an equally sharp decline in the CD4 cell count, the appearance of this immune response about three months into the infection signals the beginning of a quieter phase, when viral load remains relatively steady and CD4 cell counts decline gradually. This phase can last for years, but eventually, in most people, the slow but steady loss of CD4 cells leaves them without immune protection from everyday pathogens that healthy people never notice but are deadly to those with compromised immunity. At that point, during late-phase AIDS, the viral load may once again reach extremely high levels. Fortunately, effective antiretroviral therapy can lower virus levels dramatically well before this point, putting the disease on hold and allowing the body's immune capacity to recover.

Because the pace of HIV replication is so brisk in untreated people and because so many millions of virus

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Questions, Questions, The Future of HIV Research (continued from page 11)

copies are made each day, it is not surprising that mistakes are made as the viral genetic material is copied and processed in the cell. Most copying mistakes (transcription errors) probably result in a fatally flawed virus. But, rarely, a "mistake" is able to adapt and thrive better than the parent virus. For example, a virus might be better able to evade the body's immune defenses or to escape from control by drugs. Over time these mistakes, or mutations, accumulate. Eventually the dominant viral strain found in the blood can differ significantly from the HIV the person was originally infected with. It's likely that this is how HIV gradually escapes from immune control.

The viral load test measures the number of copies of HIV RNA in the blood, but it can also be seen as an indirect measurement of the number of productively infected CD4 T cells at any one time. When the viral load is very low it means that few cells are making new copies of HIV. The viral load test is also a quick way of telling if antiretroviral therapy is working effectively.

Although antiretroviral therapy can reduce the number of infected CD4 cells to almost zero, studies have found one or two copies of HIV RNA in the blood even after seven years of continually suppressed viral load. These viral embers are hidden in a very small number of infected CD4 cells thought to exist in a long-lived resting state, where they are unreachable by drugs. If antiretroviral drugs are removed, these embers can flare up to become a raging, active HIV infection. Unfortunately, at this time there is no known way to reach and eliminate these latently infected cells. In other words, there is no cure.

Dr. Coffin outlined several major unanswered questions that young scientists will have to wrestle with: Most importantly, what is responsible for CD4 cell depletion? Is the virus killing the CD4 cells directly? Or are toxic viral proteins killing them indirectly? Is it the anti-HIV immune activity of the body's own killer cells that is doing the job? Maybe it is some byproduct of a highly activated immune system that is exhausting the CD4 cell supply. Perhaps it is a combination of several of these factors.

Most perplexing, how can the virus depend on, yet evade destruction by, the immune cells that should be attacking it? One remarkable adaptation is the camouflage of the virus's external proteins by clouds of sugar molecules. These envelope proteins are the

best available target for immune system recognition, but they are hidden by the sugars. Finding a chink in this sugarcoated armor would be great news. But HIV is so changeable that even when these viral proteins become temporarily exposed when HIV binds to a cell, immune cells may not recognize their target.

Scientists are also studying similar viruses that cause AIDS-like disease in monkeys, but not humans, to identify crucial differences and similarities. One key finding may be that the disease-causing viruses all tend to produce high levels of immune activation, much as HIV does. Some have compared the explosion of target CD4 cells produced by runaway immune activation to pouring gasoline on a fire. Finding a way to tamp down immune activation may be one avenue of treatment.

Where does the virus in latently infected cells come from? Are they archived from early permutations of the virus that evolved before suppressive therapy was begun? Do these resting cells divide periodically and pass on the viral genome to their progeny? Would it be possible to wake these cells up and make them go through a cycle of viral production and cell death? If so, and if all new infections could be blocked by drugs, then HIV might actually be curable, according to some theorists. But we still don't know if infected cells in protected parts of the body, such as the brain, harbor enough HIV to stage a comeback when the drugs are stopped.

It should be evident from this long list of questions that young scientists coming into the field of HIV research can expect to find a lot of exciting and important work to do.

Vaccines

Richard Koup, National Institutes of Health Vaccine Research Center, Bethesda, Md.

Policy makers, politicians, and public health officials love vaccines because they promise a cheap and easy way to eliminate major public health care problems with a single shot. Finding a vaccine for HIV has been one of the most difficult scientific challenges in fighting this disease. Beginning in the mid 1980s, various leaders have periodically said to expect an AIDS vaccine within five to 10 years. Current estimates bandied about at the Denver conference say it will be at least 10 years before a vaccine can be expected. But work continues, and vaccine research is increasingly finding the funding it deserves.

Koup described vaccines as "the most powerful biomedical intervention" ever developed. Koup suggested

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that we may be on the brink of a vaccine revolution as a host of new technologies based on manipulating genetic material are perfected.

A vaccine works by exposing the body's immune system to a bit of material that "looks like" a pathogen but does not cause disease itself. Pathogens can be any disease-causing bug, such as a bacterium, virus, or fungus. Once the immune system has been primed to recognize this characteristic bit of matter, it will respond much faster and more effectively if and when the pathogen bearing that characteristic shows up in person. Traditional vaccines use killed or weakened versions of pathogens to educate the immune system to recognize the real danger.

This simple approach hasn't worked with HIV because the virus is particularly adept at hiding from the immune system. Meanwhile HIV targets and destroys the very immune cells that should be fighting it. Natural immunity does seem to provide some control over HIV, at least in the beginning, but because HIV is so changeable, over time this control declines as the immune system no longer recognized its foe.

There are two main wings to the immune system: defense by neutralizing antibodies, which attack pathogens directly; and defense by killer T cells, which mainly destroy cells that have become infected. It's probable that a truly effective vaccine will need to engage both divisions of the immune system in fighting HIV. While there has been some modest success in stimulating the cell mediated wing to recognize HIV, the challenge for antibodies has been much greater.

Remember that the proteins carried on the outside of HIV are highly variable and are shrouded in sugar. We know very well what certain key parts of these proteins look like, and we can make antibodies to attack them, but they are as effective as an assassin seeking his victim at a costume party where everyone is wearing a mask—and the masks are constantly changing.

The challenge is to make an antibody that will recognize a vulnerable feature of the exposed HIV protein that is stable both physically and genetically. A few artificially constructed antibodies have been able to achieve some success, but getting the body to generate such broadly neutralizing antibodies on its own in sufficient quantities remains a challenge with no solution in sight.

Much more is known about inducing cell-mediated immune responses to HIV—and if HIV would stand still, these responses might offer very effective viral suppression. Unfortunately the experimental evidence so far suggests that cellular immunity is not very effective at blocking HIV from establishing an infection in the first

place. While a therapeutic vaccine could be very important for people living with HIV (and this is likely the first HIV vaccine product we will see) what the policy makers and public health officials really want is a preventative vaccine.

One recent startling finding about the impact of HIV in the gut has stimulated much interest in the role of mucosal immunity. It's been shown that shortly after infection, HIV rapidly and dramatically destroys vast numbers of CD4 T cells that reside in lymphoid tissue lining the intestines. Because this wholesale destruction happens within the first two or three weeks of infection, an immune system that had been primed to recognize HIV might be able to minimize the damage and possibly alter the natural course of HIV disease. Other avenues of research are looking at ways to stimulate immune responses in these vulnerable mucosal tissues.

Because HIV is constantly evolving in the body, the HIV transmitted from one person to another may have a different genetic signature from the virus the first person was infected with. As the virus passes from person to person, over time the genetic "distance" from the original virus increases. If an infected person moves to a different part of the world and introduces HIV there, eventually different identifiable subtypes of HIV will be associated with different global regions. The evolving genetics may not greatly affect how the virus works or how it causes disease as much as they represent changes in the fine details of viral proteins that could be targets for immune recognition. For example, people have unique faces that identify them as individuals, and the variation in facial appearance around the world is great, but everyone still has eyes and ears that perform consistent functions. The challenge for designing a vaccine that will work for everyone all around the world is to find the key unchanging features across all viral strains that can serve as immune targets.

So to sum up the situation for HIV vaccines, there are a few vaccine candidates moving forward to clinical trials that may stimulate some cellular immune response, but while these might offer modest viral suppression after an infection has taken hold, they will probably provide only minimal protection from transmission. To do that, vaccines that stimulate neutralizing antibodies will probably be needed, and currently those remain out of reach.

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Questions, Questions, The Future of HIV Research (continued from page 13)

Drugs

Scott Hammer, Columbia University, New York City

The best-attended sessions at the Retrovirus Conference are devoted to antiretroviral drug therapy—mainly because the biggest and splashiest research comes from drug trials. A significant market for antiretroviral drugs has developed in the past decade, and the pharmaceutical industry is willing to invest large amounts of money in research to refine and develop new antiretroviral drugs.

This year is the tenth anniversary of learning that triple combination drug therapy can suppress HIV replication and prolong life. There are now over 20 drugs approved in the three main classes, and new drugs are being developed to block the virus at other points in its life cycle. Several entry inhibitors are well along in development, and one, Fuzeon, has already been approved as the first of this fourth class. Another new class of drugs is meant to block the viral protein integrase, which is responsible for stitching the viral genes into the cell's DNA. Other targets for drug development include the packaging and maturation of newly formed virions. For the most part, antiretroviral drug research is alive and well.

When potent antiretroviral drugs are taken consistently, there is usually an initial rapid decline in viral load that occurs within the first week or two. Then, during the next eight weeks or so, virus levels continue to drop to where they are no longer detectable by the standard HIV RNA assay. If a person can develop good habits for taking the drugs on time and can tolerate any side effects, then there is a good chance that he or she can continue with undetectable virus indefinitely—with no, or only minimal, evolution occurring among the few viral holdouts. But not everyone can achieve this optimal outcome, and more research is needed on strategies to extend the benefits of viral suppression to everyone.

Drug development is largely financed by industry, but government-funded research is also proceeding on strategies for using the drugs and treating people who have not responded to their first regimens or who may need to take a break from therapy. When therapy can safely be interrupted and for how long remain viable questions despite the recent, early closing of the large SMART study that compared continuous treatment to intermittent therapy guided by CD4 count. Because significantly more AIDS illnesses occurred in the intermittent group than in the continuous treatment group, the

trial was halted. SMART was the largest and best-organized trial of this treatment strategy, yet other, smaller studies that used higher and safer CD4 counts for triggering interruption have showed promising results. While interruption can't be recommended as a strategy, the fact that many people will require interruption due to fatigue, toxicity, or other life issues means that interruption strategies still deserve to be studied. Knowing the best way to manage these patients remains a significant unanswered question.

Another strategy under investigation is simplification of treatment by reducing the number of drugs in the regimen once viral suppression has been achieved. Studies of this strategy using single-drug therapy with boosted Kaletra or Reyataz are under way. There is also a critical, unmet need for drug regimens that can reliably suppress virus in people with extensive treatment histories who have accumulated multiple drug-resistant mutations. Some of the most exciting research is focusing on the possibility of forcing drug-resistant virus into a weakened state by using nonsuppressive drugs to maintain mutations that hobble the virus.

Much basic science is being done to understand the impact and interplay of drug resistance mutations. In the future it will be important to track the impact of resistance around the globe as antiretroviral drugs come into broader usage, particularly in the developing world. Patterns of drug resistance and response may be different in different parts of the world, depending on which HIV subtype is prevalent. Other questions from the developing world that need attention are how best to prevent mother-to-child transmission of HIV with simple regimens and how best to treat infants and children who do become infected. One novel drug study is investigating if taking Viread daily as a preventative measure can prevent HIV infection in healthy people who are at risk for becoming infected. While this does not seem like an optimal approach to prevention, given the state of vaccine research, it may well be a viable stopgap measure to help hold down new infection rates in vulnerable populations until something better arrives.

GMHC Treatment Issues, December 2005 Vol 19, No 12

New Label on HIV Drug to Warn of Bleeding

The Associated Press

WASHINGTON—The strict “black-box” warning on the label of an HIV drug approved just last year is being updated to warn of sometimes fatal bleeding within the brain or skull tissue, health officials said Friday.

The Food and Drug Administration said it has received 14 reports of intracranial hemorrhaging in patients treated in clinical trials with the drug, Aptivus, in combination with the older HIV drug ritonavir.

Eight of those patients died, among the 6,840 enrolled in trials of the drug combination.

Many of the hemorrhage patients had other medical conditions or were taking other drugs that could have contributed to the bleeding, the FDA said. Further investigations seek to assess the drug’s role.

The new warnings recommend doctors use caution in prescribing Aptivus, also known as tipranavir, to patients at risk for increased bleeding. Examples include people who have suffered trauma or undergone

surgery, or who are taking anticoagulants.

The FDA approved Aptivus in June 2005; it approved ritonavir, sold as Norvir, in 1996.

Aptivus’ black-box warning, the strictest a prescription drug can bear, previously warned only of the risk of severe liver disease when used with ritonavir. The two drugs are always taken together, along with other HIV drugs.

Aptivus is made by Boehringer Ingelheim Pharmaceuticals Inc.

On the Net:

Food and Drug Administration letter to doctors:
http://www.fda.gov/medwatch/safety/2006/Aptivus-tipranavir_DHCP.pdf

Updated Aptivus label: http://www.fda.gov/medwatch/safety/2006/Aptivus_PI.pdf

Washington Post June 30, 2006



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Alcohol and the Liver (continued from page 5)

so a person over 60 years old has less total body water than someone under 40 years old.

Another reason women metabolize alcohol differently is that women have less of the enzyme (ADH) that metabolizes alcohol than men. This means that women who drink the same amount of alcohol as men will achieve a higher concentration of alcohol in the blood.

Because of these gender differences the amount of alcohol for a healthy adult (without liver disease) differs for women and men – women should not drink more than 1 alcoholic drink a day and men should not drink more than 2 alcoholic drinks per day.

Excess Alcohol

The liver can only absorb and metabolize so much alcohol. The excess is distributed to other areas of the body. If the alcohol can not be processed by the liver it can greatly affect other organs in the body and a person's psychological well being. Excess alcohol use can cause a variety of problems including:

- Hypertension (high blood pressure)
- Irritation of the gastrointestinal system causing ulcers, gastritis, and inadequate absorption of nutrients
- Central nervous system disorders, including brain disorders, vitamin B deficiency, and peripheral neuropathy
- Male and female impotence
- Depression and anxiety as well as many social problems

If you are a person living with hepatitis C, the message is clear: mixing alcohol and hepatitis C will decrease the way the body is able to control hepatitis C and lead to faster liver disease progression. If you can not stop drinking consider seeking help from family, friends and medical providers. Alcoholism is an insidious disease that affects millions of Americans and destroys many lives. Resources listed below can offer help and guidance to stop drinking.

Resources

HCSP Factsheet: [Alcohol and HCV](#)

HCSP Factsheet: [Tips for Staying Alcohol-Free at Social Events](#)

www.alcoholics-anonymous.org

www.hcvanonymous.com

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Anti-HIV Therapy Update (continued from page 6)

on this, but it looks possible to make it on to the market by the end of 2006.

The final and some think most impactful, anticipated development is the first one-pill-a-day full anti-HIV drug regimen. This new pill will combine three elements of one of the most highly recommended combinations—[Sustiva](#) (efavirenz), [Viread](#) (tenofovir) and [Emtriva](#) (emtricitabine, FTC). While another pill on the market, [Trizivir](#), contains three drugs—[Retrovir](#) (AZT, zidovudine), [Epivir](#) (3TC, lamivudine) and [Ziagen](#) (abacavir)—it is not considered sufficiently potent to serve as a full treatment regimen. It also requires two daily doses. The new combination is a single pill that is taken just once a day.

This achievement required the cooperation of two companies, Gilead Sciences and Bristol-Myers-Squibb, each of which will sell the drug. This level of cooperation, unprecedented in HIV, is good for patients, good for payers (if it's priced fairly) and good for business. The new three-drug combination has been submitted to the FDA for approval and it should be in drug stores by the end of 2006. Because of its advantages, it's likely to be approved faster than this. Let's hope that this will inspire greater cooperation between other pharmaceutical companies.

Looking a bit further into the future, 2007 may see the approval of another type of EI, called a CCR5 inhibitor. Though some experimental drugs of this type have failed in clinical studies, at least one (from Pfizer) continues to show strong performance and another (from Schering) is being studied in treatment-experienced people.

A closing note of caution: While we have hopes for all of the new drugs and products mentioned above, the full story isn't known yet about any of them. Most of the drugs discussed here are experimental and haven't yet been fully proven to be effective. Even at their best, they will still require lifetime maintenance, which is not a cure for HIV disease. At Project Inform we will continue to work toward the goal of a cure, which must be the real goal of AIDS treatment research. Until then, we welcome all advances in HIV care and treatment.

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41st EASL Coverage (continued from page 4)

being developed by Schering-Plough. In this open-label crossover study, 26 prior non-responders with genotype 1 HCV were treated with SCH503034 monotherapy (200 or 400 mg three times daily), Peg-Intron monotherapy, or the combination (all subjects received all three regimens in differing orders). The 400 mg SCH503034/Peg-Intron combination was most effective, with 40% (4 out of 10 patients) achieving undetectable HCV RNA; the average viral load reduction in this arm was 2.9 log IU/L. The combination regimen was well-tolerated; side effects were generally mild-to-moderate, and mostly attributable to interferon. One patient developed a temporary SCH503034 resistance mutation.

Promising data on another new oral HCV protease inhibitor, Vertex's VX-950, were presented by H. Reesink and colleagues (abstract 737). In this Phase Ib study, 20 treatment-naïve patients with genotype 1 HCV were randomly assigned to receive 750 mg VX-950 monotherapy three times daily, Pegasys monotherapy, or the combination. After 14 days, the combination arm was most effective, with 50% (4 out of 8 patients) achieving undetectable HCV viral load and a median viral load decrease of 5.5 log IU/L, compared with 4.0 log IU/L in the VX-950 monotherapy arm and 1.0 log IU/L in the Pegasys monotherapy arm. All patients then continued on standard Pegasys plus ribavirin; after 12 more weeks, eight had undetectable HCV RNA. VX-950 was well-tolerated, with no serious adverse events or discontinuations. However, development of drug resistance is a concern with protease inhibitors, especially when used alone. Previously research showed that drug-resistant mutations (A156T, A156V, V36M/A/L, T54A, R155K/T/S/M) can emerge with exposure to VX-750. But, as T. Kieffer and colleagues (abstract 12) reported at EASL, gene sequence analysis showed that "wild-type" (non-resistant) HCV re-emerged as the dominant type within 3-7 months after VX-750 was stopped.

Early data on another new type of experimental agent, Coley Pharmaceutical Group's toll-like receptor agonist CPG 10101 (Actilon) was reported in two presentations by McHutchison and colleagues. In a Phase 1b study (abstract 111), 60 previous non-responders, most with genotype 1, were randomly assigned to receive CPG 10101 in various doses by subcutaneous injection once or twice weekly for four weeks. Patients receiving CPG 10101 experienced reduced HCV viral load, which was associated with improved measures of immune function such as cytokine levels and activation of T-cells, B-cells, and natural killer cells. The agent was generally well-tolerated, producing flu-like symptoms. Another trial (abstract 730) looked at CPG 10101 in combination with pegylated interferon plus ribavirin. Here, 74 genotype 1 patients who relapsed after prior therapy were randomly assigned to receive 0.2 mg/kg once weekly CPG 10101

alone or in various combinations with pegylated interferon, ribavirin, or both, or else standard therapy, for 12 weeks. In this study, 86% (12 out of 14 patients) receiving all three agents achieved early virological response at week 12, compared to 60% (9 out of 15) of those receiving standard therapy; 50% (7 out of 14) and 15% (2 out of 13), respectively, achieved undetectable HCV RNA. Patients receiving CPG 10101 plus either pegylated interferon or ribavirin – but not both – were less likely to respond (57% and 21% undetectable, respectively); CPG 10101 alone was not effective.

Ritonavir Boosting

Finally, D.J. Kempf from Abbott Laboratories and colleagues (abstract 4) reported data showing that the antiretroviral drug ritonavir (Norvir) can increase serum concentrations of experimental HCV protease inhibitors. Ritonavir, itself an HIV protease inhibitor, is used at low doses in anti-HIV therapy to "boost" blood levels of other drugs in its class; this works because ritonavir inhibits the activity of cytochrome P450 enzymes, thus slowing clearance of other drugs. In laboratory cell cultures and in rats, ritonavir strongly inhibited metabolism of both VX-950 and SCH 503034. Raising blood levels of HCV protease inhibitors may enhance their efficacy and reduce the development of drug resistance, but may also worsen side effects.

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Healthwise (continued from page 8)

American Heart Association – www.justmove.org
 Centers for Disease Control – www.cdc.gov/nccddphp/dnpa/physical/index.htm
 Mayo Clinic – www.mayoclinic.com/health/fitness/SM99999
 National Institute on Aging – www.niapublications.org/Agepages/exercise.asp
 Office of Disease Prevention and Health Promotion – www.healthypeople.gov
 The President's Council on Physical Fitness and Sports – <http://www.fitness.gov>
 PrimusWeb.com – www.primusweb.com/fitnesspartner
 StrongWomen.com – www.strongwomen.com
 U.S. Department of Health and Human Services – www.smallstep.gov

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Update on Structured Treatment Interruptions (continued from page 1)

ment interruption, the immune system would become more able to recognize and control HIV on its own. This is sometimes called autoimmunization, where it's hoped that enhancing a person's exposure to HIV in a controlled manner can create a more potent and effective response against it.

The results of this research, however, were exactly the opposite of what was hoped. People living with HIV the longest were actually more likely to have more potent CTL response. Those who had started therapy soon after being infected with HIV had a fairly weak CTL response that could be boosted somewhat during an STI, but then decreased again after restarting treatment. Similar results have been found in several other STI studies in people with long-term infection.

Several studies have combined STIs with immune therapies, like IL-2 (Interleukin-2, Proleukin) or therapeutic vaccines. The hope is that they may, when used with an STI, provide the needed lift to orchestrate a stronger immune response to HIV. Although several studies are still ongoing, the results so far have not been promising. As such, people who hope to "boost" their immune response to HIV should not look to STIs as a strategy.

Helping people with treatment fatigue

Simply put, treatment fatigue is when a person is "tired" of taking anti-HIV medicines. For people who wish to stop their therapy due to treatment fatigue, the data are conflicting. Results from the various STI studies show that some people can successfully take a break from treatment without developing drug resistance, treatment failure or symptoms of disease progression. For others, such interruptions can be harmful. Several factors have emerged that may help predict when a person may have a worse outcome during their time off treatment. These are:

- low CD4+ count (below 200) before starting anti-HIV therapy,
- high HIV level (above 55,000) before starting anti-HIV therapy,
- poorer control of virus while on therapy or other signs of drug resistance, and
- earlier opportunistic infection (OI).

In most studies, at least one-third of volunteers were able to stay off therapy for at least one year. The aver-

age time off therapy for the other participants ranged from 8-12 weeks. It should be noted, however, that people who interrupted their treatment had major drops in CD4+ cell counts (on average dropping 50%) compared to people who stayed on treatment. Without proper preventive medicine against OIs, these decreases could be dangerous for people whose counts drop below 200.

A recent and highly publicized study, called SMART, compared several thousand people who used constant therapy to others who stopped treatment whenever their CD4+ cell counts rose above 350. Those who took therapy "breaks" restarted treatment when their CD4+ cell counts fell to 250 or below. Overall, the study showed that people who used continuous treatment were less likely to experience death or disease progression.

Additionally, the study did not show any reduction in drug side effects in the people who cycled on and off therapy as directed by CD4+ cell counts. While this seems to argue against the use of STIs, it is important not to overstate the findings of the SMART trial. What gets lost in the observation that people on continuous therapy did better overall, it is also a fact that a great majority of those taking therapy interruptions fared well too. The actual number of people suffering disease progression or death was quite small in both groups. Perhaps the biggest surprise of the study, though, is that neither CD4+ cell counts nor viral load were able to predict who would experience problems as a result of treatment interruption.

Another unfortunate aspect of the study was that it did not call for patient volunteers to use preventive therapy against the most common opportunistic infections when their CD4+ cell counts fell to levels considered risky. Consequently, the study doesn't tell us anything about the possible role of preventive therapy as part of an STI strategy.

One important observation from SMART is that no matter what its conclusions, it will not stop people from using STIs in many situations. Treatment is still routinely interrupted when a person experiences certain major infections. It is interrupted because of drug side effects. And it will continue to be interrupted by people who suffer serious treatment fatigue. For such people, certain guidelines may be followed. Careful and increased monitoring by your doctor is critical due to the risks for disease progression and OIs. People should check their healthcare benefits (both private insurance or public assistance) to ensure that the cost of additional lab tests would be covered if needed.

Helping reduce the costs of treatment

Interest in using STIs to reduce the cost of treatment has mostly focused on the developing world, where reducing the cost of treatment would increase the number of people who have access to it. Several studies have looked at a kind of STI, called Structured Intermittent Therapy (SIT), where people cycle on and off anti-HIV drugs for specific amounts of time. Most studies to date have shown this strategy to be safe, at least for people who start anti-HIV therapy with CD4 counts above 200.

Helping reduce the side effects of anti-HIV therapy

While there is still much to learn about the effects of long-term anti-HIV drug therapy, some consequences are well understood. Two important concerns are lipodystrophy and heart disease.

Lipodystrophy is an umbrella term for three conditions related to how the body regulates and stores fat (*lipids*). First is the accumulation of fat, usually in the abdomen, the breasts, and around or behind the neck. This is called *lipohypertrophy*. The second concern is the loss of fat, usually in the arms, legs, buttocks and face. This is called *lipoatrophy*. The third problem is elevations in two kinds of fats—called cholesterol and triglycerides—circulating in the blood. This is called *hyperlipidemia*.

Studies looking at the connection between anti-HIV drugs and all three kinds of lipodystrophy have yielded somewhat confusing results. While all three problems are more common in people who have taken anti-HIV drugs, they are all sometimes seen in people with HIV who have never taken anti-HIV drugs. To date there are no studies that have shown that STIs affect the risk of lipodystrophy.

A growing set of data show that people with HIV, especially those taking anti-HIV drugs, are at a slightly higher risk of heart disease. A particularly important study on this subject was the DAD study, which found an increased risk of coronary artery disease in people on all types of anti-HIV therapy. Importantly, the DAD study also found that some of the risk was lowered when people stopped taking their anti-HIV drugs.

STIs have been studied to reduce short-term side effects and improve quality of life as well. The studies have shown conflicting results. The first attempt, which had volunteers go on and off therapy every 14 days, resulted in several people developing drug-resistant virus and losing control of their HIV levels. Another small study of continuous cycles of seven days on and seven days off therapy resulted in fewer side effects

and better quality of life for people on STIs than for people on continued therapy. HIV levels were well controlled as well. However, a similar study in Thailand had conflicting results, so it's impossible to state for certain whether STIs of this type will be safe.

The SMART trial also weighed in heavily on this issue with surprising and clear findings. Much to the surprise of many, people who interrupted therapy actually had a worse experience with drug side effects, much as they did with the occurrence of opportunistic infections. This is believed to be due to the way the immune system reacts when a person cycles on and off therapy. Whatever the reason, the SMART trial certainly didn't support the use of STIs as a way to reduce drug side effects.

STIs at CROI

Results from several new STI studies were presented at CROI or shortly thereafter. Here we focus on six studies—SMART, DART, TRIVICAN, PART, WINDOW and ACTG 5170.

SMART

The SMART study was the largest ever STI study, designed to enroll around 6,000 people. It was comparing two anti-HIV drug strategies—continuous therapy vs. CD4+ cell guided treatment interruptions. One-half of the study participants took anti-HIV drugs throughout the study. The other half started anti-HIV drugs when their CD4+ cell counts fell to 250 and then stopped anti-HIV drugs when their counts rose to 350 (restarting therapy if/when counts again fell below 250).

The SMART study's Data Safety and Monitoring Board (DSMB)—a group of scientists not connected to the study and researchers charged with protecting the safety of study participants—halted enrollment due to a higher rate of disease progression, death and other serious health problems in the STI group compared to those on continuous therapy. Further, they advised that volunteers in the STI group switch to continuous therapy due to the safety concerns that emerged from interrupting therapy.

The first public presentation of the data that led to the DSMB's decision was at this year's CROI. The researchers found higher rates of disease progression or death (2.15 times), serious AIDS-related events (5.82 times), and non-HIV related events like heart attack, liver disease (1.6 times) and death (1.6 times) among those interrupting therapy. These results led the DSMB to decide that the STI strategy used was

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too risky. In addition to closing enrollment, the researchers recommended that everyone who had stopped taking anti-HIV drugs restart them.

It is important to remember, as stated above, that the actual incidence of disease progression and death remained low overall. An increase of 2.15 times might sound impressive, but if it is 2.15 times a low number, then the result is still a low number and a low percentage of people suffering progression. This aspect of the SMART data has been largely overlooked. We point it out here in hopes that people who are using STIs and doing well need not feel overly frightened by the reports from the SMART trial. The trial significantly adds to the data that people can use in making their decisions about STIs. It does not conclude that everyone taking an STI faces imminent danger of death or disease progression as some reports have seemed to imply.

While many expected there would be more disease progression and AIDS-related problems in people on STIs, the higher rates of non-HIV health problems—especially heart disease—surprised many. In fact the researchers who designed SMART believed they would see fewer such problems in the STI group.

There are two broad lines of thinking on the SMART findings. Some question the CD4+ parameters used to start and stop therapy in the STI group, arguing that 250 might be too low and 350 might be too close to 250. Others speculated on the role that HIV itself might be playing in heart and kidney disease. These doctors and scientists wondered what role inflammation due to unchecked HIV replication might play in the higher rates of these problems seen in the people on STIs.

DART

In March 2006, researchers from the DART trial, which is studying different anti-HIV drug strategies in Africa, announced a similar decision to stop an STI arm of their study. The STI strategy used in DART was different than the CD4+ guided strategy in SMART. DART used a Structured Intermittent Therapy (SIT) strategy that had people alternating between twelve-week cycles on and off anti-HIV meds. Researchers stopped the SIT part of the study because people in that group had about four times the risk of disease progression or death than those on continuous anti-HIV drug therapy. The trial will continue to study whether health monitoring plus lab tests vs. health monitoring alone is better for people taking anti-HIV drugs in Africa. Given there are many areas of Africa without access to lab tests, it will be important to know if health monitoring alone will result in improved outcomes and the safe use of therapy. If not, anti-HIV drugs might only be available in areas where lab tests are available—an important question for developing nations.

TRIVICAN

The TRIVICAN study compared three anti-HIV drug strategies: continuous treatment (CT), CD4+ guided treatment (with the same basic criteria used in the SMART trial), and intermittent therapy (with two-month interruptions alternating with four months on therapy). The researchers halted the CD4+ guided arm due to a marked increase in the risk of disease progression and death. The other two arms of the study continue. It's unclear why the SIT arm of this study didn't show the same negative results as was observed in the DART study. Perhaps twelve weeks off therapy is just too long to let HIV remain unchecked, whereas the eight weeks being studied in TRIVICAN is reasonable. Until more research is done on this strategy, with more consistent results, it is wise for people to be cautious.

PART

One last presentation at CROI held mixed news for STIs. The PART trial compared continuous treatment to cycles of intermittent treatment. Those in the intermittent arm would alternate between cycles of three months taking anti-HIV drugs and increasingly long interruptions, starting at one month and increasing to three months by the end of the study. People had an average CD4+ cell count of 700 at the beginning of the study. Researchers reported a high dropout rate in the STI group, due to large drops in CD4+ cell counts. People with lower pre-study CD4+ cell counts, people with lower CD4 nadir (or lowest ever CD4+ cell count), and those living with HIV for a long time were more likely to see major losses in CD4+ cell counts. Importantly, most people in the STI arm who restarted treatment were able to re-suppress HIV replication. There weren't significant differences in HIV drug resistance between the arms.

WINDOW

A couple of other studies drew different conclusions. The WINDOW trial compared continuous therapy vs. six cycles of eight weeks on, eight weeks off intermittent therapy. In contrast to the SMART, DART, TRIVICAN and PART studies, WINDOW researchers found that people in both arms of the trial had low rates of HIV-related illnesses. Researchers did report higher rates of thrush (oral candidiasis) and idiopathic thrombocytopenic purpura (ITP)—both signs of immune dysfunction—in the intermittent therapy group, but they considered the differences insignificant.

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Perhaps the biggest difference between this trial and others like SMART was how the researchers chose to describe their results. Most trials focused on the rates of increased risk associated with treatment interruption. The reports from WINDOW instead focused on the overall levels of disease progression, rather than the difference between the treatment arms. Both points can be (and are) true of many of these studies.

ACTG 5170

Another study, ACTG 5170, examined what factors might predict the results from a single treatment interruption. The findings reported at CROI were consistent with many earlier studies. The researchers found that when people stopped taking their meds, they saw a rapid increase in viral load and decrease in CD4+ cell count followed by a plateau in both after a few weeks. Importantly, they also found a very low risk of disease progression. The factors in this study that helped predict the results from the single interruption were lowest ever CD4+ cell count (*nadir*) and starting the study with a detectable viral load.

What does this all mean?

How do these studies add to or change our understanding of STIs? There are several conclusions to be reached from these studies. The first is that the hope that STIs would reduce the risk of heart disease and other unintended effects of anti-HIV drug therapy was unsupported by these studies. It is important to caution that each of the studies that found negative results from STIs found them after a relatively short period of time and in an overall context of low net levels of disease progression. The question of the effects of STIs on long-term outcomes remained largely unanswered. However, people considering STIs need to be aware of these short-term risks.

Some of these results, especially those from WINDOW and ACTG 5170, support the idea that while STIs carry some known risks; they can be done safely for some people. A careful analysis of other studies, including SMART, shows the same thing, though it is not emphasized by the study investigators. It appears that STIs are safest for people who have never had very low (under 200) CD4+ cell counts and who were able to reduce viral load to undetectable levels while on anti-HIV therapy, though even this was questionable in the SMART study. None of these studies looked at the question of reinvigorating the immune response, nor have any yet examined the overall cost of therapy.

Taken together, many of these studies show that interrupting therapy carries with it some increased risk of disease progression. People considering an STI may discuss the relative risks with their doctors and develop a strategy for increased monitoring of their health while off anti-HIV treatment. Certainly no one is encouraging treat-

ment interruption when CD4+ cell counts are below 200, whatsoever. Also, there is no support for discontinuation of OI preventive or maintenance therapy when those therapies are indicated. Also, while individuals might have interest, outside of studies, to experiment with STIs, the trade off for interrupting therapy is increased monitoring. Community experience has shown time and again those who wind up in the most troubling and dire health situation are those who stop therapy and don't increase monitoring of their health, CD4+ cell counts and HIV levels.

While the results of some STI studies have not been what many had hoped, a compelling need to continue studies on this subject remains. The prospect of non-stop, life-long anti-HIV therapy is daunting for many. The possibility that this long-term treatment can contribute to a higher risk of heart disease, diabetes and other troubling health consequences also supports the need for more research.

The high hopes for STIs may have indeed faded, but the questions are far from fully settled. Some people with HIV will still want to take time off their HIV meds. This might be to reduce exposure to the drugs and their toxicities, or just due to treatment fatigue. It is vital that doctors and scientists continue to study this important topic, to better understand the safest and most helpful ways for people with HIV to interrupt their treatment.

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