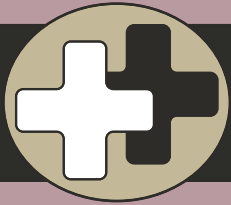


May / June 2006



Positively Aware

The Journal of the Test Positive Aware Network



One-on-One
With

U.S. Representative Jan Schakowsky

On Politics and HIV

Plus

Retrovirus Conference Update

Is it Smart to Interrupt Treatment?

Gay Games Come to the Windy City!

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A model, photograph, or author's HIV status should not be assumed based on their appearance in *Positively Aware*.

You can view these
(and other stories from previous issues)
online at
<http://www.tpan.com>

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- Speakers Bureau
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- TEAM (Treatment Education Advocacy Management)
- FASN (Family AIDS Support Network)

For detailed descriptions of programs, including days, times and locations go to http://www.tpan.com/client_services/client-services.shtml or visit www.tpan.com and click on Client Services; or call (773) 989-9400

TPAN Events Calendar

TPAN EVENTS CALENDAR

- Educational Forums and Trainings
- Positively Wired-A Free Basic Computer Skills Workshop
- Special Events

For detailed descriptions of upcoming TPAN events go to <http://www.tpan.com/events/events.shtml> or visit www.tpan.com and click on Events; or call (773) 989-9400



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GROWING PAINS



June 5th marks 25 years since the first published report of *Pneumocystis carinii* pneumonia (PCP) among five previously healthy young men in Los Angeles. Much has changed since then, some good, and some not so good.

Ten years ago the advent of HAART (highly active antiretroviral therapy) was followed by a steep and dramatic decline in AIDS deaths here in the U.S. Upcoming new advances in research and treatment, including integrase inhibitors (see The Buzz, page 44) hold hope and promise in the near future for those with limited treatment options.

Ideally we should be focusing all of our efforts fighting this virus, but instead we often find ourselves expending our dwindling energy and limited resources battling intolerance, ignorance, and politics as usual.

Case in point—a 15-page article by Celia Farber in the March issue of *Harper's* magazine entitled, "Out of Control: AIDS and the Corruption of Medical Science." The story, which is laced with inaccuracies, half-truths, twisted logic and glaring omissions, is biased and self-contradictory, while promoting the misguided theories of AIDS "denialist" Peter Duesberg, not the least of which is that HIV is not the cause of AIDS. For a comprehensive and clearly spelled out 37-page point-by-point rebuttal of the article, written by leading AIDS researchers, visit the Treatment Action Campaign's website at www.tac.org/za.

Here in Chicago, the upcoming Gay Games, July 15–22 (of which *Positively Aware* and TPAN are proud sponsors) has been dealing with ignorance on a local level. Some residents of Crystal Lake, a Chicago suburb, voiced opposition when it was learned that a rowing event was to be held there in conjunction with the Games. "I do not want these queers coming to my

hometown," one resident stated emphatically to the press. Ironically opposition to the event, which typically only draws around 50–100 people, created such a media stir that it is now sure to draw more attention and attendees than it ever would have before (kudos to the city's park district board, which voted 3–2 in favor of keeping the planned rowing event).

Meanwhile, our friends at the Illinois Family Institute (IFI), whose motto is "Fostering an environment where families can flourish," have called on President Bush to reinstate the federal ban on HIV-positive travelers to the U.S. during the Gay Games, which Chicago Mayor Richard Daley and U.S. Representative Jan Schakowsky (see interview on page 28) worked to get temporarily lifted. The Institute's reasoning that visiting "homosexuals" will flock to area bathhouses and spread their diseases just doesn't hold bathwater. Apparently the folks at IFI are not aware of the commitment, discipline and training that is required of those who compete in the Games (see Gay Games profiles on page 33). I guess they must think that it's standard practice for athletes to take the edge off and unwind with a little unprotected sex at the bathhouse before or after a competition. *Note to the IFI: Gays have families, too—HELLO—and have just as much right to flourish as anyone.*

So where do we go from here? Beginning with this issue, *Positively Aware* asks that question of people working on the front lines, like author/activist Mary Fisher, a mom living with HIV, and Howard Grossman, MD, a clinician who's been involved with a number of activist groups including ACT UP, TAG, the Coalition for Salvage Therapy (CST) and the AIDS Treatment Activists Coalition (ATAC). Speaker/youth activist Todd Murray, who has more recently joined the ranks, and who will be featured in an upcoming issue of *Posi-*

tively Aware, stated that he and others in his generation have never lived in a world without HIV. His comment gave me pause, and made me realize that in many ways, I guess, I've been lucky. Lucky to have lived and loved in a time that seemed much more innocent. Lucky to have made it to (almost) middle age, now approaching 20 years of living with HIV and being on treatment. But unlucky in the sense that I've seen, like many of you, so many of my friends suffer and die needlessly.

But while a generation of youth has grown up with AIDS lurking in the shadows, the epidemic itself is still relatively young, as we were reminded in February at the 13th Retrovirus Conference in Denver (see page 17 for conference coverage). And even though the discontinuation of the SMART study doesn't bode well for the future of treatment interruptions as we know it (see the Treatment Series on page 37), immune-based therapies, vaccine research, and new drugs in the pipeline offer a glimmer of hope to the 40 million people living worldwide with HIV.

We've come a long way, baby. But we've got a long way to go. As I wrote this, I received an e-mail from another AIDS "denialist." They seem to mutate and multiply faster than the disease which they claim doesn't exist.

Take care of yourself, and each other.

Jeff Berry
Editor
publications@tpan.com

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DRUG GUIDE CLARIFICATION AND CORRECTION

The Kaletra dose in the annual drug guide incorrectly stated that a once-daily dose cannot be taken with Lexiva or Viracept and that three tablets twice a day should be taken with those drugs. We apologize for the error.

The Kaletra dose also stated that three tablets twice a day should be taken with Sustiva or Viramune, and by people who are treatment experienced. The statement should say that this dose *can* be taken under these criteria. An Abbott Laboratories medical liaison, however, tells us that the three tablets twice a day dose "may be considered" for people who are both treatment experienced *and* taking Sustiva or Viramune.

DRUG GUIDE

On my recent trip to my healthcare provider, I was informed that it is time for me to start my antiviral regimen. How fortunate for me to find your 10th Annual HIV Drug Guide on this day. It has been very helpful so far. I never knew such a publication existed. I plan on being very proactive in my care, and make decisions with my provider that best suit me. I was also glad to see that previous issues have dealt with minority issues as well. Bravo and kudos to TPAN. I was glad when I found out that I could receive a subscription to this wonderful journal. Thank you for your help and advocacy.

Name withheld by request, Detroit

UPDATE ON MY CONDITION

I shall be leaving the bounds of imprisonment shortly. I wrote to TPAN in a letter published in July/August 1997, titled "Spitting Image." The Commonwealth of Pennsylvania convicted me on the claim that I attempted to infect two police officers through saliva! These same police did *not* have a policy for handling HIV-posi-

tive prisoners, as required under the AIDS amendments of 1988.

My humor and the information I have so consistently received from TPAN (via *Positively Aware*), along with a very liberal dose of God's infinite graces, have sustained me for the 10 years of imprisonment I have endured, due largely to my HIV-positive status (I have been positive for nearly 20 years), and I am in better shape, both physically and mentally, than a lot of the "young bucks" coming in.

My CD4 T-cell count is 407, my viral load is 103, and my weight is a solid 150 pounds. I've been on a drug regimen of [Videx and Retrovir] plus Sustiva now for eight months, after I had taken a "drug holiday" of two years from the substandard regimen of just [Videx and Retrovir] I was on for eight years. I laugh a lot, and am a voracious reader of HIV/AIDS information and law.

The future is scary sometimes, due to its inherent uncertainty, especially if one has been in a 6 by 12 foot prison cell for the past decade and has had to watch the world evolve through prison bars. I am hopeful that wherever I eventually do decide to call "home" will be a place where I will be intelligently capable of having meaningful dialogue on HIV/AIDS related issues, that advocacy and activism will ensure, and who knows, maybe we can all put our efforts together and find a cure for this hideous disease that has cost so much in terms of suffering and loss.

I sincerely thank you again for providing me with *Positively Aware*, which, along with other publications, allows me to proclaim that I am a "survivor extraordinaire."

Mark Tull, Graterford, Pennsylvania

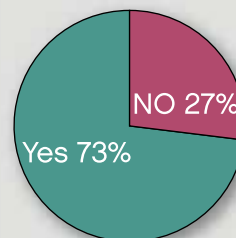
SAVED MY LIFE

"Dating and Daring to Love Again" (March/April 2005) really saved my life. I

continued on page 14

March / April PA Online Poll Results

Have you ever chosen a sex partner, or chosen not to have sex with an individual, based on their disclosed HIV status (serosorted)?



Comments:

- Yes on both counts (chosen to have sex and chosen not to have sex based on HIV status).
- I prefer to have sex with other HIV-positive men. When I have tried to be intimate with an HIV-negative man I always think of myself as "damaged."
- Of course...people do it all the time...many will not have sex with someone who is HIV-positive... it is part of our national "prevention" effort...it is a bummer, though, for those who are HIV-positive.



May / June PA Online Poll:

Have you ever undergone a treatment interruption under the advice of a doctor, or as part of a study?

Give your answer at
www.tpan.com



by Enid Vázquez

NEW RESEARCH STUDY

A new large HIV drug study is off to a very slow start, at least in Chicago. ACTG 5202 is comparing four state-of-the-art drug regimens, so what's the hold-up?

Study coordinator Baiba Berzins at Northwestern University said that doctors used to refer many patients to the clinic, but it seems they now just write out prescriptions. (I am a member of the Community Advisory Board—CAB—at Northwestern.) It's ironic that the success of the past 10 years of HIV research could be hurting treatment advances today.

People who are recently diagnosed or have never taken HIV drugs before should stop to consider joining a study before simply going on medication. It's the previous involvement of many other people with HIV in clinical studies that give them the options they have today, and those people took greater risks. Newer studies, such as this one, often involve treatment with successful drugs that have well-known—and often very tolerable or manageable—side effect profiles.

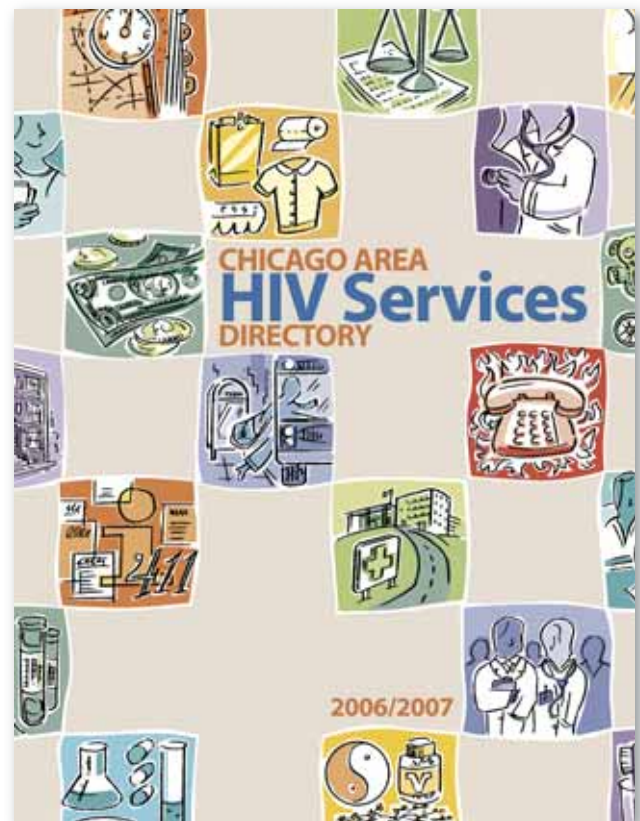
ACTG 5202, from the Adult AIDS Clinical Trials Group (AACTG), is for people who've never taken HIV drugs before (called "treatment naïve"). (They could have taken a week or less of treatment to be eligible.) The study compares Sustiva plus Epzicom; Sustiva plus Truvada; Reyataz with Norvir plus Epzicom, and Reyataz with Norvir plus Truvada.

Sustiva may be the most commonly used HIV drug in the country. An ACTG study (ACTG 384) looking at which drug regimen to start with found Sustiva plus Combivir to be far-and-away the best one of those examined (see March/April 2004 News Briefs) and Sustiva is one of the two "preferred" leading HIV drugs in U.S. treatment guidelines. Reyataz, a newer drug from the same company that makes Sustiva, is gaining on older meds in its drug class. The buzz on Reyataz is that unlike other drugs in its class, it doesn't raise blood levels of cholesterol and triglycerides, making it more heart-friendly.

Joining a study requires some work, like regular visits and blood draws, but also brings close contact with attentive health-care professionals who are cutting edge HIV treatment providers. For an AACTG site near you, visit www.aactg.org, or contact me for a list. In Chicago, visit www.hivclinicaltrials.northwestern.edu, or contact JoAnne Despotos, the CORE Center, 1-312-572-4545; Jan Fritsche, Rush University Medical Center, 1-312-942-4810; or Berzins at 1-312-695-5012. The study aims to enroll a large number of people of color.

HIV SERVICES DIRECTORY

The 2006–2007 *Chicago Area HIV Services Directory* is now available from TPAN. It lists nearly 400 service and medical providers in the Chicago area. New features of this year's directory are resources for people transitioning out of correctional facilities and their loved ones, an HIV information handbook, and a revamped online version that has more search capabilities. Funding from the Illinois Department of Health helped make the directory possible after the agency's Ryan White Title II funding was cut last year. For your free copy of the services directory, call TPAN at 1-773-989-9400. Visit www.tpan.com/online_directory/directory_index.



shtml.

continued from page 14

REVERSESET BITES THE DUST

Development of the experimental HIV drug Reverset (DFC) was discontinued in April after toxicity to the pancreas was seen. Incyte Corporation reported that the grade 4 hyperlipasemia occurring in people taking the medication “is now well above the 10% to 15% level that we believe is acceptable.” Hyperlipasemia indicates pancreatic inflammation. The condition was seen in 2% of patients taking 200 mg of DFC along with Epivir or Emtriva, but increased to 40% when taken without one of those two drugs. Paul A. Friedman, M.D., president and CEO of Incyte, said in a conference call that it’s still unknown why this would happen, but a possible (“although not necessarily probable”) reason is that those two drugs compete for cellular levels of a chemical used by Reverset. By lowering the levels of that interaction, toxicity from Reverset may be reduced. DFC, a nucleoside analog drug (like Retrovir and Viread, and the other two drugs, among others), had exhibited good potency against HIV. Reverset studies were being conducted by Pharmasset. Development of a CCR5 inhibitor, a new class of HIV drugs, continues.

TPAN GRANT CUT BY 77%

Test Positive Aware Network (TPAN), publisher of *Positively Aware*, was notified in March that one of its federally funded Ryan White CARE Act Title I grants was being cut by 77%. The grant falls under the Minority AIDS Initiative (MAI) and will dramatically affect the TEAM (Treatment Education Advocacy Management) program.

The city of Chicago received overall flat funding appropriations from Congress for Ryan White Title I in this cycle; however, the Minority AIDS Initiative was cut in half. Five clinics and TPAN, Chicago’s oldest peer-led AIDS service organization, received MAI funding for Treatment Adherence programs. TPAN sustained by far the largest cut out of all the MAI/Treatment Adherence grants.

The loss accounts for 9% of the total annual TPAN budget. Two-thirds of TPAN’s growing client caseload is people of color. The Minority AIDS Initiative is a government-sponsored program to serve minority populations, of which African Americans are the highest proportion and those most impacted by HIV in this country today.

The Chicago Department of Public Health is the Ryan White Title I grantee from the federal agency administrator, HRSA (Health Resources Services Administration) and created the formula in which TPAN’s TEAM program funding was cut.

“The TEAM program is a one-of-a-kind peer educational and empowerment training program that motivates and educates people with HIV who are newly diagnosed, and those who may have

was beginning to sink into the pit of despair after I lost my husband to AIDS in September 2005. I am still grieving for what I have lost—loss of my spouse, loss of a friend, loss of a partner on this road with HIV, and loss of life as I know it. This article let me know that there really is life after HIV when it comes to dating. I don’t know if I am ready to find someone else, but at least I know that when I am ready, I have the courage to try.

Name withheld, via the Internet

SWITCHING MEDICATIONS

Dear Dr. Berger: Because of extremely uncomfortable side effects from the medications I was taking (Kaletra, Epivir, and Zerit), I have asked my doctor to change my medications (to Truvada and the new formulation of Kaletra). I am hoping that I will get some relief from the diarrhea, sleeplessness, and tiredness. Am I doing the right thing? My T-cells are around 200 and my viral load is undetectable with the ultrasensitive test. I have also heard of HIV-positive people living med free. Do you lend any credence to that?

Daniel S. Berger, M.D., responds: Thanks for writing us. Your situation is not that uncommon and I agree with your comments. First of all, Zerit is a medication that we believe has long-term side effects that may be irreversible. These include neuropathy, that can manifest as numbness in the feet that often progress to pain; lipoatrophy, loss of fat from the face, buttocks, legs and arms, altering one’s appearance; and lastly, elevated cholesterol and other blood fats that increase the risk of heart disease. In my practice it is unusual for me to prescribe this medication. Truvada has been shown in clinical trials to be superior to other combination pills and appears to be a much more patient-friendly option, instead of your current Zerit plus Epivir regimen.

In regards to diarrhea, although Kaletra has a new formulation, there are also other new protease inhibitors that appear to cause much less diarrhea than Kaletra. It is uncertain in my mind whether your diarrhea would improve with the new formulation of Kaletra, only that there will be less pills. Kaletra, by the way, can also elevate cholesterol and other blood fats, which taken together with Zerit, can be a cardiovascular risk combo. Other protease inhibitor options that are patient friendly include Lexiva, Reyataz, and TMC-114 (which is on expanded access and expected to be approved in June). These can all be discussed with your physician. If your physician is uncomfortable with making changes, he and you may consider seeking advice and guidance or suggestions from an HIV specialist. ☒

Update on Experimental HIV Drugs

The Newest, Latest Pipeline Drugs From CROI

by Matt Sharp



ing the scope and range of options, especially for people who have developed resistance and need new drugs.

TMC-114

TMC-114 (generic name darunavir) will most likely be the next approved HIV protease inhibitor (PI), expected on the market later this year. It is very potent and showing proof of effectiveness against virus with protease resistance. At CROI, a pooled analysis of several important studies was presented that provides further information on the drug's resistance profile. The analysis showed that the drug was still effective in a third of participants who had up to nine PI resistant mutations. Also identified were 11 mutations associated with a diminished response to TMC-114.

The data also showed susceptibility to Aptivus—the latest approved protease inhibitor, even after developing the five TMC-114-associated mutations, showing

As a member of the Community Liaison Committee of CROI (Conference on Retroviruses and Opportunistic Infections), helping to formulate the program for this year's meeting, it is satisfying to see the conference a success in bringing the latest HIV research to the top scientists, clinicians and community educators from around the world.

Despite the unfortunate news from the SMART study on treatment interruption strategies (see page 37), this year's CROI offered more positive results on several new drugs and different drug classes. New data is shedding light on three new classes—the integrase inhibitors, maturation inhibitors and co-receptor antagonists. New ways to inhibit the reverse transcriptase enzyme are also being studied in the laboratory. Seeing more research on the new classes in an important meeting such as CROI is encouraging and shows that HIV drug development is moving full steam ahead, improv-

that it may be possible to take Aptivus after using TMC-114 first. TMC-114 is available in an expanded access program. (Call Tibotec at 1-866-889-2074 for further information.)

TMC-125

TMC-125 (generic name etravirine) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) also from Tibotec, but is not as far down the pipeline as TMC-114. A study was presented showing more evidence that this drug will also work against drug resistant virus. Two doses of the drug were studied in this analysis of people resistant to non-nucleoside analogs. The 800 mg twice daily dose showed an average 1.18 log viral load decrease from baseline. The 400 mg twice daily dose showed an average 1.4 log decrease. Both were significantly better than the control arm, which showed only a .19 log decrease. It will be interesting to see the results of larger studies of TMC-125, as a new NNRTI is desperately needed.

Tibotec has been focusing on compounds that work against drug resistant HIV and they are opening an unprecedented randomized study called DUET looking at how the combination of these two drugs will work in experienced patients. The issues around design for such a study are complex and this is the first trial with two experimental drugs from one company. Fuzeon is allowed in the trial, which will provide a unique opportunity for those receiving the two Tibotec drugs plus Fuzeon. At CROI an interaction study showed that the drugs can be taken together without seriously affecting each other. The DUET study is open to enrollment across the country (visit www.acria.org for trial information).

INTEGRASE INHIBITORS

Probably the most hopeful news from CROI this year was a whole new class of HIV drugs that block integrase, a critical enzyme responsible for HIV replication (see page 44). Two companies presented data from two strikingly similar drugs. However, Merck's MK-0518 is farthest along in the pipeline.

An interim 16 week analysis showed that 72% of highly treatment experienced patients reached a viral load below 50. Everyone receiving drug in the study achieved viral load reductions greater than 2 logs after two weeks on the drug. MK-0518 has no known interactions with current HIV drugs, so there will be no need for dose adjustments due to the way it is metabolized. Encouragingly, there were few adverse events in this study, but the drug is still early in development. Watch for a larger Phase III study. (Check out www.benchmark.com/secure for Phase III sites.)

Gilead presented data from their integrase inhibitor, GS-9137, in a 10-day monotherapy study. It showed a dose-related viral load response compared to the placebo arm.

The CCR5 antagonist class has suffered some setbacks recently, although two of the three drugs in development are moving forward in clinical trials.

The only real difference thus far between the two integrase drugs is that Gilead's is metabolized by the CYP3A4 enzyme and works better if boosted by 100 mg of Norvir. In fact, the arm using the smallest dose of GS-9137 (50 mg) plus 100 mg Norvir once daily showed the highest average viral load drop of 2.03 logs.

MATURATION INHIBITOR

Another new drug breaking in the news is PA-457, an HIV maturation inhibitor by Panacos. It's called maturation inhibitor because it blocks a "finishing" stage of HIV replication, when the new virus is re-packaging itself. More studies are showing that this new class is active against HIV. A monotherapy study presented at CROI showed that the higher the dose, the better the viral response.

Still, it appears that in order to be competitive, the drug may need to be studied at higher doses or boosted, as the highest viral load reduction seen in this study was a little over 1 log at the

200 mg once a day. PA-547 stays in the bloodstream a very long time and thus far appears to be well tolerated.

It is also not going to be cross resistant to the older medications since it is from a different drug class. According to a complicated scaling system used in culture assays, the company claims that PA-457 is synergistic with other antiretrovirals. Pfizer is doing other work in screening for a new maturation inhibitor. Stay tuned for yet another HIV drug class.

CCR5 ANTAGONISTS

The CCR5 antagonist class has suffered some setbacks recently, although two of the three drugs in development are moving forward in clinical trials. At CROI, maraviroc (Pfizer) and vicriviroc (Schering Plough) studies were presented.

There are many complicated issues surrounding



the development of these compounds. First of all they may work in only a select group of people, and then the drug may cause HIV to shift to using the other co-receptor that is associated with late-stage HIV. Schering Plough halted a vicriviroc study early in treatment-naïve people due to a limp response, but continued their studies in treatment-experienced people.

There were two posters presented on maraviroc at CROI. Both are showing more data on resistance and physiological details of the new agent on the CCR5 receptor.

Keep your fingers crossed for this class as it represents another option for those who are drug resistant to the current drugs.

CXCR4 ANTAGONISTS

The stage is being set for the development of CXCR4 antagonists, the other co-receptor mentioned above as associated with late-stage HIV. A Japanese research team presented *in vitro* and animal data showing promising results in this very early stage of development. The study looked at activity, specificity, toxicity and half-life in animals. Results show that this will be an oral drug most likely taken once daily.

AMD-070 by Anormed is the only other CXCR4 in development and will be moving into Phase II studies soon.

MONOCLONAL ANTIBODY

TNX-355 (being developed by Tanox) is the first monoclonal antibody that has gotten this far in HIV clinical trials. It is technically an entry inhibitor, as it blocks the CD4 receptor on the cell, preventing HIV entry.

There was one study characterizing HIV isolates from people using the drug in clinical trials. It showed that the virus tropism (the receptor that the person's HIV prefers to attach to) did not matter, whether the antibody "stuck" on the CD4 receptor or not. This drug is currently in Phase II trials and is administered by IV infusion every two



weeks. (See www.acria.org for current studies.)

REVERSE TRANSCRIPTASE

There was news of different compounds being developed that look at different ways to inhibit the reverse transcriptase enzyme, the same drugs that were the first on the market to fight HIV. If these pan out, they will provide alternatives to current drugs targeting reverse transcriptase.

There is a nucleotide analogue pro-drug that would compete with Viread. Also, an alternative to Retrovir or Zerit is moving into Phase I studies this year. And nucleotide-competing compounds would provide an alternative to current reverse transcriptase inhibitors. All are in preclinical research—still in the test tube.

FUSION INHIBITORS

It is also encouraging to see second generation fusion inhibitors being developed after Roche discontinued T-1249, the cousin of Fuzeon (T-20), a couple of years ago. Two compounds are being considered for next phase development by Trimeris. The good news is that they are focusing on compounds that would require fewer injections, specifically once a week. Thus far the studies have only been in the laboratory, as they are trying to tease out the best compound out of a battery of possibilities. One new candidate is showing 150–250 times more activity than Fuzeon.

MORE HOPE

After living 18 years with HIV and surviving the dry years where there were no drugs, I am fortunate to be alive to witness this astounding new research in HIV. Not only have we made significant progress with 25 currently approved drugs, but it is apparent that the industry has been re-invigorated to produce better drugs that may be more potent, safer and hopefully easier to take. ☩

Matt Sharp is Director of Treatment Education at TPAN.



What's New, Pussycat?

HIV and the battle for the vagina

by Enid Vázquez

Oh, to understand the vagina. How does it work, and what does the woman attached to it want? HIV stalks her, and there's still so much to learn.

And so women (along with men) do battle. They look for new compounds that can prevent infection. They examine the effect of HIV drugs on the girl. And they lend their girl to science.

With all of that, the organizers of the 13th Conference on Retroviruses and Opportunistic Infections (CROI), the most important HIV meeting in the U.S. (held this year in Denver in February), put together a session focusing, in part, on the sexual organs and the advancing research in prevention.

GRRL POWER

In her grrl power talk, "Beyond Condoms: Chemical and Physical Barriers to Protect Women from HIV," Sharon L. Hillier, Ph.D., mixed the social and the political with the biological.

No wonder. As usual, it's one thing to have a vagina, but it's another to have power over it.

When Hillier asked women in India whether they prefer a drug they take every day to prevent infection, or one to take at the time of sex, she was surprised at the answer.

"I thought they'd say they'd rather use it only if they needed it. But they said, 'We would rather use it everyday because we don't get to decide when we have sex and would rather be protected just in case,'" Hillier said.

This type of clinical research, then, needs to deal with not just physically stopping HIV in its track, but with the social



environment as well. In her work, Hillier, a professor of Obstetrics, Gynecology and Reproductive Services at the University of Pittsburgh, Magee-Women's Hospital, and other researchers attempt to learn what would fit best into the lives of women, not just what works biologically.

"What is the most acceptable to women and their partners?" Hillier asked.

Look at condoms—they work biologically, but they're not so good socially.

"There is a whole association of condoms with sex workers."

CONDOM MADNESS

She quoted Ingrid Fitzgerald, a consultant with the United Nations Fund for

Women: "There is a whole association of condoms with sex workers. If either the husband or the wife requests to use a condom, it would be a sign of infidelity or disease."

"And yet," said Hillier, "we tell women in high-risk countries to request that their partner use condoms when in fact we know that's simply not possible.

"I think particularly when we talk about ABC—abstain, be faithful, and use condoms—it's important to know that most of us, if we went home and said to our main partner, 'I really would like to use a condom tonight,' that [Fitzgerald's] statement would absolutely be seen as true," she continued. "My husband, I know, would be a little surprised," Hillier cracked.

"And so the great proportion of women at risk for HIV aren't able to use ABC," Hillier noted. "I think most of us recognize that female condoms alone—and male condoms—aren't going to provide the answer we need."

BOYS AND GIRLS

In many countries, among the youth population, the proportion of girls and young women with HIV is much higher than that of boys and young men.

Again, the biological meets the social.

It's known that the chemical environment of a young woman's vagina makes her more at risk for HIV, until around age 21. But there's more going on.

The imbalance, noted Hillier, "has, in part, to do with something I've never understood, especially since I turned 50: that men tend to

like younger women.

"There are also certain economic disparities that women face around the world

and certainly women are often-times coerced or in economically disadvantaged relationships with men who are infected and they have no capacity to protect themselves.”

What can be done, therefore, to increase the power of both the woman and the vagina?

VAGINAL TRIALS

The drive towards prevention products that can be used by women is expected to shift the balance of power.

Prevention products for women are one of two things: barrier methods or chemical methods.

Barrier methods include such things as female condoms (not to diminish the role of male condoms), diaphragms, and a vaginal ring that might only need to be changed once a month.

Chemical methods include pills and creams. They are either systemic (absorbed by the body, as with oral drugs) or topical (applied to the surface, such as a gel inserted into the vagina).

The research on topical products focuses on microbicides—“to kill a microbe” (HIV being one). They are also being developed to kill other microbes as well, for the prevention of other sexually transmitted diseases. Microbicides, currently resembling sexual lubricants, are the leading contenders for grrl power. Their potential for invisibility—for being used behind a man’s back, so to speak—has the promise of true prevention in women’s hands.

“The idea is that microbicides reduce trauma to the epithelial surface—which enhances the protective barrier.” (The epithelial layer of cells in the vagina is known to contain cells that HIV likes to attach itself to, making infection easier.) “They may reduce epithelial inflammation by altering the local innate immune response or by preventing acquisition of sexually transmitted diseases.” (The presence of other sexually transmitted diseases is known to increase the risk of becoming infected with HIV.) “They maintain the vaginal pH—we know that lower pH is less

So there’s stuff to swallow, and stuff to insert, and then again there’s the social and political playground.

conductive to HIV infection.” And, they provide lubrication.

CALLING ALL WOMEN

So there’s stuff to swallow, and stuff to insert, and then again there’s the social and political playground. To that end, Hillier says that the fact that studies are being conducted at all is a major victory for women.

“For a long time people said microbicide trials can never be done and that they’ll never be done in the developing world, that the populations are too [problematic], and we’ll never be able to get women to use the products. I’m happy to say that in 2006 the trials are well underway,” she reported.

The women in HPTN 035, of which Hillier is a researcher, have a very high 92% retention rate and 75% report using the gel product that they’re assigned with every act of coitus [vaginal intercourse between

a man and a woman]. “I think that’s pretty remarkable,” Hillier said.

Challenges

“We learned,” said Hillier, “that when we study young, sexually active women, they become pregnant. Even though we’re providing a lot of contraceptive services, about 15 out of a hundred women become pregnant, oftentimes

unplanned.

“But there’s no questioning that there are tremendous challenges in the adherence, the product usage and the incidence of pregnancy.”

ONWARD AND INWARD

“I think it’s an incredibly exciting time in HIV prevention in women,” Hillier told her audience. “There are new female barriers being developed, both female condoms and diaphragms. Five different microbicides are in studies underway worldwide and will be completed in the next year or so, showing the first evidence of whether or not there’s proof of concept for topically applied microbicides. I find the recent PK [pharmacokinetic] data coming out that finds drug levels in the genital compartments for drugs orally administered to be extremely interesting.

“But even if those [microbicides] studies fail to show a benefit, I think it’s important to note that these studies have shown something critically important. One is that these studies *can* be done in high-risk women. Two, that women are willing to participate in these trials. So I think that these studies are going to be incredibly beneficial in paving the way for future studies of more potent anti-HIV microbicides.” ☩

For a webcast or podcast of Hillier’s presentation, including her slides, visit www.retroconference.org and see the Monday presentation, “HIV Prevention Research: New Advances, Continued Challenges.” See a longer version of this article at www.tpan.com.



Metabolics and HIV

Update From the 13th CROI

by Jeff Berry

FISH OIL AND FENOFIBRATE

An Adult AIDS Clinical Trials Group (AACTG) study found that high triglyceride levels were significantly lowered when taking fish oil or fenofibrate alone, and even more of a decrease was seen when both were taken in combination.

Following an American Heart Association Scientific Statement on fish oil and triglycerides, some researchers decided to look at using the supplement in HIV patients with high triglycerides. Fish oil contains omega-3 fatty acids. Tricor is one of the brand names for fenofibrate, a drug used to lower levels of cholesterol and triglyceride. The cost of this medication starts around \$60 a month, but is available generically for about \$50 monthly.

The study, ACTG A5186, randomized 100 people with triglyceride levels of 400 and normal LDL (the good cholesterol) to 3 grams of fish oil twice a day, or 160 mg of fenofibrate once a day. At 8 weeks, 4/47 (8%) who took fish oil and 8/48 (17%) on fenofibrate had triglycerides below 200 mg/dL. Seventy-five people who were unable to get their triglycerides below 400 then combined the fish oil and fenofibrate, and, using a strict intent-to-treat analysis, 17 (23%) had triglycerides levels below 200 at 18 weeks from the start of the study.

THE ROLE OF GENETICS

There were several studies presented at this year's CROI which looked at how genetics may play a role in body fat changes or blood fat levels in those on HIV treatment, which may someday allow doctors to


There were several studies presented at this year's CROI which looked at how genetics may play a role in body fat changes or blood fat levels in those on HIV treatment.

customize an individual's treatment to fit his or her genetic profile. While these preliminary findings hold some promise, they require further study, so don't expect to see them in your doctor's office anytime soon.

HIV MEDICINES AND YOUR HEART

Increased protease inhibitor (PI) exposure was associated with an increased risk of myocardial infarction (MI), according to a new analysis of the D:A:D study (Data Collection on Adverse Events of Anti-HIV Drugs). This 11-cohort study of over 23,437 individuals in Europe, the U.S., and Australia found that for every additional year of PI therapy there was a 16% increase in risk for MI.

HARDENING OF THE ARTERIES

A 3-year follow-up study of ACTG 5078, an analysis which looked at 134 HIV-infected and uninfected adults, found that when matching for known coronary heart disease (CHD) risk factors, neither HIV infection nor PI exposure significantly affected the rate of progression of carotid intima-media thickness (IMT), a marker of early atherosclerosis (cholesterol build-up, or hardening of the arteries), suggesting that "classic" CHD factors play a more significant role than ART in the increased risk of cardiovascular events in HIV-infected individuals. (For an explanation—albeit technical—of hardening of the arteries, visit www.americanheart.org/presenter.jhtml?identifier=1243.) 



Don't Rush to HIV Treatment

Looking at the nuances of that possibly alarming report

by Stephen J. Fallon, Ph.D.

An important HIV treatment study presented at the Conference on Retroviruses and Opportunistic Infection in February has been poorly explained in the mainstream media, possibly leading persons living with HIV to dangerously misguided conclusions about when they need to start therapy.

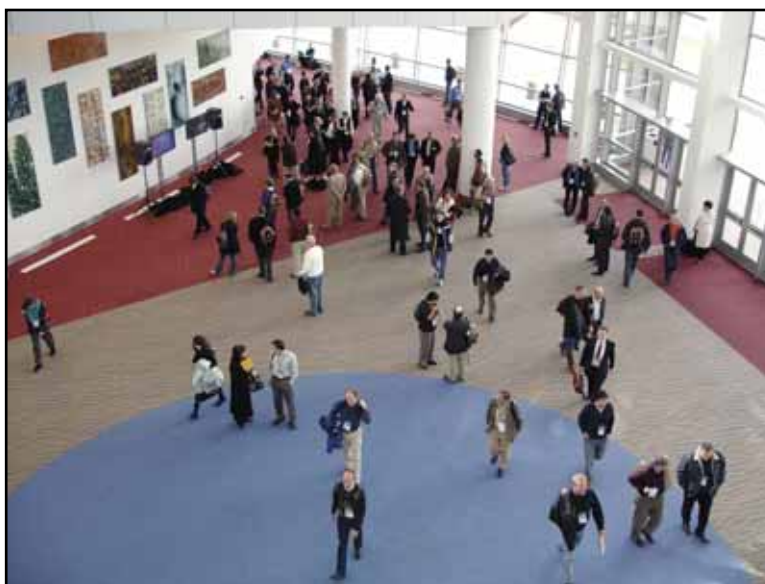
Consider the Reuters news headline: "Early Treatment Always Better for HIV, Study Finds." If you've been living with HIV for a few years without taking any treatment,

you might assume that you need to rush to your physician immediately, preferably by ambulance. Let's take a look at what the study did and didn't actually find.

BACKGROUND

First, some history. By today's standards, past HIV treatments were pretty wimpy. The best medicines available as recently as 1992 only added, on average, 2.8 months extra life expectancy to the normal span for a person diagnosed with AIDS. With the advent of three-drug treatment strategies in the mid-1990s (using two classes of medicines), AIDS deaths plummeted by 80%, and average life expectancy increased by 4.1 years in 1997.

In an historic misunderstanding of HIV's resilience, medical researchers seized on this favorable news and announced that science could soon win the battle against HIV. *Time* magazine's 1996 "Man of the Year," AIDS researcher Dr. David Ho, famously suggested that treat-



ment for just 2.3 to 3.1 years might push HIV out of the body. Ho recommended that physicians "Hit early, hit hard" with HIV medications, and clinicians around the nation complied, virtually force-feeding drug combos to their otherwise healthy patients living with HIV.

Is earlier
treatment
always better?

We now know that, in a cruel paradox, HIV actually became *more* virulent in patients who did a pretty solid (but not perfect) job of taking their pills on time than in

patients who did a very poor job of taking their meds.

Moreover, physicians began to observe in their patients health problems that were caused by treatment toxicities. Researchers also found that patients who fail on early treatment regimens may close future treatment options that would have remained open if they had not burned through certain medicines prematurely. Finally, a three-country study recently revealed that, for almost all patients, starting treat-

ment within three years of infection yields no additional benefit whatsoever.

A couple of qualifiers: remember that day of diagnosis is not the same as day of infection. If you were likely infected years ago, but just diagnosed today, your timeline begins at the time of infection. Also, treatment might depend on your condition and your symptoms.

WHAT'S NEW?

Does the new study overturn these hard learned lessons? Is earlier treatment always better? Dr. Kenneth Lichtenstein's study, released at CROI, did find that patients who waited too long to initiate treatment harmed themselves in two ways.

Lichtenstein looked over records of 2,304 patients studied between 1996 and 2005. Compared to late starters, earlier treaters were more likely to bring their virus down to undetectable levels in the bloodstream. They were also 60% less likely

to develop kidney insufficiency, 30% less likely to report peripheral neuropathy, and 60% less likely to develop lipodystrophy (loss of body fat, particularly troublesome in the face).

The study's authors acknowledged that the earlier treaters may have been more proactive about their health maintenance in many ways, so some of the benefits they enjoyed may have resulted from their faithfully taking their medicines every day.

But all this study really demonstrates is that starting treatment during the recommended period is better than waiting until past that period. To determine when treatment is really needed, your physician looks primarily to two numbers: viral load (the amount of virus in your bloodstream) and CD4s (the amount of an important part of your immune system that is still intact). Ideally, the first number should be low, and the second number high.

As recently as 1997, United States Health and Human Services guidelines



through bi-annual blood work ups.

The late starters in Lichtenstein's study were too late to reap the greatest benefits from treatment according to HHS guidelines. So it's no surprise that they fared worse. This does not mean that someone starting even earlier than recommended would do better still.

"Hit Early, Hit Hard" remains a

recommended an aggressive approach, initiating treatment for patients with even moderate viral load (20,000 copies/ml) and a hearty immune system (up to 500 CD4s). In successive years, the guidelines pushed treatment initiation out further and further, now suggesting treatment begins when viral load is over 100,000 and/or when CD4s drop below 350 (with symptoms) or near to 200 regardless of symptoms.

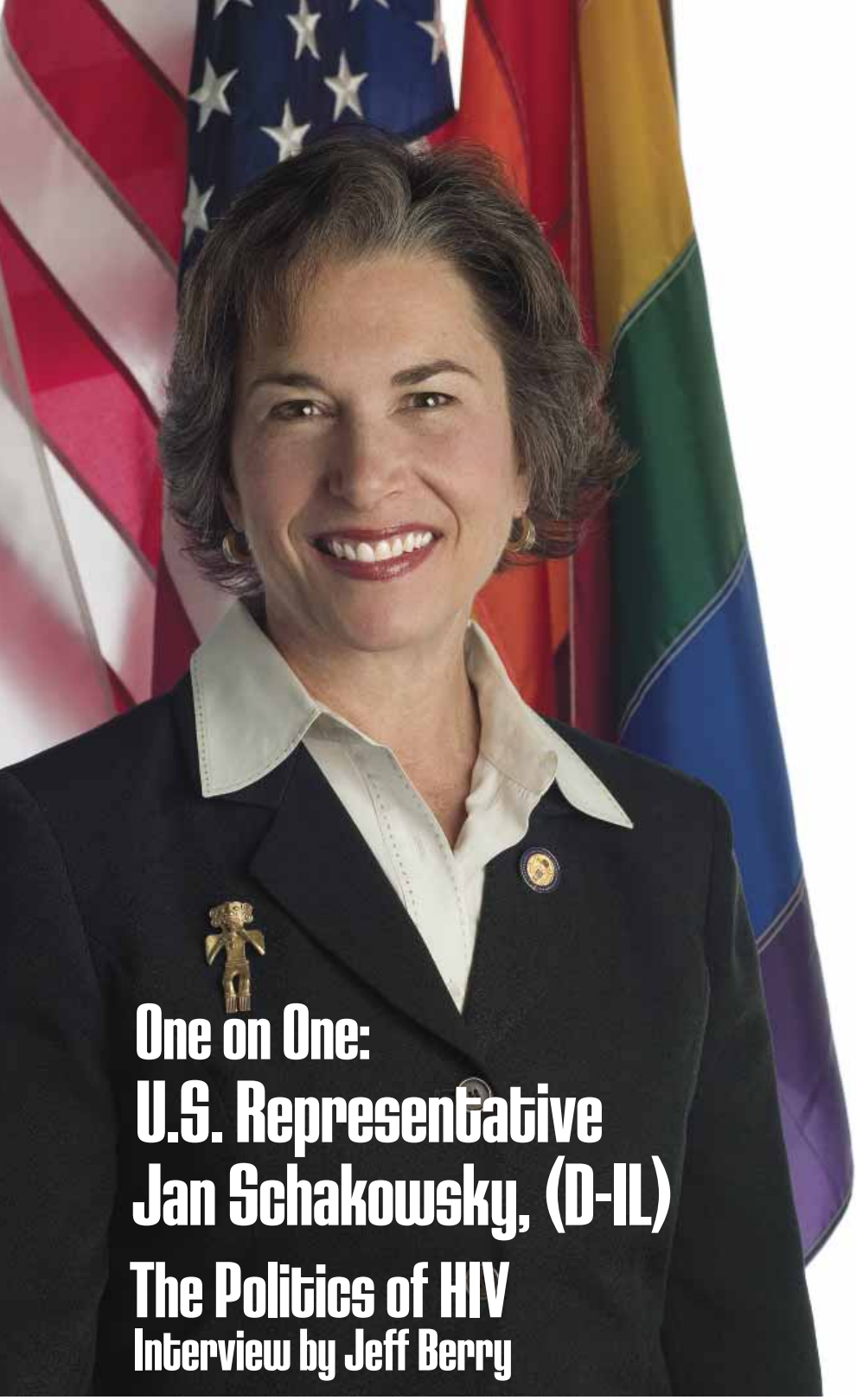
Though people living with HIV differ widely in their disease progression, these current guidelines would allow the average infected individual to postpone treatment for up to eight years following infection, merely monitoring his/her progress

discredited strategy. Perhaps the new slogan should be "Hit HIV Hard When the Time is Right." Call it the Goldilocks approach: not too early, not too late, but just right to live longer and healthier with the virus. ☚

Stephen Fallon is the President of Skills4, Inc., a healthcare and disease-prevention consulting firm that specializes HIV prevention and management. Visit his website at www.skills4.org. If you need sources for any medical information cited in his columns, e-mail him at sfallon@skills4.org.



Photo © Jeff Berry



**One on One:
U.S. Representative
Jan Schakowsky, (D-IL)
The Politics of HIV
Interview by Jeff Berry**

In an effort to keep our readers informed, earlier this year we asked a series of questions to leading Republican and Democratic officials. Beginning with this issue and up until the elections in November, you'll find their responses here in the pages of *Positively Aware*. First up, U.S. Representative Jan Schakowsky (D-IL), featured on this issue's cover, who talked to *Positively Aware* about the Ryan White CARE Act, microbicides, and the ideology of the Bush administration.

Jeff Berry: What are your own priorities on your agenda for national HIV/AIDS issues for 2006?

Jan Schakowsky: More than one million Americans are living with HIV/AIDS (over 42,000 in Illinois) and over 40,000 individuals are infected each year. Our community, our nation, and the entire world are threatened by this terrible pandemic. We need to make sure that everyone who is already infected is able to get all the information and services they need and work harder to prevent new infections.

I am a member of the House Energy and Commerce Committee, which has jurisdiction over the Ryan White CARE Act. The CARE Act's authorization expired on September 30, 2005 (although funding is continuing), and I believe it is a top priority to reauthorize this critically important program in 2006. I want to make sure that we maintain the comprehensive medical and support services that make the CARE Act so effective and that we expand the number of people who receive those services. Unfortunately, President Bush has put forward reauthorization principles that could hurt our efforts. Among his recommendations: shift some funding from Chicago and other of the hardest-hit large urban areas to rural communities, limit the amount of funding that can go to support services like job training and transportation, and lower support for community-based organizations that are so essential. While Illinois has some of the best HIV/AIDS treatment centers in the country, those centers cannot afford to lose a dime of funding at a time when the epidemic is spreading.

In addition to my efforts on the CARE Act reauthorization, I will do whatever I can to increase funding for the Housing Opportunities for People with AIDS (HOPWA) program. This assistance is particularly important in areas like Chicago where affordable housing is so scarce. I am also working to protect Medicaid and Medicare funding and to pass the Early Treatment for HIV Act, H.R. 3859. This bill would let states provide critical Medicaid services to HIV-infected individuals (rather than waiting until they have developed an AIDS diagnosis as required under current law) so that they can remain healthy and productive.

I am aggressively promoting specific measures to improve prevention. Recently, I introduced the Microbicide Development

Photo © Russell McGonagle

Act, along with my colleagues, Congressmen Chris Shays and Danny Davis. Microbicide research and development are critical to preventing HIV and other sexually transmitted diseases (STDs). Our legislation would encourage the Federal government to expand, intensify, and coordinate microbicide research and development. As gender inequalities have left women particularly vulnerable to infection, the battle to stop the spread of HIV/AIDS among women will ultimately hinge on our ability to empower women to protect themselves. Microbicides could prove to be one of the most important tools women have in preventing the transmission of HIV. (See page 20.)

JB: What is the current state of affairs with support for HIV/AIDS care and prevention today and how do you see it becoming affected in 2006 midterm and 2008 elections?

JS: Despite the ongoing epidemic, the Fiscal Year (FY) 2006 Labor-Health and Human Services (HHS)-Education appropriations bill, which I strongly opposed, froze funding for every title of the CARE Act except for the AIDS Drug Assistance Program (ADAP), which was slated to receive a \$10 million increase, an amount that would not even keep pace with drug price inflation. HOPWA received a slight increase to \$286 million which, again, doesn't keep pace with existing need or housing prices. At the same time, the budget cut Medicaid by \$6.9 billion and Medicare by \$6.4 billion over the next five years. Together, those two programs account for about 75% of all funding on HIV/AIDS. The President's FY 2007 budget proposal is more of the same. On the one hand, it would include small increases of \$95 million in the CARE Act specifically to assist state ADAPs with waiting lists and \$93 million to the Centers for Disease Control and Prevention (CDC) for testing efforts. On the other, it also proposes cuts to other essential services: \$4.9 billion in Medicaid cuts and \$36 billion in Medicare cuts as well as cuts to the National Institute of Mental Health (NIMH) and Substance Abuse and Mental Health Services Administration (SAMHSA), programs that provide necessary mental health and substance abuse treatment to those living with HIV/AIDS, a population estimated to have rates of co-morbid mental health and substance abuse problems anywhere from 30% to 80%.

These co-morbid factors greatly influence prevention as well as treatment for those at risk for and infected with HIV.

Finally, I am concerned that the Bush Administration has put ideology ahead of science on many issues, including HIV/AIDS prevention. Instead of focusing on prevention tactics that work—like needle exchange and condoms—this Administration continues to put the focus on abstinence-only education. It is also ignoring the needs to provide more prevention services in our corrections facilities, which are a major contributor to new infections.

JB: What is your policy on harm reduction and what is your perception of the crystal meth problem?

JS: Methamphetamine represents one of the fastest growing drug threats in America today, and we need a comprehensive strategy to deal with this problem. The House is currently debating H.R. 3889, the Methamphetamine Epidemic Elimination Act, which would make it more difficult for would-be producers of meth to obtain the necessary ingredients and provides more funding for enforcement. Yet, this is only one side of the fight. I believe we need a strategy that goes beyond enforcement and supply side initiatives and includes targeting demand for this drug through prevention efforts that educate Americans about its dangers. Those dangers include the risk of HIV infection through injection use and the drug's disinhibiting effects that can impair a person's impulse control and judgment, often leading to high-risk behaviors. I believe there is a role for harm reduction strategies in this fight as well, interventions designed to meet the drug abuser "where they're at" and seek to address not only the drug abuse, but the conditions that lead to the abuse and the harm resulting from it.

Meth is a community crisis and we must work with community-based organizations to develop the strategies that will be effective in preventing harm (including HIV infection and the possible spread of HIV to the abuser's sexual partners and children) while working to stop drug abuse altogether.

JB: Who would be your choice for a pro-AIDS president in 2008?

JS: I will support any Democratic candidate who will make elimination of

AIDS a priority and commit to ensuring guaranteed, affordable health care to all Americans.

JB: Where do you see AIDS research funding in 2006? Are you committed to continued funding for OAR (Office of AIDS Research)?

JS: I am a strong supporter of increased OAR funding, which holds the promise of delivering amazing breakthroughs in the prevention, treatment, and cure of HIV/AIDS. Although we were successful in completing a five-year, bipartisan effort to double National Institutes of Health (NIH) spending, of which OAR is a part, we need to continue the effort to adequately fund AIDS research. I voted against the House-passed budget resolution, which severely underfunds AIDS research and other health programs. I supported the Obey amendment which would have increased NIH spending and other critical programs by limiting future tax cuts for millionaires. The President's budget for FY 2007 proposes a freeze in NIH spending. If that recommendation is followed, OAR will again be underfunded. I plan to do whatever I can to make sure this does not happen, as it is clear that research on prevention and treatment is the only way to a cure.

JB: Are you committed to being a leader in keeping the CARE Act strong and intact for the future?

JS: Absolutely. Over the past years, I have had the opportunity to meet frequently with Illinoisans who have been given hope and a future because of the Ryan White CARE Act. I have seen the difference that the CARE Act makes for individuals, families and our community. Unfortunately, between 42% and 59% of people living with HIV/AIDS are not in regular care. To reach them, we need to expand the CARE Act and provide increased funding for prevention, treatment, support services and community-based outreach and education to every person living with HIV/AIDS. This year, as I have done in the past, I will continue to do whatever possible to ensure that the CARE Act receives the resources it needs. And, I am privileged to work with so many vocal, committed and strategic advocates in that effort. ✚

Hepatitis B: The Other Hepatitis Virus

Part Two

Treatment for HBV

by James Learned

Part One of this article in the March/April issue of *Positively Aware* discussed that infection with hepatitis B virus (HBV) is a significant problem for many people with HIV. Up to 10% of HIV-positive people in the U.S. are co-infected with chronic HBV.

HBV can cause short-term (acute) and long-term (chronic) infection. The immune system usually fights off (clears) HBV within six months of infection. If you clear the virus within that time, the antibodies that your immune system creates in response to the infection protect you in the future.

If the virus *doesn't* clear within six months, you have chronic HBV. The virus continues to reproduce in the liver, which can lead to inflammation, severe liver damage—including cirrhosis (scarring) and liver cancer—and, possibly, death.

People with weakened immune systems are more likely to develop chronic infection, and HIV/HBV co-infection can cause more problems than chronic HBV alone (mono-infection), including difficulty tolerating some HIV medications, faster progression of liver disease, and higher rates of liver failure.

TREATMENT FOR ACUTE HEPATITIS B INFECTION

Many people infected with HBV don't have noticeable symptoms and only learn that they've been infected if they have blood-work done. During acute infection, you can transmit the virus to others—primarily through unprotected sex or sharing injection drug equipment. There's no treatment available for acute HBV except to rest, drink plenty of fluids, and take medications to help ease the flu-like symptoms.

If you know that you were exposed to the virus and less than two weeks have passed from the time of exposure, a hepatitis B immune globulin (HBIG) injection may prevent the development of HBV infection or reduce the length and severity of illness. But HBIG provides only temporary protection, so the hepatitis B vaccination series is started at the same time to provide long-lasting immunity.

CHRONIC HEPATITIS B INFECTION

Hepatitis B is a complicated virus, and complex factors contribute to disease progression. Once HBV enters the liver, the virus inserts itself into the nucleus of liver cells, which makes it very difficult to eliminate. In co-infection, complex interactions occur between the two viruses.

Not everyone with chronic HBV needs treatment. The decision is made on a case-by-case basis, taking into account the following factors:

- HBV-DNA levels (hepatitis B viral load);
- liver function test results, especially ALT levels;
- the presence of hepatitis B envelope antigen (HBeAg)—fragments of the virus;
- the degree of liver damage as measured by imaging (ultrasound, CT, or MRI scans) or biopsy;
- benefits vs. risks of treatment (such as side effects);
- alcohol use;
- age;
- family history of HBV infection and liver cancer;
- the effect of symptoms on quality of life;
- other medical conditions, including HIV; and

- willingness to take HBV treatment.

Although chronic HBV is usually a slowly progressive disease, liver damage often occurs more quickly and is more serious in co-infected people. Even if you're not taking treatment for HBV, it's still important to have hepatitis B viral load and liver function checked regularly by a knowledgeable healthcare provider.

GOALS OF HBV TREATMENT

The main goal of treatment for chronic HBV is to suppress viral replication and stop liver disease progression. Higher blood HBV-DNA levels predict a higher probability of developing liver cancer. Suppressing HBV-DNA to undetectable or very low levels reduces the likelihood of developing cirrhosis, liver cancer, and liver failure.

In addition to achieving undetectable HBV-DNA, successful HBV treatment is measured by normalized ALT levels, the loss of HBeAg, and a less damaged liver. If consistently elevated ALT levels prior to treatment become consistently within normal ranges, it's a good sign of decreased liver damage.

The presence of HBeAg usually means that HBV is replicating in liver cells. If HBeAg is no longer found during treatment, it's an indication that treatment has been successful, especially if the hepatitis B e antibody (anti-HBe)—produced by the immune system in response to HBeAg—wasn't present before starting treatment and then becomes present. HBV treatment is usually stopped in patients who maintain these antibodies for at least six months.

Treatment is continued indefinitely for people who are HBeAg-negative with detectable HBV-DNA.

WHEN TO BEGIN HBV TREATMENT

There are no absolutes about when to begin HBV treatment or who should be on treatment. Many factors need to be considered when making the decision.

The American Association for the Study of Liver Diseases (AASLD) Practice Guidelines currently recommend offering treatment to people who are HBeAg-positive *or* who have HBV-DNA levels above 100,000 copies/mL and liver damage determined by consistently elevated ALT levels (two times or more above the upper limit of normal) or liver biopsy.

For people who are HBeAg-negative, treatment is recommended if HBV-DNA levels are above 10,000 copies/mL.

Generally, people are less likely to have a successful response to HBV treatment if ALT levels are relatively low (*less* than two times above the upper limit of normal) when they begin treatment.

Since recent research indicates that the risk of liver cancer increases with higher HBV-DNA levels—regardless of ALT levels—the AASLD is considering recommending that treatment be initiated based only on HBV-DNA.

If HBV-DNA levels don't reach undetectable, getting below 100,000 copies/mL usually slows the progression of liver disease, although some people with HBV-DNA levels consistently below 100,000 have severe liver disease. An undetectable HBV-DNA level is important because it reduces the development of drug-resistant HBV. Less HBV replication allows less opportunity for resistance to develop.

TREATMENT FOR CHRONIC HBV

There are many questions concerning the best treatment for chronic HBV infection—and the issue is more complicated in co-

infection. Little consistent or comparative information exists about the individual drugs, partly because they've been studied in people with different categories of chronic HBV (with or without HBeAg and higher or lower HBV-DNA levels, for example).

Two types of HBV treatment are approved by the Food and Drug Administration: injectable immunomodulators that indirectly inhibit viral replication, and oral antivirals that directly inhibit viral replication. Approved immunomodulators are Intron A (interferon alfa-2b) and Pegasys (pegylated interferon alfa-2a). Approved oral antiretrovirals are Epivir-HBV (lamivudine, 3TC), Hepsera (adefovir dipivoxil), and Baraclude (entecavir).

None of these drugs are actually approved to treat HBV in co-infection (although they can still be used), and some need to be used very carefully in people with HBV and HIV. They vary in how well they work, durability of response after treatment, side effects, the development of HBV resistance, length of treatment, and their effect on HIV.

IMMUNOMODULATORS

Most people treated with interferon (standard or pegylated) experience difficult side effects, and, for some people, these side effects are unbearable.

Intron A (interferon alfa-2b), or standard interferon, was approved in 1992 as the first treatment for chronic HBV, but is rarely used now due to its low response rate, inconvenience, and the availability of better therapies.

Pegasys (pegylated interferon alfa-2a) achieves higher sustained response rates for both HBeAg-positive and HBeAg-negative people than standard interferon. Pegylated interferon is injected subcutaneously (under the skin) once a week. Treatment lasts a year, and if you achieve a successful response (low HBV-DNA levels, normalized ALT levels), it tends to last once you finish treatment.

So far, there are no data showing the effect of pegylated interferon on HBV in co-infected people, but a few such studies are ongoing.

ORAL ANTIVIRALS

These drugs are taken once a day, have few side effects, and generally provide strong activity against HBV while you're on treatment. Unfortunately, they rarely lead to a long-lasting response. When you stop the drug, HBV-DNA and ALT levels usually return to where they were before you began treatment. This is unlikely to occur if you convert from being HBeAg-positive to HBeAg-negative and develop anti-HBe antibodies that are maintained for at least six months.

Most often, taking one of these drugs is a long-term deal. Stopping can cause sudden increased ALT levels, usually accompanied by rising HBV-DNA levels and, sometimes, serious physical symptoms. Liver function should be monitored closely for several months after stopping treatment with any of the following drugs.

Epivir-HBV (lamivudine, 3TC), a safe drug with few side effects, was developed to treat HIV. It's also active against HBV, decreasing HBV-DNA levels and significantly reducing liver damage and the risk of liver cancer. Lamivudine is effective for the treatment of both HBeAg-positive and HBeAg-negative chronic HBV.

Unfortunately, the effect of Epivir-HBV is severely limited by the development of drug-resistant HBV. The frequency of drug resistance increases over time—up to 70% after four years of treat-

ment. And resistance develops in as many as 90% of HIV/HBV co-infected people after four years of treatment.

Epivir-HBV should never be used as monotherapy (by itself) to treat HBV if you're co-infected. The dose of lamivudine in Epivir-HBV is too low for HIV. If lamivudine is taken by someone with HIV/HBV co-infection, the HIV dose (300 mg once a day or 150 mg every 12 hours) should be used as part of combination HIV therapy.

Hepsera (adefovir dipivoxil) suppresses replication of HBV without any mutations that cause drug resistance (wild-type virus) as well as lamivudine-resistant HBV. Clinical trials found Hepsera to be tolerable and safe, and side effects were similar to those seen in people taking placebo. It's important to monitor kidney function in anyone taking Hepsera. People with kidney problems may need a dose adjustment.

Studies of people who took Hepsera every day found significant decreases in HBV-DNA levels, liver improvement, normalization of ALT levels, and the loss of HBeAg in many participants after a year of treatment. These benefits were maintained—but didn't improve—in people who continued treatment for a total of four years. Like Epivir-HBV, Hepsera is effective for the treatment of both HBeAg-positive and HBeAg-negative chronic HBV.

HBV resistance to Hepsera is much lower than that for lamivudine. In 2005, researchers combined data from five studies to determine the likelihood of developing resistance to Hepsera over time. The probability of developing resistance after taking Hepsera as monotherapy for four years was 15% compared to 70% of people developing lamivudine-resistance after taking Epivir-HBV monotherapy for the same amount of time. The study also found that the probability of developing Hepsera-resistance after four years was 0% for people taking a combination of Hepsera and Epivir-HBV.

Baraclude (entecavir) was approved in 2005, so we don't have as much long-term data about it as we do for Epivir-HBV and Hepsera. Like Hepsera, Baraclude suppresses replication of wild-type HBV as well as HBV that's resistant to lamivudine. Results of a small study in people with HIV/HBV coinfection are promising.

The drug is safe and well tolerated. In clinical trials comparing Baraclude to Epivir-HBV or placebo (dummy pill), the frequency of side effects was similar in people taking either drug or the placebo.

Two large trials comparing Baraclude to Epivir-HBV in people who hadn't taken HBV treatment before—one of HBeAg-positive people and one of HBeAg-negative people showed positive results. After a year of treatment, Baraclude was more effective than Epivir-HBV in terms of improved liver damage and lower HBV-DNA levels.

Baraclude seems to have a very low rate of resistance, especially compared to Epivir-HBV. So far, only a few people have developed HBV that's resistant to Baraclude, but we only have two years of follow-up data from studies of Baraclude. Hepsera's resistance profile looked good after two years, too. It wasn't until we had four or five years of follow-up data that we learned that resistance to Hepsera can and does occur. One thing we *do* know is that people with HBV resistant to Epivir are more likely to develop resistance to Baraclude.

TREATMENT CONSIDERATIONS IN HIV/HBV CO-INFECTION

Three HIV medications are active against HBV—Emtriva (emtricitabine), Epivir (lamivudine, 3TC), and Viread (tenofovir).

Various studies indicate that Viread is effective in people with lamivudine-resistant HBV, and one study suggests that Viread is more effective against HBV than Hepsera.

Emtriva and Epivir are very similar drugs, and HBV resistance to Emtriva (as with Epivir) limits the drug's ability to suppress HBV replication. These factors make it tricky to figure out how best to treat people with HIV/HBV co-infection.

Treatment for people with co-infection needs to be individualized based on the progression of their HBV infection, HIV disease, and other factors. The following are treatment considerations for people with HIV/HBV co-infection.

IF TREATMENT IS NEEDED FOR HIV BUT NOT FOR HBV

Avoid using Viread, Emtriva, or Epivir as the only drug with anti-HBV activity in an HIV combination. Use two of these drugs in the combination or save them all for later, when treating the HBV infection might be necessary.

IF TREATMENT IS NEEDED FOR HBV BUT NOT FOR HIV

Consider using pegylated interferon, Baraclude, or Hepsera to treat HBV. Combining Baraclude and Hepsera may be the best bet. Avoid Epivir-HBV, since Epivir monotherapy is very likely to cause Epivir- and Emtriva-resistant HIV. Epivir should only be used as part of a strong HIV combination unless your HIV is already resistant to the drug.

IF TREATMENT IS NEEDED FOR BOTH HIV AND HBV

Use Viread with either Epivir or Emtriva as part of your HIV regimen, since each of these drugs is active against HBV. Truvada combines Viread and Emtriva in a single, convenient pill.

WHEN STOPPING AN HIV DRUG WITH ACTIVITY AGAINST HBV

If someone with HIV/HBV co-infection stops taking Epivir, Viread or Emtriva for any reason, liver function should be carefully monitored. Taking Hepsera may prevent hepatitis B flares. The formulations Combivir, Trizivir, Epzicom, and Truvada contain two or more HIV drugs, at least one of which is also active against HBV. Stopping any of these formulations could cause hepatitis B flares as well.

THE FUTURE OF HBV TREATMENT IN CO-INFECTION

Much progress has been made in treating chronic HBV over the last few years. Although information about the effectiveness of these treatments in co-infection is far from complete, many co-infection trials are now enrolling. At least 20 drugs are being studied to treat chronic HBV. Viread (tenofovir) may be the most promising.

It's possible that the future of HBV treatment is combination therapy. At least nine combination therapy trials are ongoing. With high rates of HBV-resistance to the oral antivirals over the long-term, the use of two or more drugs might be the way to go. Although there's little information available to support this strategy yet, considering what we know about the development of drug resistance using monotherapy in HIV, it makes sense. The potential benefits of combination therapy for HBV—especially with drugs that are relatively safe—deserve attention. Stay tuned! ☞

James Learned is a treatment writer and health educator living in New York City (James_Learned@prodigy.net).

Gay Games Profiles

Athletes with HIV show their winning attitudes

by Keith R. Green

During July 15-22, 12,000 athletes from around the world will descend on Chicago to take part in the 2006 Gay Games. Following are profiles of three of the many courageous HIV-positive athletes taking part in this summer's festivities in the Windy City. For more information on the Games, see the ad on page 47 or visit www.gaygameschicago.org.



CONSCIOUS SODEN

Conscious Soden is a woman not to be played with. And, as her name implies, she's absolutely aware of that. Whether studying electronics and engineering while in the United States Navy or hustling hard as the production assistant for the *Queen Latifah Show* or even hosting her own talk show for the Oxygen Media Network, Conscious' life is a true testimony to hard work and determination.

Haunted by a traumatic childhood and an early adult life of drug and alcohol abuse, Conscious could very well be the poster child for the old saying, "you can't keep a good woman down"—a theory she intends to validate, yet again, as she plays for the gold in Women's Basketball during this summer's Gay Games.

"Basketball is my first love and no matter what I went through in my life, a good game of ball always helped me through the day," says 40-year old Conscious, who currently resides in sunny Miami Beach. "At one time, my performance was hindered a bit due to illness that resulted from being HIV-positive. But I feel really strong now."

It is that sense of strength and resilience that convinced executives at Showtime (home of *Queer as Folk*), to transform Conscious' life-changing autobiography, *Getting Unstuck*, into a motion picture starring hip-hop diva and television sweetheart Eve.

"You can overcome all drama and still succeed," says Conscious with incredible certainty. "I did."



CRAIG GOODMAN

Just being able to compete in this year's Gay Games is more than enough reward for Craig Goodman, a long-term survivor of AIDS. To win a gold medal in bowling, well, that would be the icing on the cake.

Since his last visit to the Games, at Vancouver in 1990, Craig's physical health has endured many ups and downs that severely threatened his dreams of returning—but even that was not enough to crush his determination. The support and encouragement from his family and the many life-long friends that he has made along the way, has transformed his hope and desire of once again competing in the Games into reality.

"This has been a personal goal of mine," he says with great pride. "At one point I needed to be in a wheelchair to get around Disneyland. I could not be on my feet too long and needed the aid of a cane just to walk. But today, I have very few restrictions."

Few restrictions indeed! Craig currently bowls in three leagues a week and manages a bowling center in his hometown of Van Nuys, California—a regimen that he hopes will pay off when it's time to bowl for the gold. "Some people don't believe that there is strong competition in gay bowling," he says. "There is!"

It was this realization that helped Craig to let go of a lot of his own internalized homophobia. "It was hard for me to overcome the fear that only pansies were involved in gay bowling," he bravely admits. "I never thought that I would ever reach the competition level that I am now involved in."

Asked about how he feels he'll do in this year's competition, Craig's response is both honest and optimistic. "Bowling is a very mental game and I have a tendency to wander," he says. "But I want this to be my best outing yet."

JAMES BALLARD

"I guess you can say that I'm slightly competitive," says James Ballard, who has won so many medals from competing in the Gay Games that he stopped counting...after his 40th one. "But I am inspired by those who try their hardest because, win or lose, they are raising the bar."

An avid swimmer since his brother pushed him into a swimming pool at the age of 10, James' passion for swimming has raised many bars along the way—and a couple of eyebrows as well. While his resume boasts such esteemed honors as world masters records (as in more than one) in his sport, James is also vividly able to recount the prejudices he encountered in the early days of AIDS, belonging to an openly gay swim squad.

"In San Francisco (1986), we had to travel to Oakland to find a pool because nobody wanted a group of gay swimmers to take over their pool," he says. "Sadly, however, this was not my first experience with being thrown out of a pool in the darker days of AIDS ignorance."

It was days like these that help James to appreciate the opening ceremonies of the Games, of which this will be his sixth. "When I walked into the Olympic (sized) venues in Sydney and Montreal and Atlanta, I reflect on how far we have reached," he says like a father proud of his baby's first steps. "I am simply thankful that I have made this journey with my friends, family and our community." ☞





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Treatment Interruptions

Reviewing what we've learned so far

by Kaleo Staszko, MD

Treatment of HIV is interrupted often and for many reasons. Technically, skipping a dose of your meds or even taking them an hour late is a treatment interruption of sorts. Not infrequently, patients have to weigh the advice of their physician to continue treatment against difficult personal or economic realities. Or a physician may recognize that a patient may temporarily be too distracted by medical illness, drug addiction, financial hardship, or another personal issue to make a commitment to taking HIV medicines as directed. Occasionally, meds have to be stopped due to a severe side effect or toxicity such as hyperlactatemia caused by NRTIs. In these sorts of situations, patients derive some clearly defined benefit from stopping treatment that they have decided outweighs the risks posed by untreated HIV. It is understood, however, that the price one pays for the benefits from interrupting treatment in these settings may be diminished control of HIV and progressive impairment of the immune system.

In contrast, the concept of strategic treatment interruption (or structured treatment interruption) is that treatment can be interrupted in some specific manner for the express purpose of improving outcomes such as restoration of control of HIV in patients experiencing virologic failure, reducing exposure to HIV medications, minimizing complications of treatment, or improving patients' well being through structured "drug holidays" and easier-to-take regimens that are as or more effective than standard therapy. Another compelling feature of any treatment strategy that is found to be as effective as standard, continuous HAART (Highly Active Antiretroviral Therapy), but uses less medicine over time, would be a substantial reduction in cost. For example, a fixed-length treatment interruption regimen with patients spending two months on and four months off meds would allow an AIDS Drug Assistance Program with a limited budget to provide three times as many people with antiretroviral medications each year. Note, however, that any treatment strategy that seems to save money initially but turns out to be less effective than standard HAART, will likely prove far more expensive to the state in the long run due to the cost of treating complications of HIV and AIDS which could have been prevented.

Treatment interruption as a strategy to improve clinical outcomes in HIV management was first explored as a potential means of combating multi-drug resistant virus in heavily treatment experienced patients. HIV becomes resistant to a drug when it mutates in a way that renders the drug ineffective. Resistance mutations, however, often come at a cost to the virus in terms of fitness. That is to say, resistance mutations can decrease the ability of HIV to multiply, but that without resistance mutations, HIV could not multiply at all in the presence of drugs. Remove the drugs from the equation, however, and the formerly crucial resistance mutation is now a liability to the virus. In this setting, wild-type (meaning without drug resistance mutations) virus, because it is more fit,

rapidly becomes the predominant virus and resistant virus rapidly becomes undetectable.

It was therefore hoped that during a treatment interruption, competition with wild-type virus would rapidly eliminate drug resistant virus. Unfortunately, it has been demonstrated repeatedly and convincingly that treatment interruption, when undertaken in highly drug resistant patients, does not eliminate drug-resistance, which returns promptly upon restarting meds; and can, in fact, lead to additional resistance and more rapid progression of HIV. This is not to say that treatment should never be interrupted in patients with resistance to multiple drugs, but that treatment interruption in this setting does not work as a strategy for improving control of HIV and is likely to cause more harm than good.

Just because treatment interruption is not a viable strategy for achieving better virologic control in heavily treated patients with lots of drug resistance doesn't mean it may not be advantageous for other patients in other settings. Interrupting treatment when a patient's regimen is failing might produce entirely different results than when treatment is working very well. Accordingly, patients responding to HAART have participated in many recent clinical trials involving treatment interruptions. Among the key issues addressed by recent trials are the following.

- For patients on HAART whose CD4-cell count has increased to normal levels, will stopping HAART always cause the CD4-cells to rapidly drop again or will T-cell counts remain stable for a period of time?
- Can HAART be safely stopped once the CD4-cell count reaches 500? What about 350? And how low can the CD4-cells be safely allowed to drop during a treatment interruption before meds should be re-started?
- For patients doing well on standard HAART, could taking meds intermittently, every other week for example, keep the virus in check?
- Do patients who interrupt treatment experience an increased rate of drug resistance and/or virologic failure compared with patients on continuous therapy?
- Does reduced exposure to HIV medications for patients on non-continuous therapy result in fewer treatment-related cardiovascular, kidney, or liver problems?

- How do the various treatment strategies—standard continuous therapy, fixed-length treatment interruption (for example, week on week off), and CD4-cell count guided treatment interruption—compare with each other?

Paramount in the design of any clinical trial is the safety of its participants. In a randomized, controlled trial of non-continuous treatment of HIV, the primary safety concern is that the experi-

mental treatment strategy will prove to be inferior to standard therapy, posing the dangers of more rapid progression of HIV, increased risk for complications of HIV and AIDS, and drug resistance leading to increased difficulty controlling HIV when therapy is re-started. However, because longterm HAART, while life-saving, can be dangerous itself, investigation of potentially safer treatment strategies is warranted. Logically, any treatment strategy that involves reduced patient exposure to anti-HIV medications is

Because longterm HAART, while life-saving, can be dangerous itself, investigation of potentially safer treatment strategies is warranted.

likely to pose a significantly lower risk than standard therapy of treatment-related illnesses. Before randomized clinical trials with large numbers of individuals could be undertaken, a body of data from smaller studies and retrospective analyses was gathered that supported the idea that patients who have just started HAART and patients whose meds are working very well would not be subject to the safety concerns that pertain to the failed treatment strategy of interrupting therapy in order to restore drug efficacy in heavily treatment experienced patients.

In 2005, the International Study Group on CD4-monitored Treatment Interruptions published a study in the journal *AIDS* that prospectively evaluated 139 patients with undetectable viral loads and CD4 counts greater than 500 who agreed to interrupt treatment until their CD4 counts dropped to below 350. All patients had been on HAART for a minimum of 12 months and were initially started on treatment when their CD4 counts had dropped below 350 but not below 250. Patients were able to stay off therapy with minimal risk of progression to AIDS for a median time of 14 months. The study looked at only a small number of patients and larger trials are needed to confirm the results. Also, the study was not designed to identify strategic advantages to interrupting treatment. A particular strength of this study is that the key features of treatment history that define the cohort (viral load below 50 and CD4 above 500 after 12 or more months of treatment and CD4 nadir—lowest point ever—above 250) will be fairly common in large numbers of

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patients receiving standard therapy for HIV in “real world” settings outside of clinical trials. Most patients, for example, who are being treated according to current CDC guidelines would share these characteristics. The results would seem to suggest, therefore, that for a very large number of patients, interrupting treatment might at least be done safely. However, whether or not this kind of CD4-guided treatment interruption offers any strategic advantage in patients’ lifelong fight against HIV remained unclear.

One important feature of any non-continuous treatment strategy should be a decrease in the adverse effects of anti-HIV medications. Standard HAART, given continuously, can keep HIV under control and restore immune system health indefinitely. However, a growing number of illnesses are now known or suspected to occur more frequently in patients on HAART. Among these are cardiovascular disease, including heart attack and stroke, liver disease, kidney disease, blood cell disorders, and lipodystrophy and lipoatrophy. The latest news on treatment interruptions, from this year’s Conference on Retroviruses and Opportunistic Infections (CROI), presented a setback to side effect management.

The SMART trial was designed to prove that even if patients who interrupted treatment experienced slightly worse outcomes in terms of progression of HIV, that this would be offset by significant reductions in the rates of treatment associated adverse events. A total of 6,000 patients were to have been recruited and randomized to receive either continuous HAART or to stop meds at the beginning of the study. The patients in the treatment interruption arm would then resume treatment when the CD4 count fell below 250 and then interrupt therapy again when the CD4 count rose above 350 and so on. The study was halted in January, however, when preliminary review of the first two years of data confirmed that patients who interrupted treatment were not only more likely to experience HIV disease progression, but were also more likely to experience serious treatment-related adverse events, namely heart attack, stroke, coronary artery disease requiring surgery, and kidney or liver disease. So in this large randomized trial (5,472 patients were enrolled at the time the study was stopped), designed specifically to evaluate CD4-guided treatment interruptions as a treatment strategy, the data strongly suggest that not only is interrupting treatment in this way unsafe because HIV is less well controlled, but that it is also futile. In other words, treatment interruption did not reduce the risk of treatment-related adverse events as hoped. Instead, patients in the treatment interruption arm had a signifi-

cantly higher risk of heart, liver, and kidney problems and nearly double the likelihood of death (1.7% vs 0.9%) than those on continuous therapy.

Data from SMART make a very strong case against CD4-guided treatment interruptions, though the possibility remains that results might be better with higher CD4 cut-offs. Also, other treatment strategies are being studied. Several other clinical trials evaluating various non-continuous treatment strategies have presented data this year.

The Staccato study randomized 558 patients on HAART (most on a regimen that included a boosted protease inhibitor drug) to one of three arms: week on-week off (patients in this arm took their medicines every other week), CD4-guided therapy in which patients stopped and started meds when their CD4 count went above or below 350, and standard, continuous therapy.

The week on-week off arm was stopped early due to inferior performance. The patients in the CD4-guided treatment interruption arm had more HIV-related diseases such as thrush and lower CD4 counts. On the plus side, patients in this arm also experienced less diarrhea, less neuropathy, and had lower cholesterol. There was no difference in virologic control or the emergence of drug resistance in the two groups.

In the media, a big deal has been made about comparing findings from SMART and Staccato and the two sets of data have even been declared contradictory by some. Taken in context, however, the data from SMART which show that CD4-guided therapy is dangerous because of a greater risk of HIV progression combined with an increased risk of treatment-related medical problems, says something altogether different about interrupted treatment than the data from Staccato. While Staccato does show that treatment interruptions may not cause increased rates of drug resistance (especially if there’s a boosted protease inhibitor in the regimen), it failed to show that the patients in the treatment interruption arm had any strategic advantage in terms of safety or efficacy compared with the patients on standard therapy.

The Trivacan trial conducted in Ivory Coast by the French National Agency for AIDS Research was designed to compare a CD4-guided treatment interruption arm with a fixed-length treatment interruption arm. The 840 participants (77% women), who had been on HAART a minimum of six months with a minimum CD4 count of 350 and a maximum viral load of 300, were randomized to CD4-guided treatment using CD4 counts of 350 and 250 to

One important feature of any non-continuous treatment strategy should be a decrease in the adverse effects of anti-HIV medications.

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stop and re-start treatment, or to a fixed-length arm of two months on—four months off, or to standard, continuous HAART. Ninety-one percent of participants were on AZT [Retrovir] + 3TC [Epivir] + Sustiva. In October 2005, the CD4-guided treatment interruption arm was stopped by the data safety monitoring board because serious illness was significantly more frequent among patients in this arm. Recently presented 19 month follow-up data at CROI showed that the over-all incidence of serious illness was 2.6 times greater in the CD4-guided treatment interruption arm than in the continuous treatment arm. Those receiving CD4-guided treatment were 16 times more likely to be diagnosed with invasive bacterial infections and 85% of these infections were caused by antibiotic resistant bacteria. They were also three times more likely to have severe thrush and 1.5 times more likely to be diagnosed with TB (tuberculosis). No data was presented from the fixed length (two months on—four months off) treatment interruption arm which is continuing.

Another trial, however, with a similar fixed-length treatment interruption arm was terminated on March 15 after a review of preliminary data revealed that patients in the treatment interruption arm were significantly more likely to experience HIV related illnesses. DART (Development of Antiretroviral Therapy in Africa) randomized 799 patients with a minimum CD4 count of 300 after 12 to 18 months of HAART to either standard, continuous HAART or to a 12 week on-12 week off fixed length treatment interruption arm. The rate of HIV-related illness (the most common being esophageal Candidiasis) was over four times greater in the treatment interruption arm.

CONCLUSION

Treatment interruptions will always have a place when certain specific interests of an individual patient conflict with the need to treat that individual's HIV or when individual patients experience serious medication toxicities or intolerable side effects. However, if the goal is treating HIV in order to allow patients to live free from the many dangers of immune system impairment and to prevent the premature disability and death that inevitably occurs with untreated AIDS, then it must be said that no treatment interruption strategy has yet been demonstrated to be superior to continuous treatment with HAART. This is not to say that future clinical trials may not identify more successful treatment strategies. Also, with the development of new classes of drugs such as entry inhibitors and integrase inhibitors, the development of successful non-continuous treatment strategies may be greatly enhanced. A successful therapeutic vaccine or some novel approach to treating HIV that has yet to be conceived might very well set the stage for the ultimate treatment interruption. At present, un-interrupted therapy with HAART seems the best way to ensure that people who need treatment for HIV today will be around when that happens. ☒

Kaleo Staszko, M.D., specializes in providing comprehensive primary care for adults with HIV at NorthStar Medical Center on Chicago's North Side. He is also an investigator in several clinical trials of novel therapies for HIV and HIV-associated lipodystrophy. He may be reached via e-mail at kstaszko@nstarmedical.com.

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AIDS 25

Twenty-five years into the epidemic, we at Positively Aware thought it might be good to take a moment to reflect upon where we've been, as well as where we're headed. We asked a few special people to share their thoughts with us.

Personal reflections on the epidemic



AND SO WE PREPARED TO DIE

by Mary Fisher

I was young then, with a toddler and a preschooler at home. It was 1991. The virus was a final legacy of a marriage already ended. I knew television studios and White House travels—not AIDS clinics, or how to find the right doctor, or whether there were other women like me.

“The AIDS community” that had grown up was predominantly a community of gay men learning to convert condos into hospices. There had been a spurt of AZT-inspired hope in the ‘80s, but the hope fizzled; AZT helped but it didn’t heal. The infected were, we knew, fighting a losing battle, bailing a sinking ship, holding back

a viral tidal wave that would eventually take our lives. And so we prepared to die.

I started journals for my sons so, when I was gone and they could read, they would know I had loved them. I wrote and rewrote wills, worried deeply about guardianships, sought answers no one had. I took on dying as I had learned to take on everything: It was a project. I accepted it, organized it and planned for it. I decided to speak out, as publicly as possible, because I only had a few months or years.

The dying assumed that the “AIDS crisis” would mount, that voices demanding support and care would become louder and more persuasive, that ignorance and stigma would be replaced by reasoned, compassionate policies. If science were to defeat the virus, it would come too late for us. Our job was to speak truth to power, quickly, and prepare to die.

I am not so suicidal as to wish that ARTs (antiretroviral therapies, “the cocktail”) had never come along. But the truth is, I was no more prepared in 1996 for the prospect of a long life than I had been in 1991 for the promise of a short one.

What I’ve learned since ARTs have prolonged our lives is that cultural change is hard. Africa is still poor, Asia still in denial, America has gone to another war. Satellites and the Internet have taught us to think globally during this decade, but millions of dusty orphans wandering the Sub-Saharan move us to no more than a sigh. Headlines have moved on. Celebrities have taken up more glitzy causes. Communities of color, of women, of immigrants lack the resources (knowledge, power, money) the gay community had; these neighborhoods host dying very quietly. Those who cannot access ARTs will die; those of us who have access live in daily guilt for the very act of living.

Had we known we would live, we might have organized a better struggle for justice. We might have looked for gifted youth to become advocates, to collar Senators and protest Presidents. We might have filed lawsuits demanding justice and found journalists who would not let the story die behind the obituaries. But we didn’t know.

We worked on dying, never expecting that Iraq would take billions and the bird flu would grab the headlines, while orphans and AIDS slipped quietly out of our sight.

Mary Fisher was a television producer and an assistant to the President of the United States (George Bush) before she gained international recognition as a leading speaker, author and chronicler of the global AIDS epidemic.

by Steve Wakefield

Thanks for the gift of life and learning that has been the hallmark of my friendships with men and women living with HIV. At dinner after a TPAN lecture, I once told HIV-positive Dr. Leon McKusick that I was sorry to meet him because he was such a wonderful man. Before the end of the meal, this healer let me know “that loud screaming and yelling you hear inside is grief.” The late Dr. McKusick helped me to understand the wealth of staying in this moment and enjoying the richness of human contact.

So when Jeff [Berry] asked me to speak to “25 years into the epidemic,” my first reaction was gratitude. I wanted to run to the dance floor, shake my tambourine and kick up my heels to the “Unspeakable Joy” of being able to encounter so many who have so much to give.

Solutions to the HIV problem have always required the sound of “People with AIDS, Under Attack: What Do We Do? Act Up! Fight Back!” Continued vigilance may one day help us to see a cure or a vaccine or new weapons against this virus. The table scraps afforded by once-a-day treatments will not be enough to stave off this evolving plague. Collective human feistiness may keep our needs in front of those who can make a difference.

Scientists need resources. Scientific innovation that seeks a cure must be fund-

ed while new treatments are developed. We need each other. Current prevention messages and technologies are not delivered in ways that change behaviors despite telecommunications advances.

We need to put the public back in public health. One way would be to recognize humans as sexual beings and help them to incorporate what we know about the science of prevention. We have to make fewer partners and committed relationships sexy to the next generation. Support rational thinking. If gay marriage will help people reduce partners by providing supportive relationships, then only vote for those politicians who will fight for life. We have to help people know their status and make safer choices by protecting themselves and their partners.

We must continue to recognize life’s rich moments, brief acquaintances, and powerful friendships. We need to acknowledge them, revel in them, and celebrate them, basking in their sunshine to make this day more bearable and receiving their power in preparation for tomorrow.

Steve Wakefield, a former executive director of Test Positive Aware Network, is associate director for community education of the HIV Vaccine Trials Network.



AIDS HAS NOT GONE AWAY

by Howard Grossman, M.D.

Death was a constant companion in 1995. For those fighting the battle against HIV and AIDS things were very grim. The worst day for me was in October 1995. I had just finished sitting with one of my favorite patients as he took his last breaths. My beeper went off and another of my patients was coding upstairs. He didn’t make it. In the middle of that, the beeper went off again—it was one of my best friends being admitted to the ER with shortness of breath and sudden onset of dementia. He was dead before the night was out.

The outlook for the future was equally depressing. 1995 was the year I was involved in the test case on end-of-life choices that would later go to the Supreme Court. I remember talking with John, one of the patients I had been seeing since the mid-80s. John was a real survivor—CMV retinitis and colitis, Mycobacterium avium disease, cryptosporidiosis, multiple bouts of wasting—but he never lost his positive attitude or his willingness to try new therapies. Then he was diagnosed with lymphoma and it seemed to be the straw that broke the camel’s back. John was not the patient who joined me in the court case, but he and I talked about it a lot, about the decision to



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THE DAWN OF A NEW TREATMENT

A look at experimental HIV integrase inhibitors

by Daniel S. Berger, MD

INTRODUCTION

Combating HIV with antivirals has been restricted to attacking the virus through only one or two viral enzymes. The virus uses its enzymes, proteins that facilitate biochemical reactions, to synthesize its viral components, enabling it to replicate. As targets, our current antivirals are inhibitors of HIV's reverse transcriptase and protease enzymes. An additional treatment employs a drug that blocks HIV from fusing to the T-cell (Fuzeon), but its use has been limited because of the requirement of patient self-injection twice daily. However, a new and promising enzyme target is coming to a local clinic near you—*integrase inhibitors*.

It is estimated that up to 78% of patients who fail antiretroviral drugs have developed resistance to more than one therapeutic class of antiviral medicines and increased drug resistance is now increasingly observed, even in drug-naïve individuals (patients who've never been treated for HIV). Thus, development of a new class of antiretroviral drugs couldn't come at a better time.

WHY INTEGRASE?

HIV integrase has become the third enzyme protein being investigated as an anti-HIV therapy. However, unlike the reverse transcriptase and protease inhibitors, HIV uses the integrase enzyme to integrate itself, or incorporate its genes, into the human cell's gene (DNA), which is a unique and new viral site target.

Inhibiting integrase has been a difficult challenge for drug development; there is no complete structure of the enzyme found in the human body (*in vivo*). Pertaining to HIV, the integration stage occurs after the step where the reverse transcriptase enzyme has allowed the viral RNA to be transcribed into viral DNA (viral genes). HIV eventually forms a pre-integration complex which employs integrase to splice itself and insert its DNA into the host human cell.

In other words, integrase is absolutely necessary for the virus to trick the host cell as it becomes incorporated into it for replication; thus it is an attractive strategy and adds another target to our ammunition to protect healthy (human) cells from infection.

Discovering and developing an integrase inhibitor has proved difficult, and advancement towards human clinical trials has been slow. So finally seeing the first integrase inhibitor candidates in the clinic seems almost miraculous. Additionally, no homologue (similar structure) for integrase exists in human cells. Thus integrase inhibitors should be very specific to blocking the virus and

may limit side effects to human cells because of its specificity for the virus.

However, integrase inhibitors will need to be combined with antivirals as in all antiviral treatment cocktails consistent with HAART (highly active antiretroviral therapy). Integrase is a strategy that blocks infection and integration in cells, but for the cells that are already infected, the other antiviral components of HAART add greater effect towards halting HIV replication.

Integrase inhibitors are active against virus that is resistant to nukes, non-nukes, and protease inhibitors. For treatment-experienced patients needing new active drugs due to resistance, this class of antivirals will be very useful, assisting in the control of HIV replication. However, just as resistance is observed to existing antivirals, there is no reason to expect anything less with integrase inhibitors. But it is hoped that integrase resistant mutations may contribute to decreased replicative capacity of the virus, or a poorly viable (weakened) HIV.

DISINTEGRATING HIV INTEGRATION: THE CLINICAL STUDIES

Currently there are two integrase inhibitors in clinical development. Both Merck (MK-0518) and Gilead Sciences (GS 9137) presented results of their candidate oral integrase inhibitors in a late breaker session at the 13th Retrovirus Conference in Denver in February. Both compounds showed tremendous 2 log reduction in viral load and little or no toxicities. For the first time, there are two drugs in a completely new class that have shown preliminary data of a dramatic and profound effect on HIV.

MK-0518

Interim Phase 2 results were presented of Merck's compound, MK-0518, which was studied in 167 patients with advanced HIV. The patients were individuals failing antiretroviral therapy, having viruses resistant to at least one drug in each of the three available classes of HIV treatment. In combination with optimized background therapy (OBT)—chosen by the physician based on resistance testing—the experimental integrase inhibitor at all three doses studied (200 mg, 400 mg, and 600 mg orally, twice daily) combined with background treatment had greater antiretroviral activity than placebo.

To summarize the results, at week 16 of study, the percentage of patients achieving viral loads (HIV RNA) below 400 copies/mL ranged from 64–84% for MK-0518 plus OBT versus 22% (6 of 27 patients) for placebo plus OBT. And the percentage of patients

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achieving viral loads less than 50 copies/mL ranged from 56–72% for MK-0518 plus OBT across all doses studied (200 mg, 400 mg, and 600 mg, twice daily).

MK-0518 was generally well tolerated, and the most common side effects reported for at least five percent of patients in each dose arm was diarrhea, nausea, fatigue, headache, and itching.

GS 9137

Gilead Sciences' integrase inhibitor is unique in that it is metabolized by the liver enzyme system (it is a CYP3A4 inducer) and thus can be boosted by ritonavir, similar to most protease inhibitors. As such, GS 9137 can be dosed once daily, as opposed to MK-0518.

An early Phase I study was presented as a late-breaker presentation in Denver. Forty patients were randomized and received one of five doses of GS 9137 or placebo with food for 10 days. The study evaluated GS 9137 at 200 mg twice daily (BID), 400 mg BID, 800 mg BID, 800 mg once daily (QD), and 50 mg boosted with 100 mg ritonavir QD. At study entry, all patients were not receiving antivirals and had viral loads between 10,000 and 300,000 copies/mL and CD4 T-cells equal to or greater than 200 cells/ μ L. The patient population included both individuals naïve to treatment as well as treatment-experienced patients.

During this Phase 1 study, after 10 days of treatment, viral loads decreased by 2 logs in both the ritonavir-boosted once daily arm and the unboosted 400 mg BID dose (similar to Merck's findings). No patients discontinued or dropped out of the study.

As an author and investigator of this study presented in Denver, I can state very confidently that the drug was very well tolerated. In fact, most of our patients at NorthStar Healthcare thought they were receiving placebo, when in fact they were not. Most side effects were mild and included diarrhea, headache and nausea.

At this time NorthStar Healthcare has already started Phase 2 study of three different doses of boosted GS 9137, once daily, for treatment-experienced patients. For any inquiries, contact Curtis Hains, PA-C of NorthStar, at (773) 296-2400. ☞

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end one's life when disease became terminal. He was thinking about it.

The impact highly active antiretroviral therapy—HAART—has had on People Living with AIDS (PWAs) was often described as the “Lazarus effect.” People like my patient John, who thought his life was coming to an end, were suddenly getting better. With the advent of HAART John's chemotherapy had a chance to actually work. Within a few months he was working as an artist again, and in the fall of 1997 decided to take up scuba diving!

Everyone felt recharged. The effect for providers was so profound that it is hard even now to judge. In my practice alone in 1995 there were 37 deaths. In 1996 it dropped to 10, in 1997 to 4 and in 1998 to zero.

We still face so many challenges in HIV. As the epidemic spreads among the poorest in the U.S., there are still far too many people who do not know their HIV status and too few people who are receiving high-quality HIV care. The Centers for Disease Control (CDC) estimates that 25 percent of the over 1 million people most likely living with HIV in the U.S. are unaware of their status. That would mean that 216,000 Americans are eligible for HIV care but are not receiving it. Too many individuals in 2006 are being diagnosed with AIDS in the Emergency Room when they come in with an opportunistic infection and late-stage disease. This is particularly true in communities of color, and not just in the U.S.—the same disproportionate impact of HIV and disenfranchisement from quality care is being seen in populations of African descent in Canada and in Britain as in the U.S.

Too many people are still becoming infected with HIV. For years now, the number of new infections is hypothesized to be near 40,000 annually. People working in disease prevention have done a remarkable job in decreasing transmission from the wildfire spread of the 1980s (see the marked decline in new infections in San Francisco), but we seem to have hit a wall. Part of this is due to the fact that the U.S. government has, for years now, failed to take a science-based, non-judgmental and completely clear approach to sexual education and drug education. The amazingly dedicated public health professionals in the federal government have had their hands tied by grandstanding congress members, politicking presidents and religious bigots. Other countries, which have created mass campaigns of unflinchingly clear and graphic education with simple messages, have seen sharp decreases in new infections while the U.S. has not.

We've still lost a lot of patients since 1995. My patient John? He died in 2004. I still mourn their loss, but I cherish the extra time I had to know them. Their deaths must serve as another reminder that, for all our success, AIDS has not gone away. ☞

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