

# HCV/HIV Today

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## In Sickness and in Health

By Heidi M. Nass with Greg Milward

### A conversation about doctor-patient relationships

If you listen to enough people talk about what happened at their latest doctor's appointment, you start to get the sense that there's a bunch of patients and physicians out there who could really use some couples counseling. Even the language sounds familiar: "He doesn't listen to me," and "She doesn't do what I say." There's all the usuals—the healthy relationship, the couple who doesn't communicate, the unappreciated partner, the bully.

The doctor-patient relationship is an important one if we want to stay healthy and especially when we're sick. The beauty of this relationship is that we don't need to stay together for the kids, so we might as well find one that works.

Recently, I had the pleasure of sitting down with Greg Milward to talk about our failed relationships and those that have worked, and what it is that makes the difference. What follows is part of our conversation.

Heidi: Greg, how do you go about asking questions and raising concerns with your medical provider?

Greg: Going into my appointment with my doctor, I recognize that I have a limited amount of time to spend with him and I do some things to maximize the time. First, I prepare a memo to the doctor that does three things. It updates him on issues or problems we discussed at our last appointment. Second, I list issues that I need to discuss with him at this appointment. These can be medication issues such as side effects or other problems that I am having. Finally, I list any other general questions I have for him. I find that having put things in writing helps to make sure that all of the issues I want to cover are dealt with. My doctor also likes this because he then has something that he can put in my file that lists the issues that I brought to him to discuss.

In busy clinics, the best ally you can usually have is the other staff in the clinic. Get to know the nurses, physician's assistants and front desk personnel. Having a good working relationship with the clinic staff is almost as important as the relationship you have with your doctor.

Heidi: I think that writing down your questions and concerns also helps make them real, so to speak. Sometimes, as a means of coping, we minimize or deny what we're going through. Consequently, it's harder to bring those things

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# Surgery a Bigger Risk for HIV-Infected Patients

By Robert Preidt

## **Odds for post-op pneumonia are much higher in this group, study finds.**

WEDNESDAY, Dec. 27 (HealthDay News) – Surgical patients with HIV, the virus that causes AIDS, are more likely to develop pneumonia after their operation and to die within one year compared to uninfected patients, U.S. researchers report.

The study also found that HIV patients with a preoperative viral load (number of copies of virus in the blood) greater than 30,000 per milliliter appeared to be most likely to suffer surgical complications.

In the study, a team from Kaiser Permanente Medical Care Program-Northern California, in Oakland, analyzed surgical outcomes for 332 HIV patients who had a number of different kinds of operations (including heart, abdominal and orthopedic) between 1997 and 2002. They compared those outcomes to outcomes for 332 surgical patients without HIV.

More HIV patients developed pneumonia after surgery (2.4 percent vs. 0.3 percent), and more HIV patients died within 12 months after their surgery (3 percent vs. 0.6 percent).

The findings are published in the December issue of the journal *Archives of Surgery*.

Highly active antiretroviral therapy (HAART) has made HIV infection a chronic, manageable condition, the study authors noted.

“Consequently, many HIV-infected patients elect to undergo surgical procedures to correct physical ailments that would not have been treated previously, and undergo operative interventions in lieu of medical therapies for certain conditions,” they wrote.

“Patients with HIV are living longer and regaining a substantial amount of immune function,” the study authors concluded. “Many HIV-infected patients will require surgical attention because of a variety of disorders. In many cases, HIV serostatus (whether a person is infected with HIV) should not be a criterion when determining the need for surgery if patients have adequate viral control.”

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# AASLD: Investigational Antiviral Therapies for Hepatitis C

Liz Highleyman

Among the topics that generated the most interest at this year's annual meeting of the American Association for the Study of Liver Diseases (AASLD), held October 27-31 in Boston, was the prospect of new therapies for chronic hepatitis C virus (HCV) infection.

## STAT-C

Several investigational agents making their way through the development pipeline not only have the potential to incrementally increase the likelihood of sustained virological response, but also represent a paradigm shift in how hepatitis C is treated.

Current interferon-based therapy works by stimulating the body's natural immune response to the virus. In contrast, various novel agents – now collectively known as *specifically targeted antiviral therapy for HCV*, or “STAT-C” – directly attack HCV. Much like some of the drugs used to treat HIV, several experimental compounds inhibit HCV protease or polymerase, two enzymes the virus needs in order to reproduce.

Speaking at a satellite symposium on STAT-C sponsored by Vertex Pharmaceuticals, hepatology expert Ira Jacobson predicted that this new approach “will revolutionize the way we treat chronic HCV infection,” offering the promise of “significantly higher rates of efficacy and significantly lower durations of treatment.” However, as with HIV therapy, the success of treatment with antiviral agents is limited by the development of drug resistance.

## Telaprevir

One of the investigational agents generating the most excitement is telaprevir (VX-950), an oral HCV protease inhibitor being developed by Vertex. In the October 2006 issue of *Gastroenterology*, Henk Reesink and colleagues reported that in a Phase Ib study, telaprevir potently suppressed HCV replication in genotype 1 patients over 14 days when used alone (maximum 4.4 log decline in the 750 mg thrice-daily arm) or in combination with pegylated interferon (5.5 log decline). Researchers presented follow-up data at AASLD (abstract 1142) showing that all 15 participants who initially received telaprevir, with or without pegylated interferon, and continued on standard therapy with pegylated interferon plus ribavirin had undetectable HCV after 24 weeks of follow-up. Similarly, in a separate presentation, Maribel Rodriguez-Torres and colleagues (abstract 927) reported that eight of 12 patients enrolled in a 28-day study of triple therapy with

telaprevir, pegylated interferon, and ribavirin still had undetectable HCV RNA after stopping telaprevir and continuing standard therapy for 24 weeks.

Tara Keiffer of Vertex (abstract 92) presented data from an analysis of resistance mutations in the 14-day study. Using a highly sensitive assay, researchers analyzed the presence of HCV variants with mutations previously identified as conferring low-level (V36M/A, T54A, R155K/T) or high-level (A156V/T and 36/155) resistance to telaprevir *in vitro*. Among the eight patients assigned to receive telaprevir monotherapy, four experienced virological breakthrough or a plateau response and showed evidence of predominant HCV variants with V36M/A and R155K/T mutations by Day 14. The other four experienced continuous HCV RNA decline, even though two developed viral variants with the A156V/T mutation. The researchers concluded that telaprevir produced a “sharp reduction in wild-type virus,” allowing resistant variants to emerge. Patients who experienced virological breakthrough and switched to pegylated interferon plus ribavirin achieved undetectable viral load within 24 weeks, however, indicating that telaprevir-resistant HCV remained sensitive to standard therapy. None of the eight patients who received telaprevir in combination with pegylated interferon experienced virological breakthrough during the 14-day study, including two with resistant virus.

Telaprevir has demonstrated a good safety profile so far, with no serious drug-related adverse events in the short term. It is currently in Phase IIb trials (PROVE 1 in the U.S. and PROVE 2 in Europe).

## Valopicitabine

Douglas Dieterich (abstract 93) presented the latest data on valopicitabine (NM283), an oral HCV NS5B polymerase inhibitor being developed by Idenix Pharmaceuticals. As previously reported, valopicitabine in combination with pegylated interferon induced rapid virological suppression at four weeks in a Phase Ib trial that included 173 genotype 1 treatment-naive participants receiving oral doses ranging from 200 to 800 mg/day; however, the drug caused significant gastrointestinal side effects at higher doses. As a result the clinical trial protocol was revised.

While rapid virological response rates were greater among patients receiving higher valopicitabine doses,

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# Reality Check!

Alan Franciscus, Editor-in-Chief

One of the most frequent questions we receive is about making a decision regarding starting HCV drug treatment. The new drugs in clinical development have caused many to question whether it is better to be treated now or to wait until the newer treatments are available. This article will touch on the process of HCV drug development, some of the questions that need to be answered about the new therapies, as well as questions to ponder about starting treatment now versus waiting for the new therapies to be approved. It is important to remember that the decision to treat should always be made in consultation with a medical provider.

## New Medications

First let's take a practical look at the new medications in development. There has been a lot of news about investigational HCV drugs in clinical development within the last year.

We are entering an exciting period of HCV drug discovery that not only offers hope for medications with improved treatment outcomes, but also newer drugs that will have a potential for less side effects than the current HCV medications. However, new antiviral drugs that are farthest along in clinical development are only in phase II studies.

Phase II clinical trials are conducted to obtain preliminary data on the effectiveness of the drug and collect information about the side effects and the risks associated with taking the drug. The number of participants in a phase II study is relatively small (a few hundred to over 500 hundred). At the completion of a phase II study the data is collected and analyzed and a much larger (up to several thousand patients) phase III study is initiated. A larger population of HCV patients treated with a new drug will give us a better picture of the effectiveness of the drug, side effect profile and other important information. Once the phase III study is completed and the data is collected, the pharmaceutical company applies to the Food and Drug Administration (FDA) for marketing approval to treat the general HCV population. The FDA will review the application and data from the clinical trials and will either approve the drug for marketing, request additional studies or more information, or deny approval. It is really difficult to gauge how long it will be before new drugs are available to the general population, but it is estimated that approval of the first new antiviral drug to treat hepatitis C is 3 to 5 years from now. One certainty is that the

new drug(s) approved to treat HCV will be used in combination with pegylated interferon or pegylated interferon plus ribavirin – at least for many years to come.

## The Media Hype

The media has done a great job of making us believe that new and better drugs are going to be available soon. Almost every day we hear of a new drug that is sure to 'cure' hepatitis C and we are led to believe that the 'cure' is right around the corner. Another reason why we all want new medications is the hope that we will discover new medications that will effectively treat everyone with hepatitis C. If you have already been treated and did not respond, the new drugs offer much needed hope for the future. Due in part to the media hype and our own hopes for more effective treatment, many people believe that the newer drugs will be available in the very near future. Unfortunately, treating a disease such as HCV is a complex issue and while it is a certainty that new and improved drugs will be developed, the development process will be slower than many of us want or have been led to believe.

## Unresolved Questions

There are many issues that need to be resolved that will be answered during and after the development process. The potential of drug resistance will be at the forefront of research since we are entering an era of medications to treat hepatitis C that directly attack the virus and interfere with the HCV viral replication process. Adherence to the current *indirect* HCV medications (pegylated interferon plus ribavirin) is important because 100% adherence increases the chances for a successful sustained virological response by increasing the drug concentrations in the blood. Adherence to the new *direct* antivirals will also be critical for making sure there is the highest possible drug concentration in the blood; but adherence will become even more critical for preventing drug resistance that could render the drug ineffective. The new drugs will also have to be taken three or four times a day (at the same time every day). Most people think this is a simple matter, but it has been shown that adherence is one of the most difficult issues facing successful management and treatment of any disease.

There are many additional questions that need to be resolved including:

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What is the most effective dose and how often will it have to be taken (once every 6 hours, 8 hours, etc.)?

What is the optimal duration of treatment?

Will a sustained virological response translate into a durable or long-lasting response?

If someone develops drug resistance to a new medication, will it mean that they will not be able to be treated with the same drug or class of drugs?

Will treatment for some people consist of the long-term use of a certain drug if viral eradication can not be achieved?

What are the drug interactions between the new medications and any medications people are currently taking for other conditions?

Will the drugs create any short- or long-term health consequences?

Hopefully, these questions and more will be answered as the new drugs advance through clinical trials.

### Should I be Treated?

Most experts would agree that a person with moderate to severe liver fibrosis should be treated now rather than waiting until the newer medications are approved for treatment. Of course there are other considerations for seeking treatment, including quality of life issues (such as severe fatigue), personal issues (starting a family, career goals), insurance issues (comprehensive insurance coverage, part time disability insurance), and other personal issues.

### Should I Wait?

Since hepatitis C is a slowly progressive disease (for most people), most experts would recommend that someone with mild liver damage could safely wait until the newer medications are approved. Unfortunately, there is no "one size fits all" for hepatitis C. For instance, minimal liver damage is a predictor of successful treatment outcome. This means that a person with minimal liver damage who has that opportunity to wait for new medications should weigh the predictive factor against the possibility of waiting for the new drugs to be approved. Another issue for consideration is genotype – since the chances of achieving an SVR in people with genotype 2 and 3 are so high, many experts recommend that these individuals should be treated now.

Living with hepatitis C forces us to make many health-related decisions every day. In order to make the best possible decision it is important to educate ourselves with the facts as much as possible and carefully weigh the pros and cons before we decide on a certain course of action. This course of action should always include a discussion with a medical provider, but it is important to remember that the final decision is yours.

### Predictors of Treatment Response:

- Genotype 2 or 3
- HCV RNA or Viral Load under 800,000 IU/mL
- Age: Under 40 years old
- Gender: Females respond better than males
- Minimal liver disease
- Little or no steatosis
- Healthy weight or non-obese
- Asian or Caucasian race

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## HCV/HIV Bytes

### First Three-Drug Combination Pill Available to Treat HIV

(*Hemaware*, September/October 2006)

A novel once-a-day pill that combines three popular drugs for treating human immunodeficiency virus type 1 (HIV-1) is now available to adult patients in the US.

The benefit of the combination tablet, known as Atripla, is the ability to replace two or more pills that many HIV-positive patients now take as a first-line defense for keeping the human immunodeficiency virus at bay. Taken alone or in combination with other retroviral medications, it could help patients better adhere to their medication schedules and, in turn, help prevent drug-resistant strains of the deadly virus from developing.

Atripla also may provide some cost savings by eliminating the multiple copayments that come with purchasing the drugs separately. However, the wholesale price of the pill will be about \$1,150 for a 30-day supply, the same as for the drugs when sold separately.

"It's exciting news," says Veronica Miller, PhD, director of the Forum for Collaborative HIV Research, an independent public-private partnership based in Washington, DC, aiming to transfer emerging HIV research into care.

Gone are the days when HIV-infected patients were required to take many different pills each day, carefully choreographed according to when they ate and slept, she says. "Treatment for HIV patients had become much more simplified over the past several years, and this is one more very positive step in that direction."

The anticipated outcome is that combining these drugs into a once-daily pill will improve patient compliance and could ease supply and distribution of the pill to other countries that need these important medications. More than one million people in the US are living with HIV and AIDS, and about 40,000 new cases are reported annually. Another 40 million people around the world are infected.

What's unique about this "cocktail" treatment is that it combines medications made by different manufacturers—a first of its kind collaboration when it comes to medications to treat HIV.

Successfully combining the medications in a single tablet met with certain difficulties. Both Viread (tenofovir disoproxil fumarate) and Emtriva (emtricitabine) are

made by Gilead Sciences, Inc., and are currently sold as a combination tablet called Truvada. The third component, Sustiva (efavirenz) is made by Bristol-Myers Squibb Co. In December 2004, the companies develop and commercialize the single-tablet regimen.

The Atripla label includes a boxed warning that the drug can cause a buildup of lactic acid in the blood. The discontinuation of the drug in patients with hepatitis B (although it is not approved for this use) can cause serious flare-ups of the hepatitis B infection. Other potential serious side effects include liver toxicity, kidney impairment, and severe depression. The most common side effects experienced in the combination trial were headache, dizziness, abdominal pain, nausea, vomiting, and rash.

The July 12, 2006 approval of Atripla by the US Food and Drug Administration was completed under an expedited review process for HIV/AIDS drugs in place since May 2004. "Today's approval is a significant example of drug developers and FDA clearing the way to quickly deliver quality, life-saving HIV/AIDS drugs to people who desperately needs them in the United States and Abroad," says Andrew C. von Eschenbach, MD, FDA's Acting Commissioner of Food and Drugs, in a written statement.

### New Treatments Discussed at EASL Meeting

VIENNA, Austria – New treatments for hepatitis B and C were among the major topics discussed here at the annual meeting of the European Association for the Study of the Liver (EASL) during the last week of April.

Results from clinical trials of several experimental treatments for HCV were presented at the conference, including Vertex Pharmaceuticals' protease inhibitor VX-950. During a 14-day study, four of eight patients taking VX-950 alone had their viral levels plateau or rebound after an initial drop, and there was evidence of drug-resistant mutations of the virus emerging. All eight patients taking VX-950 combined with pegylated interferon had continuous viral decline and undetectable HCV RNA after 12 weeks of follow-on standard therapy. Another HCV protease inhibitor, Schering's SCH 503034, was found to be well

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tolerated when given with pegylated interferon. Four of 10 patients with HCV genotype 1 who were nonresponders to previous standard treatment became HCV RNA negative after 14 days of treatment.

Data presented from the ongoing phase II trial of Idenix's polymerase inhibitor valopicitabine (NM283) showed that 70 percent of treatment-naïve genotype 1 patients receiving 200 mg of NM283 plus pegylated interferon had undetectable HCV RNA after 12 weeks. Patients receiving higher doses of NM283 had their doses reduced due to gastrointestinal side effects. Two other HCV polymerase inhibitors, Roche's R1626 and ViroPharma's HCV-796, were reported to show antiviral activity and were generally well tolerated in phase I trials.

Other research discussed at the conference included the results of ACCELERATE, the largest study ever conducted in patients with HCV genotype 2 and 3, which demonstrated that 16 weeks of pegylated interferon/ribavirin treatment is less effective than 24 weeks of treatment. Valeant Pharmaceuticals reported that ViroPharma's prodrug of ribavirin designed to have a lower risk of anemia, failed to meet the efficacy endpoint in the phase III VISESR1 trial. Researchers say that weight-based dosing of ViroPharma's prodrug could improve the efficacy of the drug in future studies. Coley Pharmaceutical Group released preliminary data from a study indicating that 12 of 14 patients receiving a combination of Actilon (CPG 10101) plus pegylated interferon and ribavirin achieved an early viral response.

Results from several studies involving hepatitis B also were presented at the EASL meeting. One study demonstrated that combination therapy with lamivudine (Epivir) plus adefovir dipivoxil (Hepsera) can prevent both HBV DNA viral rebound and adefovir resistance in cirrhotic patients. Other research found that entecavir (Baraclude) was more effective than lamivudine in improving fibrosis in patients with chronic HBV. Also released at the conference were data from an ongoing study showing that, at 24 weeks, HBeAg-positive patients given telbivudine had significantly greater and more rapid hepatitis B viral suppression than those given adefovir.

Korean researchers presented the results of a 48-week phase III trial of the investigational nucleoside analog Clevudine, in which 68 percent of treatment-naïve patients had undetectable HBV DNA levels. Chinese researchers presented data from a phase II dose-escalating trial of ANA380 (LB80380), a nucleotide analog. The drug was found to be effective against HBV and well tolerated, and the researchers recommended a 90 mg daily oral dose for future studies.

*Hepatitis Magazine, July-September 2006*

## The Future of HIV Prevention

*(Acria Update, Winter 2005-06)*

An increasing number of organizations have become involved in vaccine research and development, and the number of vaccines in clinical testing had grown substantially over the past five years. This growth, however, has occurred in the context of significant challenges.

Early vaccine candidates sought to elicit a humoral immune response, aiming to produce neutralizing antibodies, leading to viral clearance after exposure. For a variety of reasons, induction of this type of immunity has proven difficult. VaxGen's candidate vaccine AIDSVAX, which employs recombinant gp120 proteins to induce an antibody-mediated immune response, was shown to be ineffective in Phase 3 trials conducted in the United States and Thailand.

Recent research has focused increasingly on cell-mediated immunity. There are currently more than 30 products in early stage trials taking place in 19 countries, the majority of which aim to elicit a cellular immune response. The products in development employ a range of strategies, including vector-based vaccines, lipopeptide vaccines, DNA vaccines, and recombinant protein vaccines. A large-scale trial of Aventis Pasteur's candidate vaccine ALVAC vCP1521, which uses a canary-pox vector, was recently begun in Thailand and should produce results within five years. AIDSVAX is being used as a booster in this trial.

Despite the promising growth of vaccines in the pipeline, significant challenges persist, and cell-mediated immunity—on which the vast majority of current candidates rely—is unlikely to confer complete protection, but rather will lower transmission risk or slow disease progression by controlling viral replication.

To speed the development of an effective vaccine, the pipeline may need to be evaluated and diversified. The differences in HIV types, or clades, around the world adds complexity, since a vaccine that is effective in producing an immune response to one clade may not have the same efficacy against another clade. These factors, and others, pose substantial challenges to development of an effective HIV vaccine.

# Don't Forget Your Head

Before You Get Behind the Wheel, Make Sure You Are In Full Control

By Tonia Poteat, PA-C

Viral load and CD4 counts are such useful indicators of viral activity and immune function that there is always the danger that the measure of “how things are going begins and ends with those two tests. While these and other lab values are undeniably important, we can't forget that the motivation for taking care of ourselves resides in our heads, not our bloodstreams. Below are just a few of the psychological issues that can affect the well-being of people with HIV.

## Depression: the slippery slope

Marilyn has found it harder and harder to wake up in the morning and has been going to bed earlier and earlier each night. She used to look forward to walking the dog in the mornings and attending her weekly women's group. Lately, she feels sluggish all day and no longer wants to do anything. She had to change her HIV medications a few weeks ago and attributes her feelings to side effects from the new medications. In fact, she's beginning to wonder if it's even worth it to keep taking her medications.

Marilyn's story is common. While it is true that some of what she feels could be due to her new medications, it's more likely that Marilyn is suffering from the most common mental health problem among people with HIV—depression. Symptoms of depression can overlap with medication side effects, so depression can be missed both by the person with symptoms and the health care provider.

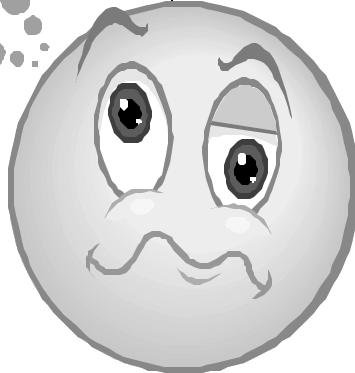
Fortunately, depression is a very treatable condition. It's quite likely that Marilyn can get back to her old self, especially if she addresses her symptoms early, reaches out for care and gets an experienced provider who listens to her. The danger is that, because of the way depression affects thinking, Marilyn will begin to accept her new reality as “just the way it is” and won't think there's anything that can help. She will also have to fight the sense of shame or failure that many people feel when they are depressed, which prevents them from getting the help they need to get better.

Treating depression is very important for both your mental and physical health. Untreated depression has

been associated with faster progression of HIV disease, poor adherence to medications, high-risk sexual behavior, drug use, and even death.

If you experience five or more of these symptoms for at least two weeks, you should talk with your health care provider about depression.

1. Sadness, hopelessness
2. Decreased interest or pleasure in activities
3. Sleeping too much or sleeping too little
4. Appetite changes with weight gain or loss
5. Loss of energy
6. Feelings of worthlessness or guilt
7. Decreased ability to concentrate
8. Psychomotor agitation (pacing, wringing hands, hair twirling) or psychomotor retardation (slowing down of thoughts, movement, or speech)
9. Recurrent thoughts of death or suicide



There are many effective treatments for depression, including several different classes of antidepressant medications and various types of counseling and psychotherapy. Most mental health providers advise treatment with a combination of psychotherapy and medications for at least six months.

## Anxiety: the monkey of the mind

Anxiety frequently accompanies depression. However, anxiety can occur alone. Anxiety can cause psychological symptoms like excessive worry or fear, as well as physiological symptoms such as breathing problems, chest palpitations, muscle tension, nausea, headache, and dizziness.

Getting an AIDS diagnosis, changing antiretroviral medications, or other serious changes in health status are common triggers for anxiety. Just like depression, treatment for anxiety usually includes a combination of medications and psychological interventions, such as psychotherapy and/or cognitive-behavioral therapy.

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## Addiction: the line between using and abusing

While some people use alcohol or recreational drugs to help them relax or to have fun, it can be difficult to tell when “use” has become “abuse” or “addiction.” The DSM (a reference book of psychiatric definitions called the Diagnostic and Statistical Manual of Mental Disorders) defines addiction as a “maladaptive pattern of substance use leading to significant distress or impairment.”

So, how do you know when use isn't really helping you and may be hurting you? A list of four questions, commonly called CAGE (Cut, Annoyed, Guilty, Eye-opener) questions, can be very helpful in determining if you have an alcohol or drug problem. If you answer “yes” to any of these questions, you may have a problem with alcohol or drugs.

1. Have you ever felt like you should cut down on your drinking or drug use?
2. Have you been annoyed by people criticizing your drinking or drug use?
3. Have you felt bad or guilty about your drinking or drug use?
4. Have you ever had a drink or used drugs early in the morning to steady your nerves or get rid of a hangover (eye-opener)?

While the short-term psychological affects of drug use may be obvious, long-term mental and physical consequences can be more subtle. For example, long-term use of a drug as simple as marijuana can lead to impaired brain function. Methamphetamines (crystal meth, crank, etc.) have been shown to have effects on the brain that last for months after the drug was last used. Physical problems like strokes and heart attacks are frequently seen after use of stimulants like cocaine. The short and long-term effects of each drug are different, so it's important to know as much as you can about any substance you put in your body.

If you use drugs and do not want to quit, harm reduction programs may be able to help you stay as healthy as possible by providing information and equipment for safer use. If you use drugs and want to quit, programs like Alcoholics Anonymous and therapeutic communities use an abstinence-based approach to dealing with drug use problems, and can provide you with a supportive environment to help you quit.

Depression, anxiety, and addiction are just a few of the mental health issues that people with HIV may confront. Remember that it's important to pay as much attention to your mental health as you do to your physical health and address any concerns early. Living well with HIV

means taking care of your whole self—body and mind.

*Tonia Poteat, PA-C, has been providing medical care to people with HIV since 1995 and is a clinician at the women's clinic of the Infectious Disease Program at Grady Hospital in Atlanta. She is also a clinical instructor for the Southeast AIDS Training and Education Center and a consultant with the Global AIDS Program of the U.S. Centers for Disease Control and Prevention (CDC). Tonia joined the fight against AIDS in 1989, when she began volunteering with AIDS Project New Haven, Connecticut.*

### Resources:

**Psychology Information Online** is a resource for information about a variety of psychological issues and conditions, including depression.

Visit [www.psychologyinfo.com/depression](http://www.psychologyinfo.com/depression).

**Anxiety Disorders Association of America** provides an overview of anxiety disorders, as well as information about treatment and statistics. Visit [www.adaa.org](http://www.adaa.org).

**The Harm Reduction Coalition (HRC)** is committed to reducing drug-related harm among individuals and communities by initiating and promoting local, regional, and national harm reduction education, interventions, and community organizing.

Visit [www.harmreduction.org](http://www.harmreduction.org).

**12steps.org** is a web site that has no official affiliation with Alcoholics Anonymous or any other 12-step group. It is a source for information and tools concerning 12-step programs. 12-step programs have been widely used in recovery programs for addictive or dysfunctional behaviors. Visit [www.12steps.org](http://www.12steps.org).

Positively Aware Fall 2006 Special Issue

# Lessons I Learned from Dr. Cruise Control

How one man's search for a doctor taught him to be an active participant in his own health care

By Greg Milward

It's impossible to write about choosing a health care provider without reflecting on my first experience as an HIV patient. It was many years ago, fresh from the hospital after a three-week stay with *Pneumocystis pneumonia* (PCP), when I found myself in the feng shui-inspired office of an infectious disease specialist in Washington, D.C. The calm, soothing environment provided no help for what came next.

Three minutes into the appointment he handed me a stack of prescriptions for HIV medications and told me to go to the pharmacy and get them filled. I asked a few questions about what was being prescribed when he abruptly told me to "just take the pills and you'll be on cruise control."

"What are you talking about?" I asked. His response was a simple, "Like I said, just take your pills and you'll be on cruise control for the rest of your life." Once again, I started to ask some questions about his prescribed course of treatment. His irritation with me became obvious and he got up to leave the exam room.

Newly diagnosed, out of the hospital for just three days, and my first appointment with my new doctor lasted less than five minutes. Actions really do speak louder than words and it was apparent from his actions that Dr. Cruise Control was dismissing my concerns and questions as irrelevant. After all, it seemed, I was just the patient; he was the doctor.

After telling me to make a follow-up appointment in three months (three months!), he left me sitting there in the exam room. I was dumbfounded. I sat there and started to cry.

Needless to say, that was the last time I saw that doctor. Cruise control is meant for automobiles—not for someone recently diagnosed with HIV or who's still getting used to the words "you have AIDS."

I look back at that experience and realize that even though my relationship with Dr. Cruise Control was short-lived, he provided a valuable lesson. In that brief encounter, it became clear that I needed to become a wise consumer of health care services; I needed to set in place a process that would help me to make a well

thought-out decision as to who I would trust to be an integral part of my health care team.

After my encounter with Dr. Cruise Control I set out to find a doctor that would work with me as a partner in my care. The most important factor in my search was coming to the realization that any doctor that I would work with from this point forward also had to be a healer.

What do I mean by "healer"? It's simple: I will not entrust my care to someone who does not care for me in a holistic manner—he or she has to treat me as a whole person, not simply as a virus who happens to be living within a human being.

A healer is as concerned about how I am feeling as he or she is with the numbers on my quarterly blood work. A healer works with me as an equal partner in my care. A healer talks with me rather than talking at me. Healers encourage me to be an active part of my care and are not threatened by the fact that I may want to explore complementary therapies as a part of my health care. They are willing to admit that they do not have all of the answers and don't expect me to put them on a pedestal and accept every word as gospel.

I realized that I needed to be able to ask questions and bring thoughts, suggestions, and questions to my appointments. I needed to be able to have any concerns or questions addressed without being made to feel like a fool. I also decided after my experience with Dr. Cruise Control that any doctor I worked with had to have specialized knowledge and experience in the treatment of HIV/AIDS. While there are many talented doctors, I wanted a provider who was at the forefront of treating HIV. I decided that I wouldn't consider any provider who did not have a significant HIV practice.

Once I tentatively decided who was going to replace Dr. Cruise Control, I had a conversation with the prospective new doctor about what his expectations were of me as a patient. Interestingly, his expectations of me were very similar to the expectations I had of him.

He asked that I be open-minded to suggestions and come to my appointments willing to discuss various treatment options. He asked for my continuing honesty

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about issues going on in my life and with my health, and he asked that I make a commitment to continue my education on issues related to living with HIV.

The thing that really made me realize that it was going to be a good match was when he told me that he approached his relationship with patients as a partnership—with both patient and doctor having a shared responsibility. He shared his belief that patients, when given the opportunity to work with their doctors as equal partners in their care can, in many ways, become their own doctors.

At that moment I remembered a quote I had read the day before that was written many years ago by Albert Schweitzer. He said, “Each patient carries his own doctor inside him. They come to us not knowing that truth. We are at our best when we give the doctor who resides within each patient a chance to go to work.” It was clear that my new doctor was empowering me—the patient—to be an active participant in my care and to awaken the “doctor” that resides within me.

The final question I asked him was whether he saw any parallels between living with HIV and being on cruise control. He laughed. He said he wished it was that simple, but it was clear that cruise control was meant for automobiles and had no place in a philosophy of HIV care.

I knew I had made the right decision.

*Greg Milward recently returned to his birthplace of Madison, Wisconsin, after 20 years in Tucson, Santa Fe and Washington, D.C. He shares his life with his partner of 24 years and the two best Labrador Retrievers in the world. He is happy to report that his approach to finding a good health care provider led him to the University of Wisconsin HIV Care Program and Dr. Frank Graziano, with whom he shares “a wonderful doctor/patient relationship.” He can be reached at [gregmilward@charter.net](mailto:gregmilward@charter.net).*

## Tip sheet for finding a good HIV care provider

1. Learn as much as you can and are willing to about HIV/AIDS because this will put you in a better position to make good assessments. Focus on finding a physician with whom you can be totally honest...and it feels okay to do so.
2. Get clear about how your health care will be paid for—do you have something that pays for your

health care—insurance? Medicare? Medicaid? Do you need a doctor who can provide care even if you don’t have a way to pay?

### 3. Ask some key questions of the physician.

- Why do you practice in HIV/AIDS?
- How many people with HIV/AIDS do you currently have in your practice?
- How long have you been practicing medicine in HIV/AIDS?
- What’s your idea of a good doctor-patient relationship—doctor in charge? Patient in charge? Team approach?
- Are you reachable by phone if I have an emergency? Who covers for you when you’re not available?
- Are you an HIV specialist? What are your credentials?

If you can, get yourself to a computer and check out the following resources:

## American Academy of HIV Medicine

On this site you can find a physician in your area who is an HIV specialist according to the American Academy of HIV Medicine (AAHIVM). The AAHIVM has established a definition for “credentialed HIV Specialist” using industry-standard criteria to measure knowledge—experience, education, and external validation. To receive and maintain credentials, a provider (physician, osteopath, physician assistant, or nurse practitioner) must continuously fulfill the requirements of the AAHIVM. Requirements include being licensed, passing a credentialing exam, taking regular courses, and maintaining a patient caseload of at least 20 every two years. Visit [www.aahivm.org](http://www.aahivm.org).

## TheBody.com

The Body has organized a variety of information from various sources on the topic of “Choosing and Working with a Provider.” The collection includes basic information, personal accounts, research, and resources. Visit [www.thebody.com/choosing.html](http://www.thebody.com/choosing.html).

Positively Aware Fall 2006 Special Issue

# Helping Your Antiretrovirals Help You

## Things to Consider When Choosing What Goes in the Tank

By Melissa Ngo, PharMD

Overwhelmed! That is the first word that comes to my mind when I think about an HIV patient who is about to begin antiretroviral therapy for the first time. I think of all the information being sent the way of someone starting therapy—by physicians, nurses, patient educators, and pharmacists. All of this information is provided in order to help with the start of this important journey, but it can definitely be overwhelming.

As a pharmacist who has worked in an HIV clinic, an outpatient pharmacy, and a medication management mail-order pharmacy, I have seen patients from a variety of perspectives. In each of these different surroundings, some things have remained consistent—patients have to deal with a myriad of things involved in starting (or switching) antiretroviral therapy, and patients do better if they understand how critical adherence is and come to terms with it. I suggest that anyone thinking about beginning a new medication regimen feel really ready for this big step before taking it.

Rarely is it imperative that antiretroviral treatment be started on an urgent basis. Therefore, you can be open with your physician if you are not yet prepared to begin therapy. Also, before beginning treatment, learn how the medications you'll be taking work in your body and the side effects they may cause. Make sure you are committed to working through complications or problems if they arise.

There are so many different opinions and suggestions about when to start antiretroviral therapy that it is hard to determine the right time for an individual person. Even though things like CD4 counts and viral loads are important factors in making this decision, the most important determinant is that the individual person is ready to start and adhere to therapy.

Adherence to an antiretroviral regimen is extremely important. If a patient starts therapy but does not take it consistently every day, or decides to stop after beginning a regimen, there is a chance of developing medication resistance. However, this does not mean that starting a particular regimen means you can never change it.

If a treatment is not working due to side effects, dosing schedule, or medication intolerability, there is always the option to change to a different combination of medications. It is crucial that the physician be informed and involved with switching therapy. Having an expert help

with the change will decrease the potential for building resistance to medications.

### Finding a regimen that suits you and your lifestyle

Are you ready to start your antiretroviral therapy? If so, there are a few things to keep in mind as you and your physician begin to choose a treatment that is right for you.

1. It is important to understand the goals and benefits of therapy. Antiretroviral medications are a cornerstone in the treatment of HIV-positive patients because of their ability to restore and maintain immune function, prevent illness and death, and improve quality of life. The more you understand about medication therapy, the more you will be able to make informed decisions.
2. Before starting therapy, it is a good idea to have baseline laboratory tests performed. These tests will help you and your provider understand where your body's pre-antiretroviral therapy starting point is. Knowing this starting point will help your physician understand your current health status with respect to what the HIV is doing and anything else, unrelated to HIV, that might be going on.

Lab tests will also guide your physician in choosing appropriate treatment. For example, if lab results indicate highly elevated lipids prior to starting therapy, your physician may want to avoid most of the protease inhibitor class, or address the elevated lipids upon initiating therapy.

3. Think about what will work for you in your life. There are many combinations of drugs to choose from when starting therapy if you are "treatment naïve"—starting your first ARV regimen ever. Things to consider when choosing a specific regimen, besides pre-treatment lab work, include:
  - total number of pills per day
  - dosing frequency
  - food considerations

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- drug interactions
- adverse medication effects and
- the potency of the regimen itself.

4. Whenever possible, make sure your choice provides a good “Plan B” option if some medication resistance emerges. This is called drug sequencing. You and your physician will likely choose a regimen that consists of medications in at least two different antiretroviral drug classes while also sparing as many other classes of drugs as possible for future use. These other drug classes will be reserved for use in the event that the virus becomes resistant to a specific class of drugs.

Your physician may do some drug resistance testing before you begin ARV therapy to determine if there are any medications to which your virus is already resistant. However, this test is often reserved for patients who are not responding to their current regimen (“treatment-experienced” patients).

With so many things to consider, you may wonder how you or your physician actually decides which combination of drugs to use. The good news is that there are guidelines to help with the decision-making process. It is important to remember, however, that one, guidelines change over time as new medications become available and more information is learned about existing medications, and two, these are just guidelines. Each individual person must find the regimen that will work best...for that person.

## Making it work

Once you start your new antiretroviral therapy, you may begin to realize that you are having trouble adhering to your regimen for one reason or another. If that happens, there are a variety of strategies that may help you.

From my experience, patients find pill boxes very helpful for organizing their medications and as a way to remember if they have taken them. Calendars can also be useful because each day can be marked to indicate that a dose was taken. Pill boxes and calendars are both inexpensive tools that can be very helpful. The good news is that adherence has gotten easier as new antiretroviral therapies have been developed that require fewer pills and fewer doses throughout the day.

## Sorting out drug side effects

Antiretroviral therapy has come a long way over the past decade. However, the longer medications are on the market, the more we find out about the side effects they can cause. It is unfortunate, but many of these therapies have

a lot of possible short-term and long-term side effects.

It is important to remember that every medication has a list of possible side effects associated with it. That does not mean that everyone taking a particular medication will develop every side effect on the list, or any of them, for that matter. It is a good idea to understand the potential side effects associated with each of your medications, though, so you’ll know what to look for if you do experience any problems after starting therapy.

If you have any side effects, or if any side effects you are experiencing become intolerable, make sure to discuss them with your physician. I have seen too many patients who have started therapy, experienced a side effect that they struggled with, then stopped therapy on their own without ever letting the doctor know there was a problem. Patients who stop therapy without speaking with the physician risk developing medication resistance because some medications need to be stopped in a particular order in order to avoid resistance.

Antiretroviral medications can have side effects that are common for the class they are in (e.g., protease inhibitors and gut distress), but there are also side effects that are specific to each medication. It would be impossible to list every side effect for every medication in this article, and probably boring. The point is this: when you start a medication, take time to learn about the side effects from your physician, pharmacist, or written information on that specific medication.

As a class, nucleoside reverse transcriptase inhibitors or NRTIs (drugs like lamivudine, abacavir, and zidovudine) all have the potential to cause some serious side effects. NRTIs can cause pancreatitis, lactic acidosis (a dangerous build-up of acid in the blood), and an enlarged, fatty liver.

Non-nucleoside reverse transcriptase inhibitors or NNRTIs (drugs like efavirenz and nevirapine) share the potential side effects of serious rash, nausea, and vomiting.

The class of protease inhibitors or PIs (drugs like ritonavir, lopinavir/ritonavir, atazanavir, and fosamprenavir) can also cause many side effects. Some of the short-term side effects include diarrhea and nausea or vomiting. Possible long-term side effects include increased cholesterol and triglyceride levels, lipodystrophy (body shape changes), cardiovascular risks, and new or worsening diabetes.

The fusion inhibitor class currently has only one medication in it—enfuvirtide. The most common side effect

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is an injection site reaction (ISR) that occurs to some extent in all patients who use it.

It would be easy to think you could expect the side effects common to a class of ARV from any drug in the class, but it's not that simple. Atazanavir, for example, does not share the same lipid-raising profile of its classmates. Likewise, abacavir has the potential for a hypersensitivity reaction (HSR) that the other NRTIs do not, and it appears to be less toxic on the cellular level than some of the others in its class. Similarly, the central nervous system effects (like dizziness, vivid dreaming, and mood changes) associated with efavirenz do not extend to the other drugs in the NNRTI class.

## Managing side effects

Managing side effects from antiretroviral therapy can sometimes be a difficult task. However, it's important to manage side effects not only because it may make you feel better, but because side effects are a leading cause of treatment non-adherence.

It is possible that a side effect could occur that cannot be managed with additional medications or other supportive measures, which could become intolerable. If that happens, it usually means discontinuing the drug (s) causing the problem and likely making a substitution, with assistance and supervision of your physician.

Some side effects occur with the start of therapy, but will resolve after a couple weeks of continued use. There are other side effects, however, that may need to be managed for the duration of therapy. If that happens, there are steps that you can take to reduce some of the more common ones.

- Nausea and vomiting often resolve without intervention within a few weeks. However, there are things that can be done to help manage these troublesome symptoms. Eating bland foods and small, frequent meals may help. In situations of severe nausea and vomiting, medications like prochlorperazine and ondansetron can also be helpful.
- Diarrhea may seem like it's just a nuisance, but it can be serious if it leads to dehydration. Remember, if you get episodes of diarrhea, it is important to drink lots of fluids in order to stay hydrated. Avoiding caffeinated beverages, alcohol, spicy foods, fried foods, and dairy products may help with diarrhea. Medications like loperamide and diphenoxylate/atropine may

also help, as well as psyllium powder and the amino acid L-glutamine.

- Intestinal gas is sometimes produced from certain foods you eat, like beans and vegetable skins. Your intestines need these kinds of fiber, though, so you can talk to your doctor about adding an enzyme called alpha-galactosidase and/or a drug called simethicone. Both are available in over-the-counter products like Beano (alpha-galactosidase) and Gas-X (simethicone). These can help your stomach digest "roughage" better.
- Peripheral neuropathy is commonly caused by some NRTIs, like ddI and d4T. Medications such as ibuprofen and topical creams that contain methyl salicylate may help minor symptoms. For more moderate to severe symptoms, medications like gabapentin or amitriptyline sometimes help.
- Muscle pain may be controlled with medications like acetaminophen and ibuprofen.

Some side effects may only be found with routine lab work. Depending on the severity, these side effects may be managed under physician supervision with either concurrent drug therapy or a change in antiretroviral therapy. Your physician should be monitoring for things such as:

- decreased renal or liver function,
- increased cholesterol or triglyceride levels,
- changes in blood glucose levels, and
- changes in red and/or white blood cell counts.

Please discuss all side effects with your physician before trying to treat them yourself. Sometimes there may be underlying causes of the symptoms that need further evaluation. Also, possible drug interactions between your ARVs and other medications you might be taking need to be considered, even if you're just using a new over-the-counter medication.

## Drug interactions

The topic of drug interactions is extensive and could comprise an entire magazine issue on its own. Every medication, even ones you think are harmless, may cause drug interactions with your current regimen of antiretrovirals.

Here's a common example that I have seen in the pharmacy. A patient experiences heartburn and comes into the pharmacy to purchase Prilosec OTC, the strongest over-the-counter medication for heartburn. The patient just happens to be on ARV therapy that includes atazanavir. The Prilosec OTC may treat the heartburn, but

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what the patient does not realize is that a simple item like Prilosec OTC decreases the absorption of the atazanavir. This reduction in atazanavir levels in your blood could lead to the development of resistance to atazanavir.

The above example hopefully illustrates the importance of discussing any new medication with your HIV physician or pharmacist. This includes, by the way, any medication started by a physician other than your HIV physician. Providers who do not practice HIV medicine often have little or no HIV-specific knowledge—so be sure to discuss any new medications with your HIV provider.

There is a constant flow of new information about ARVs and how they work, which makes it especially important to discuss all new medications with your HIV provider. Hopefully, you feel like you can be honest with your doctor about what you take and your doctor knows what to do with the information.

## New drugs and combinations

For the first time in a while, there are several promising medications in the pipeline of the antiretroviral world and a few that are new to the market. Make sure your doctor is aware of and knowledgeable about newly approved drugs and those in development. This is especially important if the existing treatments are not working for you.

Following are some examples of newly approved drugs and drugs that are currently being studied.

### Approved:

- Atripla, a combination of efavirenz, tenofovir, and emtricitabine, was approved by the FDA on July 12, 2006. It contains no new medications but it is exciting because it consists of only one pill once daily—the simplest regimen yet.
- Prezista (darunavir), a new protease inhibitor indicated for people with PI-resistant virus, was approved in June by the FDA. It is taken twice a day and, like most PIs, is boosted by ritonavir. The buzz is that it is supposed to have fewer side effects than currently used PIs, with less potential for resistance.

### In last stages of development:

- Etravirine is an NNRTI that has shown activity against NNRTI-resistant virus. It is being studied using twice-daily dosing.
- Maraviroc is an entry inhibitor (it blocks the CCR5 receptor on the CD4 cell) that's causing excitement because it represents a new class of antiretrovirals. It adds another option to existing ARV therapy, making it of potential value to people who are treatment experienced. It will likely be taken twice a day with other ARVs.
- MK-0518 is likely to be the first in a whole new class of ARVs—integrase inhibitors. It is being studied as a twice-daily drug to be taken with other ARVs. The data so far have been very promising, especially for people who are resistant to currently available medications.

### Tips:

- Go to an HIV specialist for treatment of your HIV. Make sure it is someone with whom you feel comfortable communicating your ideas, thoughts, and concerns. It should also be someone who is on top of the current research and will work to make sure you have access to all available options.
- Make sure you are ready to start therapy before actually starting therapy. Try to build a level of comfort with it.
- Always check with your HIV physician or pharmacist before adding anything new to your regimen, even over the counter medications or nutritional supplements.
- Never stop therapy without discussing it with your HIV physician first.

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follow-up data presented at AASLD showed that response rates in the different dose groups converged as treatment continued. By Week 12, 82%-92% of patients in the various arms experienced early virological response ( $\approx 2$  log decline in HCV RNA). By Week 24, the percentages with undetectable HCV RNA were similar across the dose arms; 68% of subjects receiving valopicitabine 200 mg/day achieved HCV RNA below 20 IU/mL, compared with 67% in the 800 mg/day group. "At doses as low as 200 mg/day, valopicitabine plus pegylated interferon markedly suppresses viremia in treatment-naive patients with HCV [genotype 1] infection," the researchers concluded. The 200 mg/day dose was generally well-tolerated, with fewer adverse events than observed at higher doses. The study protocol was amended to reduce the dose to 200 or 400 mg/day, and the 800 mg dose was discontinued.

## Other Antivirals in Clinical Trials

There were only a couple of presentations at AASLD on two other anti-HCV agents in development, Roche's polymerase inhibitor R1626 (a prodrug of the nucleoside analog R1479) and the non-nucleoside NS5B polymerase inhibitor HCV-796, co-developed by ViroPharma and Wyeth Pharmaceuticals.

As reported by Stuart Roberts (abstract LB2), 47 genotype 1 patients in a Phase I trial were randomly assigned to receive either oral R1626 twice daily at one of four doses (500, 1500, 3000, or 4500 mg twice daily) or else placebo for 14 days. Final results were presented for patients who received the two higher doses. After 14 days, subjects taking R1626 experienced mean HCV RNA reductions of 2.6 and 3.7 logs, respectively, in the 3000 mg and 4500 mg dose arms. Dr. Roberts characterized the decline as "the best that we have seen with all the polymerase inhibitors studied so far." R1626 exhibited good tolerability up to 3000 mg twice daily, although adverse events – including mild to moderate hematological changes – were observed at higher doses.

In a separate presentation (abstract 928), researchers reported that an *in vitro* analysis using an HCV replicon system demonstrated that R1479 (the active form of R1626 in the body) had moderate synergistic effects when combined with either conventional interferon or ribavirin, with no increase in cellular toxicity. Combining R1479 with other anti-HCV agents produced additive effects. Based on results to date, Roche has started a Phase II trial of R1626 in combination with pegylated interferon plus ribavirin.

With regard to HCV-796, Stephen Villano and colleagues (abstract 1127) reported on a study in which 102 treatment-naive participants (72 with genotype 1)

received the oral drug at various doses (50, 100, 250, 500, 1000, or 1500 mg) twice daily as monotherapy for 14 days. The maximum mean HCV RNA reductions from baseline were 1.4-1.5 log in the highest dose groups at Day 4. HCV NS5B gene sequence data, available for 58 genotype 1a patients, showed that viral load increases during HCV-796 monotherapy were associated with selection of viral variants with resistance mutations, including C316Y.

No new data were presented on Schering-Plough's protease inhibitor SCH 503034, which is currently being tested in prior pegylated interferon/ribavirin nonresponders in a large Phase II study following promising early results. It is important to remember that many investigational agents never make it out of the development pipeline, either due to suboptimal efficacy or poor safety, as illustrated by the Boehringer-Ingelheim protease inhibitor candidate BILN 2061, which was discontinued due to cardiac toxicity in animal studies.

## Preclinical Data

There were also several reports at AASLD on candidate anti-HCV agents that have yet to enter clinical trials. Hua Tan and colleagues (abstract 933) presented a poster on the oral HCV NS3/4A protease inhibitor ITMN-191, being developed by InterMune. In an *in vitro* study of ITMN-191 plus pegylated interferon using two HCV replicon systems, researchers found that the combination synergistically inhibited HCV replication at low concentrations of both drugs, suggesting that co-administration could have a potential clinical benefit and provide a greater genetic barrier to the development of ITMN-191 resistance. Phase I trials are expected to begin soon.

Data were presented on several other antiviral agents further back in the development pipeline, including:

A-837093: this NS5B polymerase inhibitor, being developed by Abbott Laboratories, suppressed HCV in genotype 1a and 1b replicon models and in chimpanzees; resistance emerged fairly rapidly when used as monotherapy, but synergistic activity and minimal cross-resistance were observed when combined with other antiviral agents (abstracts 128, 417, 432).

ACH-806: this Achillion Pharmaceuticals agent appears to work by blocking the HCV replicase complex, acting at a different stage of the replication process than protease inhibitors; viral variants resistant to ACH-806 and related compounds remained

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sensitive to other classes of anti-HCV agents (including NS3/4A protease and NS5B polymerase inhibitors) and vice versa (abstract 937).

AG-021541: this Agouron/Pfizer non-nucleoside polymerase inhibitor exhibited anti-HCV activity *in vitro*, but viral variants with resistance mutations emerged, leading to reduced sensitivity to the drug (abstract 931).

## Immune-Modulating Therapies

Researchers at AASLD also presented data on numerous experimental therapies that act at the level of the host immune system rather than against HCV itself, including:

New forms of interferon, such as albumin interferon (Albuferon) and consensus interferon (Infergen);

The toll-like receptor 9 agonist CPG10101 (Actilon), which activates dendritic cells, B-cells, and natural killer cells;

The monoclonal antibody bavituximab;

Cyclophilin inhibitors, including SCY-635 and DEBIO-025;

GI-5005, a yeast-derived targeted molecular immunogen, or "tarmogen."

## Prospects for the Future

Experts at the satellite symposium discussed the implications of the novel targeted antiviral agents and how they might alter hepatitis C therapy. According to Dr. Jacobson, STAT-C offers the prospect of developing "regimens which can cure a substantially higher proportion of patients than is presently possible."

Jean-Michel Pawlotsky said that there is "absolutely no doubt" that combination therapy is the wave of the future. While tomorrow's treatment for hepatitis C may ultimately rely on oral "cocktails," all agreed that for the foreseeable future, STAT-C drugs generally will be used in combination with pegylated interferon and possibly also ribavirin. However, the addition of antiviral agents may shorten the duration of therapy, thereby reducing the toxicity of pegylated interferon and ribavirin.

Further, use of antiviral agents in conjunction with immune-based therapies holds promise especially for "difficult to treat" patients such as prior nonresponders and relapsers. Dr. Jacobson noted that it is not yet

clear what happens when HCV is suppressed. The virus may remain present at very low levels in "reservoir" sites outside the liver, which could lead to relapse after completion of therapy. The answer to this mystery may determine whether immune modulators will always be needed in addition to antiviral agents.

The speakers also shared concerns about resistance to the antiviral agents. According to Dr. Pawlotsky, resistance cannot be avoided, but "it can be delayed or managed." Charles Rice suggested that we can expect that therapy for hepatitis C will become more complicated, like highly active antiretroviral therapy (HAART) for HIV, which revolutionized treatment but presents clinicians and patients with a "bewildering" array of therapeutic options.

All STAT-C agents now in development can select for resistance if used as monotherapy. The emergence of resistance mutations can be delayed by simultaneous use of multiple agents that attack HCV at different stages of its lifecycle. Suppressing viral replication to the greatest possible extent is the best way to prevent resistance, and therefore good adherence to therapy is critical. "As with HIV, we have to become more sophisticated about resistance," Dr. Jacobson cautioned.

In conclusion, John McHutchison said that despite their uncertainties and potential drawbacks, the development of antiviral agents that directly target HCV is a "very exciting" treatment advance. Added Dr. Jacobson, "STAT-C is a leap forward of the magnitude of HAART."

HCV Advocate December 2006. Reprint granted with permission from HCV Advocate.

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up when we're sitting in an exam room in front  
**In Sickness and in Health continued from page 1**

of our doctors, who may or may not be distracted, or focused on some other aspect of our health, or tired from whatever else they've got going on in their lives. If we write those things down, my guess is that we are much less likely to ignore them ourselves, and much more likely to treat them like the real things they are.

Do you feel like HIV-related issues form the boundary of what you bring to your HIV provider or do you approach your doctor with broader issues than that?

Greg: In my case, nothing is off limits in what I will ask my doctor about, primarily due to the fact that my infectious disease doctor also functions as my primary care provider. This isn't always the case. In situations where you are seeing an infectious disease specialist for issues related to HIV, some think that it should limit what issues you would bring to your appointment to discuss. I don't agree with this. Let the doctor decide whether or not issues are related and, if necessary, provide a referral to a specialist to deal with other issues.

Heidi: That's an important point. Some physicians trained in a particular medical specialty may not be that eager to do what amounts to primary care, even though many would argue that good long-term HIV care necessarily requires it. Someone who is an infectious disease specialist, for example, might be more focused on infections that get cleared and may not be all that interested in monitoring heart disease risk, managing diabetes, etc.—the stuff that's necessary in a lifelong infection like HIV. It's my opinion that the physician who feels that way should consider getting out of HIV practice.

Like it or not, HIV is a complicated, long-term infection that requires specialized care. Some HIV patients don't have health coverage, so having another doctor to deal with their non-HIV issues is out of the question. Besides, it can be a challenge to distinguish what's HIV-related from what's not.

As a patient, it doesn't take long to figure out that non-HIV providers often don't really have a clue about how HIV and antiretroviral therapy intersects with other "regular" health issues...which doesn't lend itself to good, comprehensive care.

There must be some questions or issues you find harder to bring up than others. I mean, the doctor's office can be an intimidating place and there's this thing that a lot of people have about, well, wanting your doctor to like you, you know? Plus, this is the person who writes the prescription for that medication you need and

decides whether to order that lab test you want—let's face it, you don't get that far without this person's okay. Even beyond that, I'm not sure all patients get the signal from the doctor that "anything goes." So, what are the kinds of things you've maybe had to work at to put on the table with your doctor?

Greg: The hardest issues for me to discuss with my doctor have been related to pain associated with peripheral neuropathy and fatigue. Chronic pain is hard to describe and, for me, there was an irrational fear when I first started to experience it that my doctor would think it was all in my head. Fatigue was also a hard one to discuss, at first. I quickly got over that, though, when my doctor convinced me that confronting issues related to fatigue was one of the key factors in improving a person's quality of life.

I know this sounds strange, but I also think that in the early days after the advent of HAART (highly active anti-retroviral therapy) there was a sense of survivor's guilt that made issues like pain and fatigue hard to discuss. After all, we had watched friends die of this disease and, for me, early on in my relationship with HIV medications there was a sense that I needed to be grateful to have the medications and just needed to deal with what I thought at the time were the "minor" issues related to fatigue and neuropathy.

Heidi: I have to think there's been a time that you didn't agree with your doctor's approach to an issue. How do you handle that kind of thing?

Greg: With my first doctor, I disagreed with his approach to the relationship between doctor and patient. I was expected to simply be the subservient patient. Since that failed doctor-patient relationship, I've been fortunate and can honestly say that I've never disagreed with my doctor's approach. I think that's because with both doctors I've had the privilege of working with since my first doctor, the relationship has been one where I was able to openly discuss, question, debate and ultimately decide with my doctor what course of treatment was going to be taken.

What about you?

Heidi: I guess my ride has been a bit bumpier but it got me to my current doctor, so it was worth it, I suppose. I've had providers who've kind of drawn some weird lines in the sand that felt a little power trippy to me and, to be honest, I found it hard to recover from that and stay in the relationship. What I really appreciate about my current doctor—and this seems like a bit of a lost art in medicine—is that he listens without the interference of his ego. I didn't say he has no ego, mind you, and I joke that I don't want to be the last appointment on his marathon clinic schedule, but I'll take his willingness to take me into account any day. I like to say that

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what makes it work is that he knows his place and I know mine—he's the advisor and expert and advocate, and I'm the one who lives with this virus. What do you do if you aren't getting what you need from your provider?

Greg: First, remember that you are the "consumer." If you don't feel that you are getting what you need from your provider I would approach it head on. Is it just not a "good fit"? This can be nothing more than a gut feeling that you don't click with a particular provider—you don't like his or her bedside manner. A doctor may be a brilliant clinician, but if you don't feel that you can bring issues to him or her to talk about open and freely, then it's probably not a relationship that will work in the long run.

Heidi: Amen. I am continually surprised by the blind trust that some people have in their providers. I've heard people say, "Well, I wouldn't want my doctor to think I'm challenging him in any way. He's the expert, not me." That scares me a little. There are brilliant physicians, of course, and there are also overworked physicians, physicians who don't keep current with research, physicians who don't treat much HIV, and, frankly, physicians who just aren't very good. My feeling is that—and I had to summon my courage early on to say this once to a physician who was skilled but was just not listening to me—when I leave the exam room, HIV comes with me; unlike you, I live with this disease, and I will die with it. That means that there are some things I am the expert on, like how I want to live with this and what I want my care to be like.

Greg: I'm guessing you no longer get care from that physician, yes?

Heidi: You got it.

If you could only say a few words to someone newly diagnosed about getting the most out of the patient-provider relationship, what would you say? This is your chance to create a motto, Greg!

Greg: Trust your gut instinct—does the relationship with your doctor feel right? Don't be afraid to change doctors if you don't feel you are getting the care you deserve. Also, remember that getting the most out of your relationship is a shared responsibility between you and the provider.

What about you? What's the message you'd give to someone just setting out?

Heidi: Hmmm. The big thing I think about is that your doctor gets to leave HIV when the workday is done; you don't. If you're not all that interested or involved in your care, why should anyone else be? Even if your doctor sometimes wishes you were less involved, shall we say, at least it becomes clear that you are in it for real—you're here to take care of yourself. I'm pretty confident that leads to better care. Heidi M. Nass is a lawyer turned treatment advocate and educator. She is based in Madison, Wisconsin, at the University of Wisconsin HIV Care Program. She may be reached at [hmn@medicine.wisc.edu](mailto:hmn@medicine.wisc.edu).

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Helping Your Antivirals Help You continued

## Resources:

### AIDS Community Research Initiative of America

In addition to a quarterly treatment newsletter and information on current clinical trials, the AIDS Community Research Initiative of America (ACRIA) offers useful publications on specific topics that can be read on-line or in hard copy. Some examples: Understanding Your Lab Results, Treatment Issues for Women, and Managing Drug Side Effects. Visit [www.acria.org](http://www.acria.org).

### AIDSInfo

An HIV/AIDS site from the National Institutes of Health (NIH). It contains links to a variety of information, including treatment guidelines, clinical trials, and fact sheets. Call 1-800-HIV-0440 (448-0440). TTY 1-800-480-3739. Outside the U.S. call 301-519-0459. Visit [www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov).

### TheBody.com

The Body is a collection of a huge variety of HIV information from a multitude of sources. It is a virtual "warehouse" of HIV information, which it offers in all kinds of formats—forums, fact sheets, articles, interviews, conference coverage... to name a few. Visit [www.thebody.com](http://www.thebody.com).

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**Expect trouble as  
an inevitable part  
of life and repeat  
to yourself the  
most comforting  
words of all:**

***"This, too,  
shall pass."***

*Ann Landers*