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Why HIV Drug Resistance Matters: An Overview

By James Learned

When we talk about HIV treatment, the issue of resistance almost always comes up. HIV drug resistance can seem to be a hopelessly complicated topic. But having a basic understanding of what resistance is, what causes it, and how it's measured can have a big impact on the success of antiretroviral treatment.

This overview is intended to help people better understand the basics of drug resistance (hopefully without being too complicated) in order to get the full benefit of treatment.

Drug resistance isn't anything new and certainly isn't limited to HIV. Most of us are familiar with drug resistance in situations outside of HIV. You may have experienced or read about wide-spread resistance to antibiotics, drug-resistant tuberculosis, or vaginal yeast infections that don't respond to conventional treatment.

The goal of any pathogen—or germ—is to survive and reproduce. Most medications are designed either to kill the offending germ or to stop it from reproducing, ideally resolving the infection. But if a germ continues to reproduce while you're on treatment, it may change—or mutate—so that the treatment can no longer kill the germ or stop it from reproducing. Over time, the treatment no longer works.

This is called drug resistance.

HIV replication

The goal of HIV treatment is to lower the amount of virus in your body (viral load) and increase your CD4 cell count so that the immune system is better able to deal with infections.

Many complex steps are necessary for HIV to make copies of itself. Two of these steps involve specific enzymes—reverse transcriptase and protease. All but one of the antiretrovirals approved by the Food and Drug Administration to treat HIV interfere with the virus's replication process by attaching—or binding—to one of these enzymes, effectively stopping HIV from replicating.

Without treatment, HIV usually reproduces very rapidly in the body, creating billions of new viral particles every day. Since HIV replication involves so many complex steps, the virus makes a lot of mistakes. And as sophisticated as HIV is, it's also a somewhat messy virus. It isn't able to correct mistakes it makes

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as it reproduces. These mistakes in HIV's genetic structure are called mutations.

Up to 90% of new viruses end up with a mutation (or mutations) that keep them from being able to infect a new CD4 T-cell or complete the replication process. Unfortunately, that still leaves millions of new viruses that go on to produce new copies of HIV. Many of these viruses also contain mutations, but they aren't harmful enough to interfere with HIV's ability to replicate.

HIV drug resistance

Simply put, HIV drug resistance means that an antiretroviral drug—or combination of drugs—can't prevent or reduce HIV replication. Our main concern is the mutations that affect currently available antiretrovirals. Specific mutations that stop a drug from being able to bind to either the reverse transcriptase or protease enzyme can make the drug less effective. This can have a negative effect on how well treatment works.

Reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors bind to HIV's reverse transcriptase enzyme. Protease inhibitors bind to the protease enzyme.

Drug resistance doesn't happen because HIV is smart. The virus doesn't have a brain and can't think about how to get around a drug. Mutations that cause resistance occur naturally and randomly. We sometimes think of HIV as intelligent and cunning, but, in fact, it survives simply because it can. It uses what it needs to replicate—white blood cells (usually CD4 cells), certain enzymes, and other materials it brings with it.

Drug resistance before starting treatment

Mutations in the genetic structure of the reverse transcriptase and protease enzymes can occur before you begin antiretroviral treatment and, more often, when you're on treatment.

When HIV enters your body, it makes both perfect copies of itself—called wild-type virus—and copies with random mutations. As both the wild-type and mutated HIV continue to replicate, populations of mixed viruses develop in your body.

Wild-type virus is the most fit and best able to replicate, so most of the HIV in your body is wild-type virus. Even though mutations continue to randomly occur, most of them are harmless and will have little or no effect if and when you begin treatment.

Unfortunately, many people who have never been on treatment have HIV that's resistant to one or many HIV drugs. If you're HIV-negative and engage in risk behaviors with someone whose virus is resistant to one or more antiretroviral, you could be infected with your partner's drug-resistant HIV.

Recent data show that 10-30% of new infections (generally defined as having been infected over the past three years) involve HIV that's resistant to at least one drug. As many as 10% of new infections involve HIV that is resistant to at least two drugs. And a recent study found that 3% of new HIV infections involved strains of HIV that were resistant to drugs in three classes of antiretrovirals (reverse transcriptase inhibitors, non-nucleosides, and protease inhibitors).

It's also possible for someone with HIV to be infected again, with drug-resistant HIV, possibly HIV that's resistant to many drugs. This is called superinfection. We don't know how often superinfection occurs, but there are several reports showing that it's possible.

If you're infected with drug-resistant HIV—either initially or through superinfection—you have fewer treatment options even before you start therapy. This could affect the likelihood of treatment being successful.

Drug resistance while on treatment

Most mutations that can influence the effectiveness of combination therapy happen while you're on treatment. When you first start antiretroviral treatment, the amount of HIV in your body goes down dramatically.

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Early Results Show Pegasys Working Where Peg-Intron Has Failed

Study Results Provide Hope for HCV Patients Who Could Not be Cured of Their Disease

Basel, 11 November 2005

Early results evaluating re-treatment strategies using Pegasys plus Copegus show benefit in patients who had been unsuccessfully treated with another pegylated interferon (Peg-Intron plus ribavirin). This means that hope may be at hand for the large and growing group of patients who could not initially be cured of their hepatitis C virus. Preliminary results from the large international trial called REPEAT¹ show that 47% of patients treated with the standard combination of Pegasys plus Copegus have undetectable amounts of virus or have a significant reduction in viral load at the important 12 week assessment. In addition, 64% of patients who received an innovative induction dose of Pegasys achieved this early viral response.

The results presented today at the American Society for the Study of the Liver (AASLD) reflect findings from the first 12 weeks of therapy from this ongoing study. These early results typically act as an excellent indicator of whether or not a person will be cured of their disease after completing the full course of therapy.

"These are very positive results for patients who have not responded to previous therapy," said Professor Patrick Marcellin, from the Hôpital Beaujon, France and one of the lead investigators of the study. "Previously these patients would have been considered difficult to treat; now there is hope for a cure."

"This is a further example of Roche defining new treatment strategies resulting in optimal therapeutic approaches for the hepatitis C patient population," said Eduard Holdener, Global Head Pharma Development at Roche. "These new results have pioneered a new solution for patients who have not responded to first-line treatments."

One of the biggest challenges in the treatment of hepatitis C patients is to find treatment options for those who do not respond to primary treatments. These new data become available at a time when a report from a large study mandated by the U.S. Health Authority demonstrated that Peg-Intron was not able to generate sustained viral response in more than 50% of patients receiving Peg-Intron as a first line treatment.²

The key findings of the 12 week results from the REPEAT study published at AASLD include:

- Amongst patients receiving a standard dose of Pegasys (180 mcg) given with Copegus for the

first 12 weeks of therapy, 47% achieved an early viral response, defined as having a significant drop in viral load or being virus free

- Amongst patients receiving the induction dose of Pegasys (360 mcg) given with Copegus for the first 12 weeks of therapy, 64% achieved an early viral response, defined as having a significant drop in viral load or being virus free
- Interim safety data also presented at the conference indicate that the innovative induction dose of Pegasys for 12 weeks given with Copegus is tolerated as well as the standard dose of Pegasys plus Copegus³
- The 12 week results from all 942 patients who received treatment in the trial will be presented in the late breaking session during AASLD

The final results of the REPEAT study are expected to be available in 2007.

Creating hope from despair

"Imagine being told that you might be cured of a disease when you thought there was no chance," said Maureen Bromage from the Eddystone Trust, Plymouth, UK. "Treatment options, like those being tested in the REPEAT trial, are needed for patients who have been unable to clear the virus after their first treatment" she said.

About REPEAT

The study presented at AASLD is known as REPEAT – Retreatment with PEGinterferon alfa2a in PATients not responding to prior peginterferon alfa2b/ribavirin combination therapy. Its purpose is to evaluate the efficacy and safety of Pegasys and Copegus combination therapy in patients who were unable to be cured using PegIntron combination therapy. In this innovative study, Pegasys and Copegus are given for the traditional 48 week period or a longer 72 week period, as well as with or without an induction dose of Pegasys for the first 12 weeks of therapy. 950 patients were randomized in the REPEAT study from Europe, North America and Latin America.

Pegasys – The Right Solution for More Patients

Pegasys is the most frequently prescribed pegylated interferon for patients infected with hepatitis C.

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HCV/HIV Bytes

Extrahepatic Manifestations: Porphyria Cutanea Tarda (PCT)

Alan Franciscus, Editor-in-Chief

Porphyria Cutanea Tarda (PCT) is one of the most common types of a condition called porphyria caused by a deficiency of an enzyme called uroporphyrinogen decarboxylase (UROD). The reduced activity of UROD results in an overproduction and build up of the protein uroporphyrinogen in the blood and urine of patients. This results in the abnormal production of heme, a compound found in all body tissues and especially in the liver and red blood cells.

PCT can be caused or triggered by hemochromatosis (accumulation of iron in the liver), heavy alcohol use, estrogens, hepatitis C and other viral infections. An inherited deficiency of UROD is responsible for about 20% of cases of PCT.

Symptoms

The symptoms of PCT are mostly confined to the skin. Skin lesions or blisters are most often seen on the hands, forearms, back of the neck and face and areas exposed to the sun. The skin may become red, blister and peel after exposure to the sun or minor trauma. PCT can also cause either darkening or lightening of the skin, increased facial hair, scarring, alopecia (hair loss), thickening of the skin, itching and premature aging of the skin. In severe cases calcium may be deposited in the skin causing non-healing ulcers.

Liver function enzymes can be abnormal although enzymes are usually only mildly elevated. A liver biopsy should be performed to assess iron stores and to check for any damage caused by PCT.

Diagnosis

Diagnosis is made based on the presence of skin lesions on physical examination, as well as by the measurement of UROD in blood, urine and stool samples.

Management

The signs and symptoms of PCT can be managed, but there is no cure. The management of PCT includes avoiding the sun, alcohol and estrogens, and restriction of iron rich foods. Short term iron depletion by phlebotomy (removal of blood) is usually the first line of treatment and can improve the signs and symptoms of PCT. Phlebotomy is stopped once iron stores and

porphyrins in the blood return to normal, but if signs and symptoms return additional phlebotomies may be required. Anti-malarial drugs, such as Chloroquine, are also used to treat PCT.

Treatment of the underlying disease (HCV) with interferon plus ribavirin has also been found to decrease skin lesions as well as UROD's found in urine.

HCV Advocate October 2005

Extrahepatic Manifestations: Lichen Planus

Alan Franciscus, Editor-in-Chief

Lichen planus is a fairly common skin disorder that may last for months to years and affects about 1 or 2% of the U.S. population. Lichen planus usually affects people between the age of 30 years and 70 years and is slightly more prevalent in women than in men. The exact cause of Lichen planus is unknown, but it seems to be triggered by stress, genetics, allergic reactions to medicines, and by viral infections such as hepatitis C. There have been studies that have found a prevalence of HCV in people with Lichen planus from 3.5% to 60%. For this reason, it has been recommended that people with Lichen planus (especially with elevated liver enzymes) should be tested for HCV.

Lichen planus typically affects the skin, nails, vulva, penis, and mucous membranes including the mouth. The symptoms appear as purple or plaque like shiny flat-topped itchy bumps. There is no cure for Lichen planus but treatment is effective in alleviating the symptoms (itching of the skin lesions) and improves the appearance of the rashes.

Skin

Lichen planus most commonly affects the skin. The bumps can appear on any skin surface, but are most often found on the inside of the wrists and ankles, the lower legs, back, and genital regions. In severe cases, the bumps can be extremely itchy and painful. When the lesions heal the skin may become discolored. The skin discoloration may fade over time. Treatment consists of topical steroids and antihistamines used to relieve the itching. Severe cases may require the use of oral corticosteroids such as cortisone or prednisone. Extreme cases may require photodynamic therapy light

treatment and prescription drugs to help control and alleviate the symptoms. Other strategies to reduce the symptoms include the use of oatmeal baths (Aveeno), and anti-itch topical creams.

Mouth

Lichen planus of the mouth usually affects the gums, tongue and inner cheeks of the mouth. It appears as white, interconnecting lines which resemble and are named after the lichen plant, but Lichen planus is not related in any way to the plant. Severe cases may involve painful sores and ulcers of the mouth. Very severe cases of Lichen planus of the mouth can slightly increase the risk of oral cancer. For this reason it is important to control the disease with medications and good oral hygiene.

Lichen planus that affects the mouth is generally found by a dentist or dental hygienist. The diagnosis may be confirmed by a biopsy. Yeast infections are commonly found in association with Lichen planus or can be triggered by topical steroids used to treat it. The treatment of the yeast infection sometimes improve the symptoms of oral Lichen planus.

Alcohol, tobacco, spicy foods, peppermint, cinnamon, citrus type foods and stressful situations trigger the symptoms and should be avoided if possible. Treatment of oral Lichen planus includes the use of topical steroids as well as controlling the triggers. Regular dental exams are recommended to look for any tissue changes. Teeth cleaning and good personal oral hygiene will improve the symptoms.

Hair

Lichen planus can also occur on the scalp and can cause permanent scarring and inflammation of hair follicles leading to permanent hair loss. To prevent permanent damage, oral steroids, plus topical steroids as well as prescribed oral medications should be taken as soon as possible to prevent permanent damage.

Nails

Lichen planus can also affect the nails leading to damage of the nail root. Symptoms include grooving, splitting, nail thinning as well as nail loss. In severe cases the nail loss can result in permanent nail root damage.

For more information on the Web:

The Texas A & M University System—Baylor College of Dentistry

<http://www.tambcd.edu/lichen/>

HCV Advocate November 2005

Book Review: Living with Hepatitis C for Dummies

Lucinda K. Porter, RN, CCRC

There are many fine books about hepatitis C (HCV). Although plentiful, I always thought hepatitis C would make an excellent subject for the "For Dummies" series. Apparently, Wiley Publishing thought so too.

Living with Hepatitis C for Dummies, by Nina L. Paul, PhD, is like others in the "For Dummies" series, complete with its trademark black and yellow cover. The author has a research background and an easy to understand writing style. This book is informative, thorough and upbeat. Dr. Paul covers all aspects of HCV, such as diagnostic tests, treatment and transmission. Her description of the hepatitis C virus and the immune system is well done. *Living with Hepatitis C* has chapters on liver transplantation, building a medical support team as well as complementary and alternative medicine.

The strongest part of the book is "Living a Good Life with Hep C." Paul offers concrete suggestions about nutrition, sleep, support, exercise, relationships, the workplace as well as other important aspects of wellness. She uses lists, tips, tables, and diagrams throughout the book. Specific groups of people with hepatitis C, such as children, veterans and those in prison are briefly addressed. The chapter for family and friends is packed with wisdom.

The weakest part of *Living with Hepatitis C for Dummies* is management of HCV treatment-related side effects. I would have preferred to see a chapter about side effect management rather than "Ten Tips for Vacationing with Hepatitis C." Also, if there was a good explanation of portal, periportal and bridging fibrosis, I could not find it. A glossary would have been helpful, but these are not typically included in the "For Dummies" books.

The strengths of this book far outnumber its weaknesses. Although a valuable resource for everyone, *Living with Hepatitis C for Dummies* is a perfect book for people who are new to the subject. I recommend it for anyone needing a general introduction to the world of HCV.

Living with Hepatitis C for Dummies

By Nina L. Paul, PhD

Wiley Publishing, Inc. 2005

292 pages

\$16.99 U.S.

HCV Advocate October 2005

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U.S. Warns of Dangers From Patch Used for Pain

By Denise Grady from *The New York Times*, 7/16/05

The government warned yesterday that painkilling skin patches could cause drug overdoses and said it was investigating reports of serious side effects and 120 deaths that might have resulted since 1990. A spokeswoman for the FDA said that the investigation was still going on and that it was not known whether the product actually caused the deaths and other problems reported in users.

The patches, containing the narcotic fentanyl, are marked under the name Duragesic by Janssen, a company owned by Johnson & Johnson. A generic version was put on the market in February by Mylan Laboratories. The patches are intended for people with moderate to severe chronic pain that require treatment around the clock for an extended period of time and that cannot be controlled by other narcotics alone, the FDA and the manufacturer say. Only those already tolerant of narcotics, as some cancer patients are, should use the patches. People recovering from surgery, or suffering from short-term pain for other reasons, should not.

The advisory warns that the patches must be used exactly as prescribed and that doctors and patients must be alert for signs of overdose like breathing difficulties, extreme tiredness and feeling of faintness or dizziness. An overdose can cause a person to stop breathing; taking off the patch will not reverse the effects because the drug has already built up in the person's system and may continue to be absorbed from the skin for 17 hours or more.

The advisory notes that people wearing the patches may suffer overdoses or other serious side effects if they drink alcohol, have an increase in body temperature or are exposed to heat from sources like heating pads, electric blankets, heat lamps, saunas, hot tubs or heated water beds. Certain medicines, including antifungals and some drugs used to treat HIV, can lead to fentanyl overdoses in people wearing the patches.

In June, Janssen sent a warning letter to doctors stating that deaths and other serious medical problems had occurred in people who were accidentally exposed to Duragesic by sitting on a patch or touching it while putting it on someone else. In addition, a patch accidentally stuck to a child who was hugged by an adult who had been wearing it; the company did not say whether the child survived.

New Strategy Shows Promise in Treating Hidden HIV Infection

By Emma Ross; From Associated Press 8/11/05

In a recent preliminary study, the anticonvulsant drug valproic acid was used to awaken dormant HIV, providing hope for an eventual treatment to eradicate it from the body.

Current HIV drugs only work when HIV multiplies, which only occurs when infected cells are activated. Many cells remain HIV-infected but not activated. Only if every dormant virus was flushed out, or every dormant cell wiped out, could patients become virus-free and stop taking medication for the rest of their lives, say experts.

Other drugs that decreased the latent pool of virus have been either too weak or had toxic side effects. Valproic acid shows more promise, said Dr. Warner Greene, director of the Gladstone Institute for Virology and Immunology at the University of California-San Francisco. Greene was not involved in the study but conducts similar research. "It's a first baby step, showing that maybe the use of [this type of drug] – far more likely in combination with one or two other agents – might be a viable approach for tackling this latency problem," said Greene. "This idea, if we could ever do it, is to purge every latently infected cell. Treat patients for probably two or three years, they'd be able to come off their antiretroviral therapy and they'd be virus-free."

In the study, Dr. David Margolis, of the University of North Carolina-Chapel Hill, and colleagues tested valproic's effect in four patients taking twice-daily doses over three months. The study found that the pool of dormant HIV-infected cells was cut by 75 percent in three of the patients. "It's a significant conceptual move forward," said Margolis, who believes the drug reactivates the virus inside dormant cells, either waking up the cell with it or killing it.

Others think talk of a cure is premature. "It didn't get all the cells," said Dr. Robert Siliciano, a professor of medicine at Johns Hopkins University in Baltimore. "That's probably because it's not really targeting the right mechanism for latency. It's got to be a 99.9999 percent reduction to be useful. When you stop the drugs, the virus explodes back so quickly, even if you had one latently infected cell left, in a matter of days you would be back to where you started from."

The full study, "Depletion of HIV-1 Infection in Vivo: A Proof-of-Concept Study," was published in *The Lancet* (2005). *HIV Notebook, Fall 2005*

Roche Raises Price of Anti-HIV Drug Fuzeon

By Tania Rodrigues

Swiss pharmaceutical company Roche has raised the wholesale acquisition cost of a one-year supply of anti-HIV drug Fuzeon (enfuvirtide) by 5%, said its U.S. biotech partner Trimeris, which co-developed the drug, reports the Dow Jones Corporate Filing. Following the increase, the drug's price stands at US \$1,850 for a 30-day supply, a Roche spokesman disclosed. However, the net cost of Fuzeon to the U.S. state AIDS Drug Assistance Programs (ADAP) will not increase, at least until the end of June 2006, based on an agreement with the ADAP Crisis Task Force, Trimeris said. According to the Securities and Exchange Commission (SEC) filing, Roche informed its U.S. wholesalers and specialty pharmacy distributors that it was increasing the price of several drugs, besides Fuzeon.

Significance: Under Trimeris collaboration agreement with Roche, the Swiss drug-maker holds the sole responsibility for the pricing of Fuzeon. This price rise, albeit not having an immediate impact on the agreement with the ADAP Crisis Task Force, is likely to fuel more controversy over Roche's pricing strategies. In 2003, the price set for Fuzeon was already viewed as a record price for a drug in this therapeutic area (see Switzerland: 24 February 2003: Roche Courts Controversy With Record Price for Fuzeon and Switzerland: 27 October 2003: Roche's Fuzeon Cost-Effective According to New Study). Reimbursement, or more specifically, the high price of the drug, remains a major barrier to sales growth, with the U.S. Center for Medicare and Medicaid Services recently revealing that Fuzeon will not be reimbursed under Medicare Part D. Fuzeon can be listed on formularies but new users must obtain prior permission (see United States: 28 June 2005: CMS Confirms Prescription-Drug Exclusions from Medicare Part D Formularies in US). However, cost remains an issue with little maneuverability, given the complex manufacturing process used to produce the drug, according to Roche and Trimeris (see Switzerland: 12 June 2004: Roche Touts Long-Term Efficacy of Fuzeon).

World Markets Analysis, October 7, 2005

Valencia University School of Medicine; Success factors for semen cleaning in men coinfecting with HIV and HCV vary

Success factors for semen cleansing in men coinfecting with HIV and HCV vary.

"Human immunodeficiency virus (HIV)/hepatitis C virus (HCV)-seropositive males can now father children safely, avoiding transmission risks to the mother and the children using sperm washing and nested polymerase chain reaction (nPCR) techniques. Nevertheless, we still lack enough data to determine the reasons why approximately 10% of the performed sperm washes remain positive, thus forcing the repetition of the treatment," investigators in Spain report.

"Semen quality in infected males is also essential to these procedures. We aimed to determine the predictive value of the semen parameters, sperm washing procedure and the infection status for the post-wash viral positivity, as well as the correlation between the semen and the disease features," said N. Garrido and colleagues, University of Valencia.

"Semen characteristics were evaluated in 136 samples provided from 125 males. We also included a control group of 125 males matched by age and length of sexual abstinence. At the time of semen retrieval, 70 of them were infected with HIV (45 also with HCV 64.3%), and 55 of them with HCV alone. nPCR for viral detection was performed in each sample."

"Thirteen out of 136 (9.5%) of the samples were positive for one or more viral detections (HIV RNA, HIV DNA and HCV RNA, when needed). From a total of 240 nPCR viral analyses, 16 were positive (6.6%). None of the seminal parameters were adequate to predict post-wash results, nor was a positive result dependent on the volumes used in the semen wash."

"A positive correlation was found between post-wash progressive motility and CD4 blood levels, as well as a negative correlation between progressive motility and time of evolution of the disease in HIV-infected males. Semen analysis, according to the World Health Organization criteria, of HIV- and HCV-affected patients showed no differences from that of non-infected males," researchers indicated.

"Moreover, low CD4 blood levels, and a long evolution of the disease do not negatively affect sperm motility," they concluded.

Garrido and colleagues published their study in *Human Reproduction* (Semen characteristics in human immunodeficiency virus (HIV)- and hepatitis C (HCV)-seropositive males: predictors of the success of viral removal after sperm washing. *Hum Reprod*, 2005;20 (4):1028-34).

For additional information, contact N. Garrido, IVI Valencia, Valencia University School of Medicine

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Valencia, Spain Nicolas.

The publisher of the journal *Human Reproduction* can be contacted at: Oxford University Press, Great Clarendon St., Oxford OX2 6DP, England.

Keywords: Valencia, Spain, AIDS, HCV, HIV, Hepatitis, Hepatitis C Virus, Hepatology, Immunology, Human Immunodeficiency Virus, Virology.

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AIDS Weekly & Law, August 4, 2005

HIV and Hepatitis Website

http://www.hivandhepatitis.com/recent/mctc/1110004_a.html This rather intimidating address leads to an easily navigated and informative website. The first thing to appear is the week's most important news story on HIV and/or hepatitis. In addition to reading the top news articles of the week, you can choose to explore many areas such as the database of antiretroviral drug interactions, or adverse reactions, or symptoms. There is also a library of articles on all aspects of HIV/AIDS.

Many websites represent the opinions and interests of a specific group. This one makes available a wide range of media sources—no editorializing, just a rather complete information resource.

An Attitude of Gratitude

It's that time of year. We're still recovering from our wonderful Thanksgiving feasts, and thinking fondly of the time we've spent with extended family. But even with Thanksgiving behind us, it's still an ideal time to reflect what we are grateful for in our lives, when we can appreciate what we have.

It's easy to pass through our busy daily lives and become swallowed up by problems. Problems, dilemmas and predicaments are inescapable. The attitude with which we face the problems is what is significant. Daily life supplies enough challenges, and to people living with a chronic disease, like a bleeding disorder, there are even more challenges. You can focus on how tiresome it is to live with hemophilia or you can choose to be grateful for everything that makes living with a bleeding disorder easier and less

burdensome. Attitude is a choice.

A list of things for which to be truly thankful:

- **Factor** – Be grateful for the relief and prevention of bleeds that factor provides.
- **Joint Replacement Surgery** – Be thankful for the technology that allows the development of joint prosthesis. The pain relief from joint replacement can be tremendous.
- **Excellent Doctors** – Be thankful for the skill, expertise and care given by doctors.
- **Physical Strength**- Be thankful for the physical strength, stamina and endurance you have.
- **Emotional Strength** – Be thankful for your ability to cope, and for courage and determination.
- **Mutual understanding from friends** – Be thankful for the camaraderie of friendship and the effort made by friends to understand and to help.
- **Love and support from family** – Be thankful for family and the unconditional love and support that is abiding.

The physical and emotional changes which come with having a chronic disease need not destroy your zeal for life. Not all change must be negative. Make your life the best it can be. Be grateful for what you have. After all, part of gratitude is attitude.

-generously modified from the article, **An Attitude of Gratitude**, by Carol & Richard Eustice at: http://arthritis.about.com/cs/inspiration/a/gratitude_p.htm

HAV Vaccination: Real World

Practices Alan Franciscus, Editor-in-Chief

People living with hepatitis C (HCV) are at risk for severe complications if they contract another liver disease such as hepatitis A (HAV). Infection with more than one hepatitis virus is called superinfection and could potentially lead to liver failure and death. For this reason, the HAV vaccine is recommended for people with chronic hepatitis C who have not been previously infected with HAV. Agencies that endorse HAV vaccination in HCV positive individuals include the World Health Organization (WHO), the National Institutes of Health (NIH), the United States Veterans Health Administration, the American Association for the Study of Liver Disease (AASLD), and others. However, despite these recommendations, little is known about real world HAV vaccination practices in HCV positive individuals.

As previously stated, hepatitis A superinfection with hepatitis C can lead to severe health consequences

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that could lead to death. In one study by Vento et al., conducted in adults with chronic hepatitis C, it was found that 41.2% of patients with acute HAV superinfection developed acute liver failure, and, tragically, 35.3% died. These deaths could have been avoided by vaccinating hepatitis C positive individuals against HAV.

This article will focus on a recently published article that appeared in the September 2005 issue of *Hepatology* by Shim et al., titled "Susceptibility to Hepatitis A in Patients with Chronic Liver Disease Due to Hepatitis C Virus Infection: Missed Opportunities for Vaccination."

In the study by Shim et al., the records of every patient at 2 main VA medical centers in New York, NY and Brooklyn, NY were reviewed. The people (1,193) who tested positive for the HCV antibody and HCV RNA (viral load) were followed for the period from January through December 2000. Detailed patient characteristics (age, sex, race/ethnicity, active or previous injection drug use, if they were homeless, sex with same sex partners, history of sexually transmitted diseases (STD), presence of cirrhosis and active psychiatric disease) were collected. The follow-up data through June 30, 2002 was collected and compared to electronic medical records for each person to establish who actually received the HAV vaccination. The findings were validated by a review of the computerized pharmacy database. HAV vaccination was defined such that patients who received at least one HAV vaccine dose out of the series of two doses required for full protection were also considered to have been vaccinated.

It was found in this large retrospective study that 640 (53.6%) individuals were tested for HAV antibody of whom 317 (49.5%) were HAV antibody negative or susceptible to infection with HAV. Only 94 or 7.9% of the 1,193 patients received one or more doses of the HAV vaccine including 85 or 26.8% of the 317 patients who were susceptible to infection with HAV.

Of the 94 patients who were vaccinated, 45 received only one dose of the HAV vaccine; 41 received two doses and 8 received three doses or more (of the two doses required for protection). Three individuals in the unvaccinated group, but who had been tested and were found to be HAV antibody negative, later acquired HAV infection and one person died of liver failure.

Since the study was only performed in a VA Center setting among mostly male patients, the authors noted that lessons learned from their study may not be able to be duplicated in other clinical settings or in women. However, it was also pointed out that the strength of the study was the large number of HCV infected patients, the availability of long term follow-up data, and the use of various databases such as the computerized patient

record system and pharmacy database to verify information.

The authors concluded that "despite published recommendation to vaccinate against HAV in patients with chronic HCV infection, we found that HAV testing and vaccination rates were low in clinical practice." The authors also noted that clinician and patient barriers to vaccination need to be addressed given the high risk of acute liver failure from infection with acute HAV infection in persons with a chronic liver disease such as HCV.

It is apparent from this study that more education and awareness of the risks of superinfection with acute HAV infection in persons with chronic hepatitis C needs to be addressed. Furthermore, the possibility of severe complications of HAV superinfection is yet another good reason why it is so important to increase public awareness and testing of hepatitis C so that people who are at risk for superinfection with HAV can be identified and receive appropriate medical care.

Hepatitis A - At a Glance

Hepatitis A (HAV) is spread through contact with food and water contaminated by the feces of an HAV infected person. The hepatitis A virus is spread when the feces (stool) of an infected person are ingested. It can also be spread by sexual contact (anal/oral), changing diapers and, although uncommon, can be spread by injection drug use.

People or groups at risk for getting and spreading HAV include workers and people in day care centers and long-term care facilities, such as nursing homes. International travelers are also at risk for HAV if they travel to countries that do not have good sanitation or water processing facilities. HAV outbreaks are also seen in restaurants when food handlers do not follow proper hygiene practices (washing hands thoroughly) and contaminate food and water.

To prevent transmission of HAV, adults and children must wash hands thoroughly, especially after using the toilet or changing diapers. People actively infected with HAV should avoid preparing food for others. Clean up spilled blood or body fluids with a 10:1 bleach solution (10 parts water to 1 part bleach). Wear gloves when touching blood, body secretions, or any cuts or sores. Do not share razors, toothbrushes, or needles. Practice safer sex including latex condoms and latex or plastic barriers for anal/oral sex.

Symptoms of HAV include mild flu-like symptoms (fever, fatigue, nausea, vomiting, loss of appetite, and general malaise), jaundice (yellowing of skin and whites of the

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AASLD 2005: Part 1

Liz Highleyman

The 56th annual meeting of the American Association for the Study of Liver Disease (AASLD) took place Nov. 11-15, 2005, in San Francisco. AASLD is the premiere liver conference in the U.S., and most new and important information about liver disease is presented at this meeting. The reports in this issue of the HCV Advocate will focus on an important new epidemiological study of HCV, experimental HCV therapies, and HIV/HCV coinfection. Look for further AASLD coverage in the Jan. 2006 issue.

How Common is Hepatitis C?

It is usually reported that about 3.9 million people in the U.S. have contracted hepatitis C, 2.7 million of whom are living with chronic infection. This estimate is based on data from a household study, the National Health and Nutrition Examination Survey (NHANES).

But Brian Edlin, MD, from Cornell University's Weill Medical College presented evidence at AASLD suggesting that this figure is an underestimate (*Abstract 65122*).¹ NHANES does not count several groups, some of which have higher rates of hepatitis C than the general population:

- Incarcerated people (nearly two million, with an estimated HCV rate of 32%)
- Homeless people (more than 800,000; estimated HCV rate 35%)
- Patients in hospitals (approximately 650,000; estimated HCV rate 17%)
- Nursing home residents (more than 1,600,000; estimated HCV rate 5%)
- Active-duty military personnel (about 1,400,000; estimated HCV rate 0.5%)

Edlin derived his population numbers from the U.S. census, the Centers for Medicare and Medicaid Services, the Bureau of Justice Statistics, and several studies published in the medical literature. He then multiplied these numbers by the estimated HCV prevalence in each group, using averages of rates seen in various studies.

Altogether, Edlin calculated that 800,000 to 1.2 million more people have contracted HCV than usually reported – for a total of about 5 million. Using accepted rates of spontaneous clearance (about 25%), 3.4 million of them currently have chronic hepatitis C. National HCV prevalence may be even higher, he suggested, because the number of unstably and sporadically housed people may greatly outnumber those who are

homeless at the time of any survey.

Edlin concluded that household surveys are “an incomplete source of information about socially marginalized populations.” Using the most accurate estimate is important, he stressed, since basing public health projections on the widely reported lower figure “may underestimate the burden of liver disease we will see in coming decades.”

HIV/HCV Coinfection News

Given that one-third or more of HIV-positive people also have HCV, and 10% or more of individuals with hepatitis C also have HIV, coinfection is a growing concern for hepatologists and HIV specialists alike.

Sexual Transmission

The issue of sexual transmission of HCV remains controversial. Mark Danta from London and colleagues presented further data showing that a variety of factors related to sexual activity and drug use have contributed to a recent cluster of more than 200 cases of apparently sexually transmitted HCV among gay HIV-positive men in the southeast U.K. (*abstract 67040*). A molecular analysis of patients' HCV genomes revealed several distinct clusters, providing evidence for common sources of transmission. The researchers also conducted a case-control study in which 60 HIV-positive gay men with acute (recently acquired) hepatitis C and 130 matched HIV-positive/HCV-negative control subjects completed questionnaires about their risk factors during the past 12 months.

The men with acute hepatitis C were more likely to inject drugs (17% vs 7%), but the rate was low compared to other HCV-infected populations. Patients with acute HCV were significantly more likely to have engaged in unprotected receptive or insertive anal intercourse, fisting, anilingus (rimming), use of sex toys, SM, and group sex. Further, the coinfecting men were more likely to meet partners in sex clubs or bathhouses (about 4% vs 1%) or on the Internet (49% vs 8%); had more sex partners in the past year (30 vs 10); were more likely to have a history of sexually transmitted disease (92% vs 78%); more often used “club drugs” and had sex under the influence of drugs (92% vs 62%); and were more likely to have shared paraphernalia for intranasal drug use (79% vs 49%). While all these factors were linked to a higher HCV rate, Danta stressed that it was

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Medicare's New Drug Program Creates Challenges

By David Munar, AIDS Foundation of Chicago

A dizzying array of rules, options, and costs await the 41 million Medicare recipients under the new prescription drug program rolling out later next year.

For people with HIV, the program offers both a new opportunity to obtain prescription drug coverage and a maze of pitfalls and barriers that threaten to undermine continuous access to lifesaving medications—the hallmark of quality HIV/AIDS care.

Medicare is the nation's healthcare insurance program for retired seniors and disabled workers, which until now has only covered inpatient services (hospitalizations) and, for an additional monthly cost (called a premium), outpatient services. Oddly enough, the basic program has not previously offered prescription drug coverage, creating a serious gap for its millions of beneficiaries. To obtain their medications, many beneficiaries have purchased supplemental private coverage, if they could afford it, or turned to Medicaid (run by their state) if they are extremely low income.

With the 2003 enactment of the Medicare Modernization Act, that landscape is changing. Beginning in October (and through May), Medicare patients will have to choose prescription drug coverage through a complicated new program known officially as "Part D." Helping the estimated 85,000 people with HIV on Medicare navigate the new program and understand their options and obligations will be a monumental task for case managers, benefit counselors, and AIDS service organizations. It's worth noting that only those eligible for Medicare will be affected—essentially people who receive a monthly Social Security Disability Income (SSDI) check and not those who receive only a Social Security Income (SSI) check.

Part Derby—History

The legislation that created Part D drew heavily on recommendations from influential pharmaceutical and insurance lobbyists and modeled the program to resemble insurance products sold in the private sector. In fact, the federal government is providing generous subsidies to health insurance companies to make prescription drug plans available across the country. Approved plans, to be announced on October 15, can decide what drugs to cover and how to structure their benefits, within the parameters established by the federal Centers for Medicare and Medicaid Services (CMS). Federal officials have stated publicly that plans will be expected to provide most HIV antiretroviral medications, which is welcome news. How plans differ in terms of extra costs and access to other needed medications will not be known

until participating plans are publicly announced.

Most Medicare recipients will have until May 15, 2006 to enroll in Part D and must pick a plan offered in their area. They will have the option to change plans only once a year. Enrolling in Part D is optional, but a penalty (higher premiums) will be assessed on those who enroll after May 15, 2006, unless they already have prescription drug coverage "of equal or greater value."

Part Daunting—Out-of-Pocket Costs

An important way to measure the value of Part D for each beneficiary will be to assess both what the program will offer in terms of benefits and what it will cost. Congress devised a peculiar cost structure for beneficiaries. Most people will have to pay a monthly premium estimated at \$37 a month (the cost will rise each year); the first \$250 of their drug costs; 25% of their drug costs between \$250 and \$2,250; 100% of their drug costs between \$2,250 and \$5,100 (this is the so-called "donut hole"); and then 5% of drug costs beyond \$5,100 for a given year. In other words, a beneficiary with high drug costs (like beneficiaries with HIV) will have to pay \$3,600 out-of-pocket (not counting monthly premiums) before Part D picks up 95% of drug costs. The cost calculator re-sets each year.

What does this all mean for the average person with HIV? The individual cost burden is higher for people with lower incomes and/or high drug costs.

Lisa

Consider, for example, Lisa's situation. Lisa is a retired nurse's assistant whose annual income from SSDI and investments is \$28,716 (\$2,393 per month). Her drug costs for Trizivir, Kaletra, and a cholesterol lowering medication are around \$15,000 per year (\$1,250 per month). Her annual out-of-pocket costs (including monthly premiums) would be approximately \$4,539 (16% of her gross income). Out-of-pocket costs would rise to \$1,287 in months three and four during the "donut hole" period (more than half her monthly gross income). She would pay \$99.50 in months 6 through 12.

The financial burden becomes even steeper on individuals with lower incomes. If Lisa's income were \$15,000 a year (\$1,250 per month) and her drug costs remained the same, she would pay more than she receives in months three and four. The annual cost of the program would be 30% of her gross income.

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HealthWise: Influenza

Lucinda K. Porter, RN, CCRC

One of the worst disasters in history was not a war, hurricane, earthquake, or tsunami. It was the influenza pandemic in 1918-19. It is called a pandemic because it affected the entire world - 20 to 25% of the world, in fact. Sometimes called the Spanish flu, it caused the death of 20 to 50 million people worldwide. More people died in a single year from this than from 4 years during the 14th century's bubonic plague. In the United States, 675 thousand Americans died. This is 10 times the number of Americans who had just been killed in World War I.

Public health officials warn us that the world is at risk for another pandemic. Immunizations are one of the best defenses against diseases and epidemics. Contrary to popular myths, vaccination does not give us the disease. It protects us.

Influenza, also known as the "flu" affects an average of 5% to 20% of the United States' population. According to the Centers for Disease Control (CDC), every year more than 200,000 people are hospitalized and about 36,000 people die from flu-related complications. Infants, young children, elderly and people with certain health conditions are at the greatest risk for serious complications.

The best way to prevent passing on the flu is by not getting it. The best way to avoid the flu is through vaccination. Unfortunately, this year we may have another vaccine shortage. The impact of Hurricane Katrina on vaccine supplies is not known yet. We can do our part by learning if we should or should not get a flu shot and acting on that information.

Flu shots are available in October. The CDC advises that those at high risk get the first round of flu shots. If there is no vaccine shortage, flu shots will be available for everyone beginning October 24, 2005. Those given first priority are:

- People aged 65 years and older
- Residents of long-term care facilities
- Children aged 6–23 months
- Children from 6 months to 18 years of age who are receiving long-term aspirin therapy
- Pregnant women
- Health-care personnel who provide direct patient care
- People living with or caring for children less than 6 months of age
- People aged 2–64 years with chronic health conditions. These include asthma or other chronic lung

problems, heart or kidney disease, cancer, diabetes, sickle-cell disease, HIV or other immune compromised conditions such as those requiring the use of corticosteroids, and neuro-muscular conditions (such as multiple sclerosis, Alzheimer's and spinal cord injuries)

Missing from this list is specific mention of those with chronic hepatitis C infection (HCV), cirrhosis, and those undergoing HCV treatment. Having HCV is not an automatic qualification. If you have complications from HCV, or you are waiting for a liver transplant, your medical provider may recommend that you have an early flu shot.

Receiving HCV treatment is not an automatic qualification for a flu shot. Some experts believe that patients have a lower flu risk during treatment because interferon stimulates the immune system. Others feel that since interferon lowers the white blood cell count, infection risk may increase. Patients can be vaccinated during treatment, it is just not known if they should be given priority. Treatment may provide an excellent time to get a flu shot since interferon stimulates the immune response.

Those who should not get a flu shot are:

- People who have a severe allergy to chicken eggs
- People who have had a severe reaction to a flu shot in the past
- People who developed Guillain-Barré syndrome (GBS) within 6 weeks of getting a flu shot in the past
- Children under 6 months old
- People with a moderate or severe illness with a fever. These people can be vaccinated once their symptoms lessen.

There are two types of vaccines. The standard flu shot contains "killed" virus. The only "side effect" is a sore, possibly red injection site. There is a nasal-spray vaccine that contains live, weakened virus. This nasal spray form is not subjected to prioritization and can be given to healthy people between 5 and 49 years old and by those who are not pregnant. Unlike the flu shot, the spray can cause mild flu-like symptoms. Both types provide flu protection approximately 2 weeks after being administered.

Sometimes people have a cold and they use the expression, "I have the flu." This is a common mistake.

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HealthWise: Smoking and Hepatitis C

Lucinda K. Porter, RN, CCRC

There is an important event on the third Thursday of every November. No, I am not talking about the U.S. holiday, Thanksgiving. That is on the fourth Thursday. The third Thursday is the American Cancer Society's (ACS) Great American Smokeout. Since 1977, the ACS has waged a campaign encouraging smokers to refrain from smoking for one day. The ACS hopes that one day of abstinence from smoking will lead to a lifetime of freedom.

Freedom describes precisely one of the benefits gained after quitting smoking. Freedom from a life dependent on managing a habit that the majority of smokers wish they did not have. I know the feeling. I was a one to two pack a day smoker starting in my adolescence and quitting in my early thirties. Quitting smoking was the single hardest thing I ever did. As far as challenges are concerned, it tops my list of accomplishments, ahead of having and raising a child, nursing school, a year of HCV treatment, and a solo climb of Mount Whitney.

When I quit smoking, I vowed I would not become a villainous reformed smoker. I believe I have kept my promise. I am sympathetic to the hideous and all-encompassing nature of this addiction. However, compassion does not mean silence and if there are any smokers still with me at this point, I hope you will consider quitting.

I doubt I need to mention that smoking and health do not mix. Smoking leads to the death of one in ten people worldwide. There is evidence that smoking may lead to more HCV-related inflammation. Nearly a half a million people die annually in the U.S. because of smoking. That is a half a million preventable deaths. Compare that to 8,000 to 12,000 HCV-related deaths and it is clear why tobacco dependence is such a problem. More people die from secondhand smoke (35,000) than from HCV.

Freedom and health are only two of the rewards gained after quitting smoking. There are economic gains as well as the chance to be a positive role model for our children. The guilt from harming the lungs of our loved ones with our secondhand smoke is a burden that is lifted after quitting. Ostracism and standing out in the cold in order to smoke is another incentive for quitting.

In spite of all the reasons to quit, people continue to smoke. That is because it is hard to quit. Withdrawal is very unpleasant. Some claim that smoking is a way to cope with stress. Some have had trouble quitting in the past. Smokers are afraid to gain weight. There are argu-

ments showing the flaws in these reasons. For instance, the average weight gain is less than ten pounds. Are yellow teeth and premature aging more attractive than a temporary weight gain? There are ways to avoid or minimize weight gain. Besides, a well-nourished alive body seems so much better than a thin but dead skeleton.

Just like drugs and alcohol, there is help for tobacco dependence. There are many free resources for help in quitting (see *Resources*). Medicare offers smoking cessation coverage for some individuals. Many health insurance companies cover treatment for it. There are books, groups, telephone services, and online support. Acupuncture, acupressure, hypnosis, biofeedback, massage, and stress reduction may also help.

Experts agree that success is most likely to occur with the use of simultaneous tools. These include prescription and non-prescription interventions, counseling and support. Studies show that people who seek outside help are more likely to quit smoking permanently than those who try to quit on their own.

People can and do quit on their own. Whether you do this alone or with support is your choice, with "choice" being the important word here. Has the addictive nature of tobacco robbed you of the freedom to choose health over smoking? If you are ready to reclaim your freedom from cigarettes, I suggest you make a plan. The resources at the end of this article can help you formulate a plan. It has been said, "failing to plan is planning to fail." Make a plan, stick to it and you increase your chances of success. If the plan does not work, make a new plan. Never give up. The average smoker has five to seven attempts to quit before doing so permanently.

Seven minutes of life is lost with each cigarette that is smoked. You do the math. Life is short enough. Mark your calendars. The next Great American Smokeout is November 17.

Resources

For more resources and information, look in the HCV and Wellness Fact Sheet section - www.hcvadvocate.org

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HealthWise: Influenza—continued

Although both are caused by viruses, the flu is more severe than a cold.

The CDC lists the following symptoms of the flu:

- Fever (usually high)
- Headache
- Extreme fatigue
- Dry Cough
- Sore throat
- Runny or stuffy nose
- Muscle aches
- Intestinal problems such as nausea, vomiting and diarrhea

The flu travels from person to person, usually by coughing and sneezing. A good way to get the flu is by touching your nose, eyes or mouth after touching something contaminated with the virus. Healthy adults can pass on the flu to others a day before they show any flu symptoms and for up to 5 days after they become ill. This means you can pass on the flu before you even know you have it.

There are steps you can take to protect yourself and others from the flu:

- Keep your distance from people who are sick
- If you have the flu, avoid close contact with people
- If you are sick, stay home from work, school and other public places
- Cover your mouth with tissue when you cough or sneeze
- If you do not have tissue close by, turn your head and cough into your upper sleeve
- Properly dispose of used tissue
- If you have the flu, wash your hands before touching food or objects that other people may use
- If you don't have the flu, wash your hands after touching publicly shared objects
- Clean publicly shared items, such as telephones, keyboards, and faucet handles
- If soap and water are not available, use sanitizing wipes or gels to clean your hands
- Keep yourself healthy by developing good sleeping, eating, and exercise habits

If you do get the flu, be sure to rest and drink plenty of liquids. To reduce fever, stay cool, but not cold. Acetaminophen, removing layers of blankets and clothing, and lukewarm sponge baths can provide relief. Call your medical provider if you cannot get symptoms under control, such as fever, vomiting, or diarrhea. Since you can pass this on to others, call for advice and let your medical provider determine if you need to be seen.

There are antiviral medications that can reduce the severity of the flu. These are effective if taken within the first 48 hours of the flu. Call your medical provider as soon as you show signs of the flu and discuss whether or not antiviral medication is appropriate for you.

Know your flu risk. If you are advised to, get a flu shot. If you are not at risk, wait until those who need it are vaccinated first. If there is leftover vaccine, you may have a chance to get a flu shot later in the winter. Flu shot or no flu shot, remember to take good care of yourself.

For more information: www.cdc.gov/flu

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HealthWise: Smoking and Hepatitis C— continued

- American Cancer Society (ACS) – www.cancer.org Toll free: 1-800-227-2345; A practical and user-friendly web site for those wanting help with tobacco addiction. A good place to begin is to type “guide to quitting smoking” in the search box.
- American Lung Association (ALA) – www.lungusa.org Toll free 1-800-586-4872; Click on “tobacco control” for information about tobacco. ALA has an online tobacco cessation program called “Freedom from Smoking” along with lots of useful tools and information.
- National Institutes of Health’s (NIH) Medline-Plus www.nlm.nih.gov/medlineplus/smokingcessation.html and www.nlm.nih.gov/medlineplus/smoking.html. Toll call 1-301-496-4000; Medline is a service of the NIH and the National Library of Medicine (NLM). These web addresses link to an enormous amount of information about tobacco and smoking, much of it focused on quitting. Also from the NIH www.quitsmoking.com/clearingair.htm
- SmokeFree.Gov - www.smokefree.gov National Network of Tobacco Cessation Quitlines Toll free 1-800-QUITNOW (1-800-784-8669) TTY 1-800-332-8615; A national network of U.S. government agencies offering phone and instant messaging assistance for tobacco dependence. Ask for your state or Canada’s toll free number for help quitting smoking.
- Access to a free booklet Clearing the Air: Quit Smoking Today (www.smokefree.gov/pubs/clearing_the_air.pdf)

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Medicare's New Drug Program Creates Challenges—continued

Part Deal—The Low-Income Subsidy

Some very low-income beneficiaries will receive what is being billed at “extra help” so that out-of-pocket costs are lower. Beneficiaries with incomes below 150% of the federal poverty level (\$14,355 for a single individual and \$19,245 for couple in 2005) and limited assets (such as investments or savings) can qualify for the Low-Income Subsidy (LIS). People who qualify for LIS pay lower premiums, \$1 to \$5 per prescription, or none at all based on their income, and become exempt from the “donut hole.”

People who are dually eligible for Medicaid and Medicare will be automatically enrolled in LIS. This includes people who receive Medicaid assistance to maximize Medicare benefits. All others must complete an LIS application form and meet eligibility criteria to receive the extra help. People who think they may qualify, and who are not dually eligible, will need to elect Part D, apply for LIS, and select a drug plan to receive Part D coverage.

Part Dizzying—True Out-of-Pocket Costs (TrOOP)

The architects of Part D designed the program to require “cost-sharing” so that beneficiaries bear responsibility for covering a portion of their drug costs. Cost-sharing is higher for individuals above 150% of poverty and lower—but not entirely eliminated—for the program's poorest members. For most recipients, cost-sharing is steepest in the donut-hole during which 100% of drug costs are borne by the beneficiary.

Beneficiaries receive the most generous coverage after surpassing the donut hole. At this level—called catastrophic coverage—the program pays 95% of a recipient's drug costs for the rest of the year.

The sum of expenditures needed to reach catastrophic coverage is known as TrOOP: True Out-of-Pocket Costs. Federal regulations define approved ways beneficiaries can receive assistance with meeting out-of-pocket costs that continue to count toward TrOOP. Beneficiaries may receive other forms of assistance but such expenditures do not count toward TrOOP.

What counts as TrOOP? Fully state-funded “State Pharmaceutical Assistance Programs” can help beneficiaries pay premiums, deductibles, and co-payments (including during the donut hole). All these expenditures count toward TrOOP. Other ways to meet TrOOP include when a family member, private organization

(including charitable organizations), or even a Patient Assistance Program pays incurred drug costs.

What does this all mean for the average person with HIV? Beneficiaries need to explore whether their state has an approved assistance program, and if not, whether one can be created (federal regulations limit what states can do if they don't already have a State Pharmaceutical Assistance Program).

For example, Illinois has established a program to help low-income beneficiaries pay Part D premiums, co-payments, some of the deductible, and some medications during the donut hole. These expenditures help beneficiaries reach the catastrophic level where coverage is most generous. These strategies also help the state maximize scarce healthcare dollars and promote better healthcare.

Part Dispiriting—ADAP

Many unanswered questions remain about the intersection of state AIDS Drug Assistance Programs (ADAP) and Part D. Earlier this year, CMS rejected calls by AIDS advocates to allow ADAP expenditures to count as TrOOP. While it appears ADAPs will be able to provide assistance to Medicare beneficiaries, ADAPs will have little incentive to do so as such expenditures virtually guarantee that recipients remain in the donut hole (no drug coverage) for the rest of the year.

Allowing ADAP expenditures to count as TrOOP would have helped already cash-strapped programs further stretch their budgets and provide continuity of care for a highly vulnerable population. It would have also provided a powerful incentive for states to invest in their ADAP with state dollars.

As such, some states (especially those with waiting lists) are moving ahead to remove ADAP recipients who qualify for Part D—a dangerous move for the health of these individual. Because most people assisted by or waiting for ADAP have incomes below 200% of poverty and high drug costs, their out-of-pocket expenditures will make Part D completely unaffordable.

With remarkable shortsightedness, federal officials indicated recently that they will require enrollment in Part D as a condition to receive ADAP (in states what don't exclude them altogether). This will essentially force a monthly premium upon one class of ADAP recipients and pave the way for new, arduous requirements to further diminish services to this vulnerable population.

In addition to ADAP appropriations advocacy, people

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Medicare's New Drug Program Creates Challenges—continued

with HIV/AIDS and their allies need to urge state officials to preserve ADAP benefits for eligible Medicare recipients, explore coverage for Part D premiums and deductibles, and enlist state support in advocacy to make Part D less onerous.

Part "Devil's in the Details"

It's not hard to imagine disabled and elderly recipients needing help understanding the program, their options, and how to avert a life-threatening gap in drug coverage. Because of the complexity of the program and the many variables for recipients at different income levels, Medicare recipients are encouraged to consult with a benefits specialist.

Medicare-eligible ADAP recipients and the dual eligible are especially encouraged to carefully plan their enrollment and use of Part D. Dual eligibles will be in a particularly precarious situation at the end of this year when their prescription drug coverage through Medicaid ends by law. They will need to rely solely on Part D for their medication needs.

Thankfully, their out-of-pocket costs will be lower than most Part D recipients and they will have the ability to switch plans at any time—an option not readily available to most recipients. Still, dual eligibles are among the poorest and sickest in the Medicare population and a gap in treatment could prove fatal.

Try the Project Inform Treatment Hotline for more information; call 1-800-822-7422.

Part Darwinism

In the best of cases, Part D will evolve into a more comprehensive and less-Byzantine program that provides affordable benefits to retired and disabled workers. But this will happen only if we remain committed and vocal about its shortcomings, and continue to press government officials for real and immediate remedies.

David Ernesto Munar is the AIDS Foundation of Chicago's associate director. Thanks to Tom Coburn of Health & Disability Advocates for help in preparing this article.

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HAV Vaccination: Real World Practices - continued

eyes), pale colored stools and dark urine. Many people have no symptoms, especially children.

When a person is infected with HAV the body's immune system will clear the virus on its own and the person will then be immune to catching HAV again. People who have been previously infected with HAV do not need to be vaccinated since their bodies have developed HAV antibodies to protect them. Generally, most people do not have any serious complications from HAV except people with pre-existing liver diseases such as hepatitis B or hepatitis C who may develop severe complications such as acute liver failure and possibly death.

The HAV vaccine is considered safe and effective. The two-dose vaccine is administered by injection, with the second dose given 6-12 months after the first. Most experts believe that the HAV vaccine will provide protection from HAV for at least 10 years and longer. HAV vaccines are manufactured by Glaxo-SmithKline (Havrix) and Merck & Co. (Vaqta). There is also a combination HAV and HBV vaccine available called Twinrix made by Glaxo-SmithKline.

For more information about HAV see HCSP's Fact Sheet – *Hepatitis A: What You Need to Know*.

Reference:

Michael Shim, Inessa Khaykis, James Park, and Edmund J. Bini. Susceptibility to Hepatitis A in Patients With Chronic Liver Disease Due to Hepatitis C Virus Infection: Missed Opportunities for Vaccination. *Hepatology*, September, 2005.

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"difficult to tease out" how much each individual factor contributed. He recommended that education about safe sex and drug-sharing practices should be the focus of public health interventions for this population.

Interestingly, outbreaks of sexually transmitted HCV like the one in London and Brighton have not been seen in the U.S. Srigayatri Bollepalli and colleagues looked at HCV risk factors among HIV-positive and HIV-negative people in Arizona (*abstract 65573*). They found that injection drug use was the only significant risk factor that predicted HCV infection among HIV-positive men who have sex with men, and concluded that "[s]exual transmission of HCV among HIV[-positive] patients is extremely rare."

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Why HIV Drug Resistance Matters—continued

No combination completely stops HIV from reproducing, but treatment significantly lowers levels of all viral populations in the body, both wild-type and mutated virus. Just as wild-type virus is the most fit and most able to replicate, it's also the most sensitive to antiretroviral treatment.

When you have a viral load test soon after you begin treatment and see a dramatically lower number, most of that decrease is due to the effect of the drugs on your wild-type virus.

The flip side of wild-type virus's sensitivity to antiretrovirals is that any HIV in your body with certain mutations in the reverse transcriptase or protease enzymes has a survival advantage. Depending on the mutations, the drug can't bind to the enzyme and can't interfere with HIV's replication process.

This is called selective pressure. Drug-resistant virus is able to replicate despite the presence of the drug.

Even though there's less HIV in your body, the virus with the relevant mutation(s) can become the dominant strain over time. As the mutated virus continues to replicate, it makes copies of HIV with the same mutation and other mutations can also develop.

The Xerox machine

The HIV replication process is a bit like using a Xerox machine. You start with a nice, clear original of your document (the wild-type). You make a copy of the original and, in the process, you may copy a speck of dirt (a mutation) that's on the glass of the copier.

When you make a copy of the copy, that speck of dirt is copied, too. As you go on to make copies from each copy, the mutation continues to show up—along with many others. After a while, your original document has become an unreadable blur, complete with many Xeroxed specks of dirt (multiple mutations).

As discussed above, most mutations harm the virus, making HIV unable to complete the replication process (an unreadable blur). But other mutations severely limit a drug's effectiveness. The drug can no longer bind to the enzyme that HIV uses to replicate. As a result, the amount of drug-resistant virus increases and so does your viral load.

Drug resistance would usually happen very quickly if you took only one antiretroviral. For example, only one mutation (called the M184V) in the reverse transcrip-

tase enzyme makes HIV completely resistant to both Efavir (3TC, lamivudine) and Emtriva (emtricitabine). If you took either of these drugs alone, your virus would develop resistance within just a couple of weeks.

Resistance to the non-nucleosides is similar. One mutation (the K103N) in the reverse transcriptase enzyme can cause HIV to become highly resistant to all three non-nucleosides—Viramune (nevirapine), Sustiva (efavirenz), and Rescriptor (delavirdine). This is an example of cross-resistance. Depending on the mutation, if HIV develops resistance to one drug, it can be resistant to other drugs in the same class because of the same or similar resistance patterns—even if you've never taken those other drugs.

Some antiretrovirals require more than one mutation in the relevant enzyme to cause resistance to that particular drug. This is especially true with protease inhibitors.

Each antiretroviral is associated with at least one mutation—called the primary mutation—that causes the most drug resistance. Other mutations—called secondary mutations—sometimes make HIV less sensitive to a drug, but they don't usually cause complete resistance unless the primary mutation is also present.

As more mutations—both primary and secondary—occur, the likelihood of HIV becoming resistant to a given antiretroviral increases. The concept of multiple mutations can be difficult to understand. This is about when many of us throw up our hands in surrender. Some people dutifully track the primary and secondary mutations of every available antiretroviral and those that are in development, but it isn't necessary for everyone to do that.

You don't need all of that information in your head in order to make informed decisions about treatment or to develop treatment strategies. Coming up with good questions to ask your healthcare provider and knowledgeable advocates can be as valuable as memorizing the mutations that keep a drug from working.

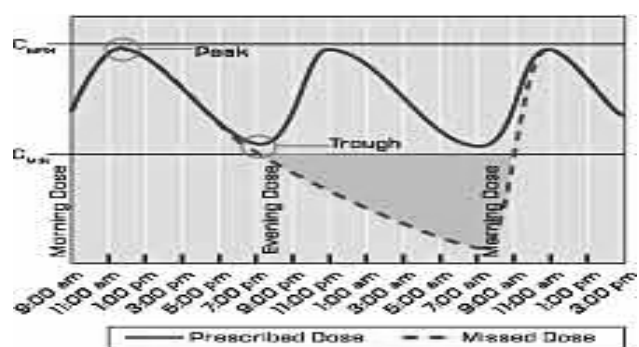
Now some good news. Having resistance to a drug doesn't necessarily mean that it can't still be useful. A drug that your virus is resistant to may still work for you, just not as well as it used to. There are varying degrees of resistance—partial and complete. And although mutations like the ones described above can cause complete resistance to one (or more) drug, mutated HIV is almost always sensitive to the other drugs in a combination. That's why we use

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multiple drug regimens.

HIV with specific mutations may be resistant to one of the drugs in your combination, but the other antiretrovirals in the regimen bind to the protease enzyme or to a different part of the reverse transcriptase enzyme and successfully stop HIV replication.

The bottom line concerning the development of drug resistance is that the less virus there is (the lower your viral load), the less likely it is that HIV will develop mutations.



Peak and trough levels

- This graph shows levels in your body of an antiretroviral that's dosed twice a day.
- The first dose is taken at 7 am.
- The amount of drug quickly rises to the highest level (peak) and then slowly begins to fall, reaching the lowest level (trough) before 7 pm—time for the next dose.
- Cmax is the maximum concentration of the drug in your blood. The Cmax should be low enough to keep short-term side effects like nausea or headaches from being intolerable.
- If drug levels rise above the peak (Cmax)—because you took more than the prescribed dose, for example—the side effects can be serious.
- Cmin is the minimum concentration of a drug in your body between one dose and the next.
- If drug levels fall below the trough (Cmin), the drug may not be effective. If drug levels drop too low, HIV can replicate freely and may develop resistance to the drug.
- When doses are taken at the right time, drug levels stay within the therapeutic range—between the Cmax and the Cmin—ensuring that there is enough drug in your body to slow down or stop HIV from reproducing.
- But if you miss your 7 pm dose (dotted line),

the trough level gets way too low (see the shaded area above).

- The chance of developing resistance to the drug increases greatly, since there isn't enough drug in your body to control HIV replication.

Adherence, absorption, and pharmacokinetics

Often, a combination stops working no matter how adherent a person is. This doesn't usually happen quickly—certainly nowhere near as quickly as it would if you took only one or two drugs. But it can still happen. When it does, some healthcare and service providers assume that the individual isn't adhering to his or her regimen. That's sometimes the case, but other things can also contribute to the development of resistance while you're on treatment.

If the amount of drug in your body falls below therapeutic levels—for any reason—you won't have enough of the drug in your system to stop or slow down HIV replication. The drug may inhibit wild-type virus from replicating, but it won't have an effect on HIV with mutations that keep that drug from binding to the relevant enzyme. This allows the mutated HIV to continue to reproduce, creating more viruses with that same mutation.

Poor adherence can cause drug resistance to develop. Adherence means taking your medications on time, taking the prescribed dose, and taking them the correct way (with or without food, for example).

After you take a dose, levels of the drug quickly rise to the highest level (peak) and then slowly begin falling, reaching the lowest level (trough) before you take the next dose. Skipping doses or not taking a drug correctly can cause the trough level to get too low.

When the amount of drug in your body falls below the trough level, the chance of developing resistance is increased since HIV can reproduce more freely and accumulate more mutations. (See graphic.)

Some people who are meticulous about adherence get very nervous if they miss even one dose, afraid that their HIV will immediately become resistant to their regimen. Missing the occasional dose isn't a big problem. Resistance develops when you regularly miss doses.

According to estimates, you need to be up to 95% adherent in order for your regimen to be most effective. This degree of adherence is very high. For example, if you're on a twice-a-day regimen, it means missing fewer than four doses a month. And if you're on a

once-a-day regimen, it means missing one dose a month—at most.

Poor adherence can cause drug resistance and, possibly, cross-resistance, too.

If you have trouble sticking to your schedule, be honest with your healthcare provider about it. He or she may be able to prescribe a simpler regimen or help you come up with strategies that work for you. If not, in the long run it may be better for you not to be on antiretrovirals until the reasons for your difficulties with adherence have been addressed.

Poor absorption can also affect levels of a drug. If a drug isn't properly absorbed into your bloodstream, drug levels can be too low. This would allow HIV to reproduce without interference and, in the process, accumulate drug-resistant mutations.

If you vomit or have diarrhea shortly after taking your dose, for example, the drug you just took could be expelled from your gut right away, reducing or eliminating the amount of drug absorbed.

As mentioned above, some antiretrovirals have food restrictions, most of which are necessary for the drugs to be absorbed properly. If these food restrictions aren't followed, drug levels can become too low to be effective. Most antiretrovirals don't have any food restrictions these days, but some do. For example, both Kaletra (lopinavir/ritonavir) and Viracept (nelfinavir) should be taken with a meal or light snack. Reyataz (atazanavir) should be taken with food, ideally a complete, nutritious meal.

Drug absorption can also be reduced if you have an intestinal infection. So if you're having nausea, abdominal pain, constipation, diarrhea, or any other symptoms of a possible infection, have it checked out.

Pharmacokinetics—the way that a drug is absorbed, distributed, metabolized, and eliminated from the body—can also affect the development of HIV drug resistance.

Some people process drugs faster or slower than other people do, which can speed up or slow down the rate at which a drug clears your body. So if two people take the exact same dose of a drug, the level of drug may be higher in one person than it is in the other one. Factors that can contribute to this include weight, height, age, and, possibly, race and gender.

We all know that people metabolize food differently—some of us eat as much as we want and stay thin, while other people carefully watch their diet and continue to gain weight. These differences in metabolism are similar to the way we process other substances,

including drugs.

The prescribed dose of an antiretroviral is based on the dose that was found to be safest and most effective in clinical trials for *most* trial participants. Some people may be able to take a lower dose and keep their viral load low or undetectable, while others might need a higher dose to get the same response. There's a lot we don't know about this issue, including how to figure out who may need a dose that's lower or higher than the one that's prescribed.

Finally, many over-the-counter and prescription medications, illegal drugs, herbs, vitamins, and supplements interact with a lot of the antiretrovirals and shouldn't be taken together. Many antiretrovirals also interact with each other. Interactions are complex. Some lower antiretroviral drug levels, which could allow the development of mutations. Pay attention to possible interactions and tell your provider about everything that you're taking.

Drug resistance when stopping treatment

People sometimes stop treatment—because of toxicity, because another health problem requires a treatment interruption, because they've been responding well and decide to discontinue therapy for a while, or because they're just plain tired of taking medication. If you stop treatment for *any* reason, work closely with your healthcare provider. Careful planning is important.

Depending on your regimen, if you stop all of your antiretrovirals at once, your virus could develop resistance to one or more of the drugs you were taking. This is most likely to happen if one of your drugs has a long half-life, meaning that drug levels stay high in your body for a long time after you take a dose.

For example, it can take up to three weeks for Sustiva (efavirenz) to be eliminated from your body after you stop taking it. If you stop Sustiva at the same time as you stop taking other antiretrovirals with shorter half-lives, it's like being on Sustiva by itself for a while. This gives a survival advantage to any virus in your body with the mutation that makes it resistant to Sustiva. During that short time after stopping your drugs, much of your HIV could become completely resistant to Sustiva and become resistant to Viramune and Rescriptor, too.

If you plan to stop a regimen that includes Sustiva, it's probably safest to stop the Sustiva one or two weeks before stopping the other drugs in your combination. It may also be possible to switch from Sustiva to a drug with a shorter half-life for a while before stopping everything.

Most antiretrovirals have relatively short half-lives—including most of the ones that are dosed once a day. But the half-life of Viramune, for example, is also long enough to require careful planning with your provider to avoid the development of resistance if you're stopping a regimen that includes that drug.

Figuring out if your HIV is drug-resistant

Regular viral load testing is the quickest way to tell whether treatment is working. If your viral load doesn't reach very low or undetectable levels within a few months after you begin treatment, it's a sign that something's off. Similarly, if an undetectable viral load becomes detectable and continues to go up while you're still on treatment, it's a sign that your regimen isn't working properly.

Viral load tests can't tell why your regimen isn't working. A detectable or increasing viral load doesn't necessarily mean that drug-resistance has occurred. But it could mean that you're at risk of developing drug resistance because there's more HIV replication going on. It's important to find out what's happening.

Viral load tests can't tell whether your HIV is resistant to one drug or, perhaps, your whole regimen. They can't tell which drug or combination may be most effective for you in the future, either.

This is where drug resistance testing comes in.

Resistance Testing

There are two types of drug resistance tests. Genotype tests look for specific mutations in the genetic structure of your reverse transcriptase and protease enzymes that could cause drug resistance. Phenotype tests measure the sensitivity of your HIV to specific antiretrovirals.

If your regimen isn't working, genotype and phenotype tests can help you and your provider figure out which drug or drugs your virus is resistant to and which ones you're most likely to respond to. This information can help you put together a new regimen that's likely to be effective.

Resistance tests are recommended in many situations. The Department of Health and Human Services' Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents suggest that HIV drug resistance testing should be done:

- If you're switching regimens because your current regimen is failing;
- If your viral load doesn't drop significantly

shortly after beginning treatment;

- Before starting treatment during acute (initial) HIV infection if the test is done within a few weeks after infection; and, possibly,
- Before starting treatment if you may have been infected with drug-resistant virus.

Avoiding HIV drug resistance

There are many ways that you can slow down the development of drug resistance:

The more you know about antiretrovirals, the better prepared you'll be to make treatment choices that can help you avoid drug resistance.

- The first regimen you take may be your best chance to suppress HIV the most and prevent drug resistance from developing.
- It's also important to take your medications as prescribed. Missing doses, not taking the right number of pills, not taking them at the right time, or taking medication on an empty stomach if it's supposed to be taken with food, can cause viral load to increase and drug-resistant mutations to develop.
- A good relationship with your healthcare provider can help with all of this. Communicate honestly with your provider. Ask questions, talk about any problems you're having, and tell him or her everything you're taking—including over-the-counter medications, herbs, and any other legal or illegal drugs.

Taking these steps can help avoid drug resistance from getting a chance to develop and leave you more options in the future.

Letters and Numbers

When we read about mutations that cause resistance to HIV drugs or look at the results of a genotype test, mutations are listed as a letter followed by a number and then another letter. This way of describing a mutation may seem confusing, but it's really very straightforward.

HIV is made up of proteins, and proteins are made up of amino acids. A codon tells us which amino acid is found at a specific spot in a protein chain. The reverse transcriptase and protease enzymes are protein chains made up of codons. The amino acids in a protein chain are numbered starting at one end of the chain.

With reverse transcriptase, for example, the 184th amino acid in the protein chain is called position 184. A mutation in reverse transcriptase means that a different amino acid has replaced the one that would be located at that place in wild-type virus. Each mutation

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is given a specific name to tell it apart from other mutations.

Why HIV Drug Resistance Matters—continued

The first letter in a mutation stands for the amino acid that's found at that position in wild-type virus. The number in the middle is the codon, where the mutation is located. And the final letter stands for the amino acid that's there instead of what we'd find in wild-type virus (the mutation).

Some examples:

- M184V is the mutation that makes HIV resistant to both Epivir and Emtriva. M184V tells us that there's a mutation at codon 184 in HIV's reverse transcriptase enzyme. At that position, the amino acid methionine (M) has been replaced by valine (V), another amino acid.
- K103N is the mutation that can cause resistance to all three non-nucleosides. K103N tells

us that there's a mutation at codon 103 in the reverse transcriptase enzyme. At that position, the amino acid lysine (abbreviated as K) has been replaced by asparagine, another amino acid (abbreviated as N).

- D30N is the most common mutation in the protease enzyme that can cause resistance to the protease inhibitor Viracept (nelfinavir). This mutation alone doesn't cause cross-resistance to other protease inhibitors. D30N means that there's a mutation at codon 30 in the protease enzyme. At that position, aspartic acid (abbreviated as D) has been replaced by asparagine.

James Learner was Director of Treatment Education at AIDS Community Research Initiative of America (ACRIA) until June of this year. He writes in various community-based publications and conducts trainings on HIV and viral hepatitis treatment issues. E-mail James_Learner@prodigy.net.

(Continued from page 3)

Early Results Show Pegasys Working - continued

An extensive clinical study programme has demonstrated its safety and efficacy in the broadest range of patients including those with difficult-to-treat disease. The benefits of Pegasys are derived from its unique 40 kilodalton branched PEG molecule which ensures sustained viral control for patients throughout the once-weekly dosing interval.

In addition to becoming the only treatment approved for hepatitis C patients who are co-infected with HIV, Pegasys is the only approved medication in the EU for hepatitis C patients with 'normal' levels of alanine aminotransferases (ALT) – a patient population previously thought not to benefit from treatment. Pegasys also been approved in over 40 countries around the world for the treatment of chronic hepatitis B including the EU, Switzerland, Hong Kong, New Zealand, Taiwan and Thailand and is the only pegylated interferon with this indication.

About Roche

Headquartered in Basel, Switzerland, Roche is one of the world's leading research-focused healthcare groups in the fields of pharmaceuticals and diagnostics. As a supplier of innovative products and services for the prevention, diagnosis and treatment of disease, the Group contributes on a broad range of fronts to improving people's health and quality of life. Roche is a world leader in Diagnostics, the leading supplier of medicines for cancer and transplantation and a market leader in virology. In 2004, sales by the Pharmaceuticals Divi-

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*The tragedy of life
is not that it ends
so soon,
but that we wait
so long to begin it.*

-W.M. Lewis

