

## Considering HCV Treatment? Know Your Genotype and Viral Load

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Alan Franciscus, Editor in Chief

In the past, many reports listed the overall sustained virological response (SVR) rates of HCV medications regardless of genotype—this was misleading because SVR rates are dramatically affected by genotype. Now, many physicians quote the pivotal trial results of currently available HCV therapies by genotype. However, a physician recently pointed out that the data now demonstrates that the amount of HCV RNA in the blood (viral load) also affects treatment response rates and commented that this is an important consideration to include along with genotype when interpreting HCV treatment response rates. In this article, I will review the current data available on sustained virological response rates broken down by genotype and viral load.

### HCV RNA – Viral Load

HCV Viral load tests measure the amount of HCV circulating in the blood. HCV viral load is expressed as either copies per milliliter of blood or as a standard unit of measurement called International Units (IU). HCV viral load tests are used to confirm active HCV infection, to predict medical treatment response, and to measure how well HCV medications are working.

A low viral load (LVL) is defined as <2 million copies/ml or 800,000 IU/ml and a high viral load (HVL) is defined as >2 million copies/ml or

800,000 IU/ml. Even though the pivotal pegylated interferon combination trials used different assays, in general a low viral load (LVL) is defined as < 2,000,000 copies/ml. or 800,000 IU/ml. For exact conversions by assay please refer back to the *May Advocate Newsletter*.

### Genotype

HCV has many different strains called genotypes. There are enough genetic differences to classify them into six major genotypes: 1, 2, 3, 4, 5, and 6. Genotype information is important when considering HCV treatment since some genotypes respond more favorably to medications than others with, non-1 genotype responding more favorably. Genotype also determines the length of therapy needed with genotype 2 and 3 requiring only 24 weeks in comparison to genotype 1 and 4 require 48 weeks. At this time there is not enough data to make definitive recommendations on other genotypes.

### Genotype and Viral Load

Breaking HCV down by genotype and viral load in the United States further clarifies the issues of treatment response rates: genotype 1 comprises 74% of the overall population—49.5% with a high and 24.5% with a low viral load. That means that two-thirds of patients with genotype 1 have genotype 1 high viral load or to look at it another way—one-half of the U.S population



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with hepatitis C have genotype 1 high viral load. This contrasts with 26% of the population with genotype non-1—of which 17.4% have a high and 8.6% have a low viral load.

Therefore in the United States, regardless of genotype, two thirds of the hepatitis C population has a high viral load.

### Standard of Care – PEG Plus Ribavirin

Pegylated interferon and ribavirin is now the standard of care for the treatment of hepatitis C. There are two available pegylated interferon combinations, Peg Intron (pegylated interferon alpha 2b – Schering Plough) plus Rebetol (Schering's branded ribavirin) and Pegasys (pegylated interferon alpha 2a – Roche) plus Copegus (Roche's

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# Websites

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Lucinda K. Porter, RN, CCRC

It is common for patients to use the Internet. The “Web” can be a source of useful as well as misleading information. The Internet should never replace medical advice, but it can sometimes enhance medical knowledge. This month’s article contains a compilation of some web sites that have made it to my “favorite” list. For those without Web access, many public libraries offer Internet service. Also, neither the HCV Advocate nor I endorse particular products or advertising connected with these web sites. If privacy is a concern for you, some of these sites require registration. Revealing your email address can put you at risk for unsolicited email (called “spam”). Finally, a word of caution - excessive computer use can have a negative impact on one’s health. Remember to take breaks. Walk, stretch, rest your eyes, and engage in other activities.

My favorite hepatitis web site is unlikely to surprise any regular HCV Advocate readers. A colleague recently described the HCV Advocate web site as “one stop shopping for information about hepatitis C.” This site is constantly updated. There are articles written by experts from a

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variety of fields, including information about support groups, disability, hepatitis B, and HIV/ HCV coinfection. There are many other fine hepatitis C-related web sites, too many to list in this article. I recommend starting with the HCV Advocate home page and linking to other sites from there: [www.hcvadvocate.org](http://www.hcvadvocate.org).

For general medical information, I recommend Healthfinder. This site is provided by the United State’s

Office of Disease and Health Promotion:

[www.healthfinder.gov](http://www.healthfinder.gov). The Medical Library Association has listed Healthfinder as one of the “top ten” most useful web sites. The list includes other web sites that I would include on my list, such as the Mayo Clinic [www.mayo.edu](http://www.mayo.edu), and Medline [www.medlineplus.gov](http://www.medlineplus.gov). This list can be accessed from Healthfinder’s home page.

Another informative web site is Web MD: [www.webmd.com](http://www.webmd.com). This web site is easy to use and usually provides good basic information. There is a link to Medscape, another web site worth exploring. For more in-depth research, the National Library of Medicine has a web site known as PubMed: [www.ncbi.nlm.nih.gov/PubMed](http://www.ncbi.nlm.nih.gov/PubMed).

The Internet can provide useful tools for health promotion. Prevention magazine’s web site offers a variety of articles ranging from recipes to tools for calculating calories and body mass index: [www.prevention.com](http://www.prevention.com). The United States Department of Agriculture (USDA) has a food database on its web site. The database can be downloaded to personal computers or personal digital assistants (PDA): [www.nal.usda.gov/fnic/foodcomp](http://www.nal.usda.gov/fnic/foodcomp).

RealAge.com provides interesting health assessment tools. These tools can motivate making health changes: [www.realage.com](http://www.realage.com). Another creative Internet source encompassing the concept of change is “my goals.com.” For those wanting a boost with achieving their goals, check out [www.mygoals.com](http://www.mygoals.com).

For those interested in herbs, HerbMed is packed with information: [www.herbmed.org](http://www.herbmed.org). Consumer Lab offers an excellent service for those interested in the quality of supplements. This subscription-based web site is growing. Some general information can be accessed without a subscription: [www.consumerlab.com](http://www.consumerlab.com).

Finally, life is not complete without some humor. There are many web sites devoted to this topic. Laugh Lab struck me as amusing: [www.laughlab.co.uk](http://www.laughlab.co.uk). Another diversion is [www.laughter.com](http://www.laughter.com). Enjoy!

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# Hepatitis C in Our Prisons

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Kara Wright, PA-C

Conservatively, about 4 million Americans harbor the hepatitis C virus. Our 2 million prisoners are not included in this estimate. According to the Centers for Disease Control (CDC), among prison inmates, 16%-41% have serologic evidence of HCV infection, and 12%-35% have chronic HCV infection. This translates into about 240,000 to 700,000 chronically infected individuals out of 2 million inmates. Now compare this with the 1.6% for the general population.

It is difficult to determine the actual infection rate among prisoners. Many states do not routinely test for HCV. In addition, even in states that do test, many prisoners will refuse to be tested. According to states that have screened for it, anywhere from 20-60% of our prisoners are actually infected with hepatitis C. For example, Texas is faced with a 28% infection rate among male inmates and 37% rate among women inmates. California found a 39.4% HCV seroprevalence among the prison population.

According to a national study of 36 states, only one state, Colorado, routinely tests inmates for HCV. The HCV seroprevalence in Colorado prisoners is 30%.

Canada reports that the documented rate of HCV infection among prisoners continues to rise. Statistics show that in 2001, 23.6% of Canadian federal prisoners were infected with HCV.

Hepatitis C continues to be a growing epidemic, even more so than HIV. It is estimated that <1 million Americans are infected with HIV as compared to the 4 million infected with hepatitis C. Canada reports HIV infects 1.8% of their inmates and is up only 0.1% from the previous year.

The prison population is at an

increased risk of contracting hepatitis C. In general, prisoners tend to engage in more risky behaviors, such as IV drug use, intranasal cocaine use and tattooing. Even while incarcerated, the infection is passed from inmate to inmate by such practices as unsterilized tattooing or piercing, violent unprotected sex, fighting with blood to blood contact, sharing of personal

*Statistics show that in 2001, 23.6% of Canadian federal prisoners were infected with HCV.*

hygiene items such as razors and even IV or intranasal drug use which takes place behind prison walls.

The biggest obstacle to treating our prisoners is the cost of treatment. With the current medication regimes, cost per inmate could be \$24,000 to \$36,000 for treatment. Even if older forms of treatment were used, such as standard three times a week interferon, costs would be at least \$10,000 per inmate. This would substantially burden the medical budget of prison systems today.

Another factor to take into account is that prisoners may begin treatment and be released before the end of treatment. This would often lead to treatment failure since there is often no follow up after inmate release. Many released prisoners do not have medical insurance and are unsure how to obtain

medical treatment once released.

Compliance is always a concern among patients taking hepatitis C treatment. A program to ensure compliance would need to be instituted in prisons in order to help treatment success rates.

Some say prisoners are incubators for the disease and will, often unknowingly, spread the disease to others once released. Inmates who have not been tested will not know that they have a chronic infection that can be spread to others. Also, if prisoners are not treated, the disease progresses. The cost to society may be more if prisoners are not treated. We may be releasing people into the community who are sicker than when first imprisoned. Patients with more advanced liver disease obviously have more complications and incur more costs. Advocates for prisoners say that not treating inmates in need of care is both a violation of the 8<sup>th</sup> amendment (prohibiting "cruel and unusual punishment"), as well as a violation of a landmark 1976 Supreme Court ruling in *Estelle v. Gamble*, which determined that inmates have a right to adequate medical care for serious medical needs.

In current news, there is a pending class action lawsuit in Oregon regarding prisoners' rights to be treated for hepatitis C. The court is asking to expand testing and treatment for prisoners with HCV.

As HCV infection continues to rise, the debate will continue regarding treatment of our prisoners. Cost versus benefit will continue to be a hot topic, and pending court cases will determine their fate.



# TREATMENT

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branded ribavirin). There have not been any large head to head trials of these pegylated products but in their development programs both companies compared their pegylated combination to standard interferon plus ribavirin with almost fifty percent of the same investigator sites, so some accurate comparisons can be drawn from the data between the two PEG products as it relates to efficacy or effectiveness in certain genotype and viral load groups.

## Peg Intron Plus Rebetol

Firstly, I reviewed the data on Peg Intron 1.5µg/kg plus 800mg Rebetol. Schering only conducted one combination trial, the data for which was published in *The Lancet* vol. 358, September 22<sup>nd</sup>, 2001 by Michael Manns. There is also additional supplemental information available from the FDA web site review of the Mann's data as well as the US FDA package insert (USPI) for Peg Intron. **See Table 1 for results.**

It is clear from the results shown in **Table 1** that the perceived advantage of Peg Intron plus Rebetol in genotype 1 is not entirely accurate. The overall SVR for genotype 1 patients with Peg Intron is totally driven by the improved efficacy in genotype 1 low viral load patient. Patients with genotype 1 and a high viral load (1/2 of the U.S. population with hepatitis C), will not get any increased efficacy or effectiveness over Rebetron

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**TABLE 1**

### Sustained Virologic Response for Genotype 1

	Overall (All genotype 1 patients)	High Viral Load (>2 million copies/ml)	Low Viral Load (<2 million copies/ml)
Peg Intron 1.5µg/kg + Rebetol 800mg	42% (Lancet)	30% (USPI) 29% (FDA)	72% (FDA)
Rebetron (Intron A + 1000-1200mg Rebetol)	33% (Lancet)	29% (USPI) 28% (FDA)	44% (FDA)
<b>Difference</b>	<b>+9%</b>	<b>+1%</b>	<b>+28%</b>

### Sustained Virologic Response for Genotype 2/3

	Overall (All genotype NON-1 patients)	High Viral Load (>2 million copies/ml)	Low Viral Load (<2 million copies/ml)
Peg Intron 1.5µg/kg + Rebetol 800mg	82% (Lancet)	72% NON-1 (FDA)	72% NON-1 (FDA)
Rebetron (Intron A + 1000-1200mg Rebetol)	79% (Lancet)	74% NON -1(FDA)	44% NON-1 (FDA)
<b>Difference</b>	<b>+3%</b>	<b>-2%</b>	<b>+28%</b>

**TABLE 2**

### Sustained Virologic Response for Genotype 1

	Overall (All genotype 1 patients)	High Viral Load (>2 million copies/ml)	Low Viral Load (<2 million copies/ml)
Pegasys 180µg + Copegus 1000-1200 mg	46% (NEJM) 51% (EASL)	41% (NEJM) 46% (Roche Medical Affairs for Hadzyannis trial) 43% (USPI)	56% (NEJM) 61% (NEJM) (Roche Medical Affairs for Hadzyannis trial)
Rebetron (Intron A + 1000-1200mg Rebetol)	36% (NEJM)	33% (NEJM) 28% (FDA)	43% (NEJM)
<b>Difference</b>	<b>+10-15%</b>	<b>+8-13%</b>	<b>+13-18%</b>

### Sustained Virologic Response for Genotype 2/3

	Overall (All genotype NON-1 patients)	High Viral Load (>2 million copies/ml)	Low Viral Load (<2 million copies/ml)
Pegasys 180µg + Copegus 1000-1200mg	76% (NEJM) 78% NON-1 (EASL 2002)	74% (NEJM)	81% (NEJM)
Rebetron (Intron A + 1000-1200mg Rebetol)	61% (NEJM)	58% (NEJM)	65% (NEJM)
<b>Difference</b>	<b>+15-17%</b>	<b>+16%</b>	<b>+16%</b>

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with Peg Intron plus Rebetol combination therapy in the doses studied. It is also interesting to note that the genotype non-1 efficacy in high viral load patients is also no better than Rebeton. In summary two thirds of the patients in the United States with hepatitis C have no increased efficacy with Peg Intron plus Rebetol in the doses studied in Schering's development program.

One could argue that if higher doses of Rebetol were used in the original trial then the results would be better across all patients but is that really true? A retrospective analysis of the pivotal trial which is included in the *Lancet* publication looked at a subset of patients that received >10.6mg/kg of Rebetol. Because everyone in the prospective trial received only 800mg of Rebetol, the retrospective analysis was only looking at a subset of patients that were lighter, probably female who have prognostic factors in their favor for an SVR. To extrapolate the results from that subset across all patients is not a medically sound approach to a retrospective analysis and so Schering is now trying to prospectively look at this and a very large trial known as the WIN-R trial is underway. According to FDA documents the reason that Schering did not originally study higher doses of Rebetol in the Peg Intron 1.5µg/kg arm is that they were concerned about potential additive drug toxicities. The original pivotal trial had a dose modification rate of 42% with only 800mg Rebetol, which is sure to increase with higher doses of Rebetol. This issue however may be overcome in the WIN-R trial as it does allow for the use of growth factors such as erythropoietin (EPO) and granulocyte macrophage colony-stimulating factor (GM-CSF). But how available are they to the general population with hepatitis C?

### **Pegasys plus Copegus**

Now let's review the data on Pegasys 180µg plus 1000-1200mg Copegus.

## **Clinical Trials – Prospective vs. Retrospective**

*The most reliable research results come from a prospective study, which is carefully planned and conducted in a standard manner with well-defined patient populations as well as a protocol that includes predetermined primary and secondary endpoints. This is considered the gold standard of clinical research. On the other hand, a retrospective study looks back in time, which is subject to bias because certain assumptions are made that may not be valid. For instance, a retrospective study may look at previous study results and try to ascertain if treatment response rates would be improved using a higher dose of the study drug. However, you can not draw any concrete conclusions since you did not actually study the tolerability at a higher dose in all participants. Retrospective studies are, however, useful in determining what should be studied prospectively and therefore do have a role in medical science.*

Roche conducted two trials, the first is published in the *New England Journal of Medicine* 2002; 347(13):975-82 and the second was presented at EASL 2002 by Hadziyannis and is awaiting publication. Both studies are included in the FDA approved USPI. **See Table 2 for results.**

The data for Pegasys plus Copegus shows a marked improvement over standard interferon plus ribavirin combination in all patient types regardless of genotype or viral load. So why the difference in the results between the PEGs?

### **A Peg is Not a Peg**

Many people refer to the two pegylated interferons as though they are the same products but manufactured by different companies—based upon the prospective data that is available to date this doesn't seem to be the case. Interestingly, the information that was brought to my attention as it relates to the differences in the PEG's efficacy in high viral load patients may explain the differences in the PEG's. It is believed that this difference is a result of the different types of pegylation processes used by each company. Peg Intron is the result of earlier pegylation technology using a smaller linear peg that weakly attaches to the interferon molecule, which is the reason that Peg

Intron comes in a powered form that requires reconstitution—it is unstable. This type of pegylation helped in the fact that Peg Intron doesn't need to be dosed three times a week, but it still acts similarly to standard interferon with periods at the end of each week when there is no detectable Peg Intron. It has not been determined how much interferon is needed to suppress the hepatitis C virus but one could theorize that if there is no drug in the body of someone with a high viral load—there is an opportunity for the virus to replicate, mutate and bounce back. This may explain the lack of improvement in response rates of Peg Intron over standard interferon in patients with a high viral load regardless of genotype.

Pegasys on the other hand is the result of later pegylation technology which uses a larger branched peg that very tightly attaches to the interferon, which explains why it is stable enough to be made in a ready made liquid formulation—it is very stable. This type of pegylation provides Pegasys with constant suppression of the hepatitis C virus from the first dose injected to when therapy is completed. Levels of Pegasys gradually increase until around week 5-8 when steady state is established

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# Noninvasive Markers for Liver Fibrosis

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Liz Highleyman

A liver biopsy, in which a small sample of tissue is extracted with a needle and examined under a microscope, is considered the “gold standard” for gauging the extent of liver damage in people with chronic hepatitis. Biopsies can detect tissue changes that indicate fibrosis and cirrhosis. Traditionally, because interferon-based treatment for hepatitis C has been only moderately effective and comes with considerable side effects, most experts have recommended that people with minimal fibrosis should not be treated, and liver biopsy has been considered the best method for making such a determination. Repeated biopsies (every 3-5 years) are used to determine how fast fibrosis is progressing and whether treatment is working.

But liver biopsy is an invasive and expensive procedure that causes pain for about one-third of patients, and anxiety for many more. In addition, though rare (less than 1%), biopsy complications can occur, including excessive bleeding and infection. And, even under the best of circumstances, biopsies fail to accurately diagnose the stage of liver fibrosis about 20% of the time. Thus, researchers have sought other markers that could signal liver damage without the need for biopsy.

A number of factors have been associated with a greater risk of liver fibrosis, including older age, male sex, and alcohol consumption. Elevated levels of alanine transaminase (ALT), a liver enzyme, are associated with liver inflammation, but are not a good indicator of fibrosis. Some of the biochemical markers that have been proposed as indicators of liver disease progression include alpha2-macroglobulin, apolipoprotein A1, haptoglobin, bilirubin, gamma-glutamyl-transpeptidase (GGT), cholesterol,

platelet count, and prothrombin time. Is it possible to develop an algorithm to estimate the extent of liver damage using easy, widely available, and inexpensive noninvasive measurements?

Different research teams have studied various indices, or combinations of biochemical markers, comparing index readings with biopsy results to see how well they agree about the extent of fibrosis. Dr. Thierry Poynard and colleagues from Paris have derived an index called FibroTest, which

***Both Fibrotest and Forns’ index are very good at predicting the absence of fibrosis in people with low scores, but somewhat less so at accurately diagnosing the presence of liver damage in people with high scores.***

includes alpha2-macroglobulin, apolipoprotein A1, haptoglobin, total bilirubin, and GGT, as well as age and sex. They reported in the April 7, 2001 issue of *The Lancet* that for people with very low scores (below 0.10 on a scale of zero to 1.00), the index has a negative predictive value as high as 100% (that is, it says fibrosis is not present when in fact it is not). The positive predictive value for scores above 0.60 is over 90% (that is, it correctly says fibrosis is present when in fact it is). In the March 28, 2003 issue of *AIDS*, Poynard’s team reported that

FibroTest also accurately predicts liver fibrosis in people with HCV/HIV coinfection, and they reported in the March 2002 *Journal of Viral Hepatitis* that index scores decreased in patients who achieved a sustained virological response to interferon treatment. Use of the five FibroTest variables plus ALT—a combined index called ActiTest—allows for the prediction of inflammatory activity along with fibrosis. (For more on FibroTest and ActiTest, see [www.biopredictive.com](http://www.biopredictive.com).)

Dr. Xavier Forns and colleagues from Barcelona have developed a fibrosis index that includes age, GGT, platelet count, and cholesterol levels. They reported in the October 2002 issue of *Hepatology* that this index correctly predicted the absence of stage 2-4 fibrosis—a negative predictive value—in 96% of those with a low score below 4.2. It was not as successful in identifying the presence of fibrosis in people with high scores above 6.9 (a positive predictive value of 66%), and some patients with minimal damage were incorrectly identified as having advanced fibrosis. Furthermore, some 50-60% of patients had scores in the mid-range between 4.2 and 6.9, and could not be classified as having or not having fibrosis. But Dr. Forns’ team concluded that their index could make biopsies unnecessary for about one-third of patients with mild liver disease.

To date, biochemical markers have some disadvantages. Both Fibrotest and Forns’ index are very good at predicting the absence of fibrosis in people with low scores, but somewhat less so at accurately diagnosing the presence of liver damage in people

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# Safe Injection Sites in Vancouver, BC

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CD Mazoff, PhD

On May 6<sup>th</sup> I attended a community forum on the use of supervised injection sites as a solution to curbing the spread of disease and public nuisance in Vancouver, British Columbia, Canada, by Dr. Ethan Nadelmann, executive director of the New York-based Drug Policy Alliance.

Dr. Nadelmann was invited to Vancouver by a committee of health and community outreach professionals who advocate a harm reduction-based response to drug addiction, and by

medical marijuana, safe injection sites, and heroin maintenance programs are worried that the U.S. government will be vocal in its opposition to Canada's implementation of these programs. Many fear economic sanctions.

Vancouver's new strategy for dealing with a huge drug problem focuses on strengthening four "pillars"—enforcement, treatment, harm reduction, and prevention, and has shifted away from pure policing and punishment to a more compassionate

ism and the drug companies who continue to profit through the sales of "good" drugs while funding programs to stop the sale of "bad" drugs.

He pointed out that there are more people in the U.S. in jails today on drug charges than the total amount of persons in jail for all charges in the European Union. He also pointed out that the prison population in the U.S. is disproportionately Black, that 25% of the U.S. Black population has lost the right to vote because they have drug related records, and that the biggest killers of Canadian Aboriginals are drugs and alcohol.

Like it or not, the gradual genocide of non White races through drug and alcohol abuse has to be seen as continuing evidence of systemic racism in North America. Why? That's another issue. Something to do with population densities. Apparently societies with smaller population densities also have less problems with substance abuse. Come to think of it, slums (composed of the poor, and the "different") are where the problems are severest.

It was also pointed out that 3 persons die a day in Canada due to some drug related cause, and that although this makes the deaths from SARS pale in insignificance, the Canadian Government immediately jumped into the SARS problem with verve and cash. Not so for the addicted.

Dr. Nadelmann tried to lay to rest the many misconceptions about supervised or safe injection sites, which actually reduce public nuisance and addicts injecting on the street.

"Some people believe supervised injection sites are evil, immoral and sick just as needle exchanges were once opposed, and that society is

***"It is perceived that safe injection sites condone injection drug use. In fact, what safe sites do is keep people alive and open doors to healthy options like treatment and counselling that they might not otherwise encounter. Instead of making people criminals, safe injection sites help people turn their lives around and reduce the spread of deadly disease,"***

*Ethan Nadelmann, PhD*

Tides Canada, a national public Foundation. In attendance were representatives of Health Canada, Coast Health Authority, CTV (Canadian Television Network), CBC (Canadian Broadcasting Corporation), the former Mayor of Vancouver, Philip Owen, who designed and pushed through the safe injection site program, Dr Martin Schechter of the Canadian HIV Centre for Excellence, and other concerned groups and individuals.

The title of Dr. Nadelmann's address was, "Supervised injection sites and the four-pillar approach to drug policy: How will the U.S. respond?" Canadians, on the verge of implementing social policies such as access to

and health caring model, similar to those being used in some European countries at the moment.

Dr. Nadelmann is a widely published scholar and former professor at some of the most prestigious universities in the world (McGill, Princeton), and so it is hard to put into a few words the salient points of an extremely well-articulated and non-stop 2 hour talk. Let me put it this way. He covered everything and he made his points, well.

In the context of trying to understand why it is that we continue to punish those who, if anything, really should be receiving support and medical treatment, Dr. Nadelmann laid the blame firmly on institutionalized rac-

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## SAFE INJECTION SITES

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better off punishing addicts than helping them. But this is an extremely short-sighted view that treats drug addiction as a criminal rather than a health issue, and research proves that the criminal approach doesn't work."

Just as needle exchanges save lives and stop the spread of HIV and hepatitis C, supervised injection sites are a humane and sensible approach for injection drug use, and can be an entry point into the health system for addicts, said Dr. Nadelmann who *Rolling Stone* magazine called the point man for drug policy reform efforts.

"It is perceived that safe injection sites condone injection drug use. In fact, what safe sites do is keep people alive and open doors to healthy options like treatment and counselling that they might not otherwise encounter. Instead of making people criminals, safe injection sites help people turn their lives around and reduce the spread of deadly disease," he said.

I agree with Dr. Nadelmann that it is time we reduced the stigma of addiction and began to treat it as we do other diseases—diabetes—for example. The biggest problem with methadone treatment has not been that methadone doesn't work, but that unlike the diabetic who can take his or her insulin privately at home, the person on methadone treatment is dragged before the public wearing a ball and chain.

The complications and consequences of following the prohibitionist model have been costly and fatal, mostly among the poor, and the "different." The simplistic assumptions of the "just say no" approach do not work. What is needed is awareness and compassion.

*For more information, please visit [www.drugpolicy.org](http://www.drugpolicy.org)*



## NONINVASIVE MARKERS

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with high scores. Both algorithms are less useful in people with mid-range or indeterminate scores (though Fibrotest does yield an almost linear relationship between index scores and fibrosis). While the indices can differentiate between minimal (stage 0-1) and significant (stage 2-4) fibrosis, they cannot accurately distinguish between specific histological stages (for example, stage 2 versus stage 3). In addition, several factors other than fibrosis may affect index values. Cholesterol levels, for instance, can vary by HCV genotype. Levels of GGT and other liver enzymes tend to be higher in men than in women. Platelet count is poorly standardized among laboratories (FibroTest omits it for this reason). Most measurements can vary over time, and Dr. Keyur Patel of Duke University suggests that an average of three or more values taken over 4-6 months may yield a better number to plug into an index than a single measurement. Finally, doctors don't yet know how to use biochemical markers to gauge liver disease progression—for example, how much should an index score decrease to indicate that interferon treatment is working?

As Dr. Nezam Afdhal from Beth Israel Deaconess Medical Center in Boston notes in an editorial in the May 2003 issue of *Hepatology*, these biochemical markers do not really measure fibrosis *per se*, but rather reflect changes in liver function associated with advancing disease. However, there are other biochemical markers—including tissue inhibitor of metalloproteinase and hyaluronic acid level—that may actually reflect changes in the extracellular matrix, which accumulates as fibrosis progresses. Studies

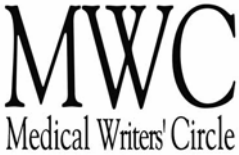
of such markers are underway, and while none have so far been found that serve as good predictors of fibrosis on their own, they may be used as part of an algorithm or index along with other variables.

Some experts believe that with new, better hepatitis C treatments that benefit more patients, liver biopsies may now be less necessary to help doctors decide who should be treated. Dr. Afdhal, for example, argues that "we can, to some extent, categorize almost a third of patients into those with mild disease and use this information for decision analysis without a liver biopsy." In an editorial accompanying the Poynard team's *AIDS* article, Dr. Vincent Soriano from Madrid and colleagues proposed that liver biopsy may be "even less justifiable" for HCV/HIV coinfecting patients, since this group is more likely to experience rapid liver disease progression and appears more likely to suffer biopsy-related complications. "[M]ost patients with HCV/HIV coinfection should be considered as candidates for therapy," the researchers suggest, regardless of the extent of existing fibrosis. The discovery of new biochemical markers of liver disease progression and the development of predictive combination indices is an area of considerable promise. Concludes Dr. Afdhal, "As newer, better tolerated, and more efficacious therapies are developed, the need for biopsying all HCV patients to grade and stage disease may become redundant. Therefore, the development of noninvasive tests that can differentiate between patients with mild disease versus those with more significant fibrosis could have a widespread clinical utility in managing HCV patients in the future."





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Medical Writers' Circle is a publication of the Hepatitis C Support Project. It consists of a series of articles written by medical professionals about the management and treatment of hepatitis C. The articles are available for printing at the Hepatitis C Support Project website.



## TREATMENT

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We know that the hepatitis C virus replicates trillion of virions a day and that constant suppression of the virus is critical, especially in patients with a high viral load (>2 million copies/ml).

In summary, we have known for a while that it is not enough to just look at overall treatment response rates. We now know, however, that viral load and genotype should also be separated out when reporting treatment response rates. Patients and health care providers should be carefully reviewing all data, including medication, viral load and genotype as well as carefully questioning how the prospective data is being marketed and which can be misleading.



### SOME FREQUENTLY USED TERMS

**Genotype**  
genetic variation in the structure of HCV. There are six major genotypes, designated by the numbers 1 through 6. There are also many subtypes, e.g., 1a, 1b, 2a, etc. In the U.S., genotype 1 is predominant (approximately 70-75% of patients).

**Biochemical response**  
how a person's serum ALT responds to treatment. When a patient's elevated serum ALT level becomes normal after HCV therapy has been initiated, this is considered a biochemical response.

**Pegylated Interferon (PEG-INTRON, PEGASYS)**  
a form of interferon that has a long half-life in the body and can be injected less often (typically once per week). Pegylated interferon is approved for the treatment of HCV. See also standard interferon.

**Interferon (IFN)**  
a naturally occurring protein in the human body produced by the immune system. Interferon interferes with viral replication. Genetically engineered products based on the natural protein have been developed by several pharmaceutical companies, and are approved for the treatment of chronic HCV infection.

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*The HCV Advocate* offers information about various forms of intervention in order to serve our community. By providing information about any form of medication, treatment, therapy or diet we are neither promoting nor recommending use, but simply offering information in the belief that the best decision is an educated one.

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