Hep C BC

presents

Peppermint Patti's FAQs

Version 10.1

A big thank you to HCV Advocate for permissions for the current research updates, to all the community organizations that pitched in, and to Patricia Johnson for her inspiration.

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When a person is infected with hepatitis C, the virus often lives in the liver for decades. It often gives few signs it has entered the body or is attacking the liver. Up to 80% of people who have hepatitis C notice no symptoms.
The virus has reached epidemic proportions, infecting an estimated 300,000 Canadians, 3.2 million Americans and 130-150 million people worldwide. Hepatitis C is a leading cause of cirrhosis and liver cancer, and is the most common reason for liver transplants in the United States and Canada.

It can take decades for symptoms such as jaundice, fatigue, dark urine, abdominal pain, loss of appetite and nausea to occur, and at this point the liver may be badly damaged. When the liver is failing badly, often the only option still available is a liver transplant. It is important to get tested before symptoms occur, to allow for early treatment of the disease before too much damage is done.

Among those at greatest risk for hepatitis C are hemophiliacs, current or past intravenous drug users, dialysis patients, transfusion/transplant patients, healthcare workers and those engaging in high-risk sexual activities. 350-500,000 people die each year from hepatitis C.

*We are proud to say that this is the first edition of our FAQ that can say that there is a **CURE** for hepatitis C, thanks to the new direct-acting antivirals (DAAs). Indeed, "HCV is probably the only chronic human viral infectious agent that can be completely eradicated." The challenge now is to reach those infected and get them treated.*

Sources: www.phac-aspc.gc.ca/hepc/index-eng.php
www.azdhs.gov/phs/oids/hepc/stats.htm
www.cdc.gov/hepatitis/c/cfaq.htm
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HepCBC - HEPV-L HEPATITIS C FAQ v10.1

APRIL 2015

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This FAQ is dedicated to the memory of David H. Kehrer, LTC John Heintz (Peters) and his wife Patricia, Daniel Bodiford, Dr. Horst Irmler, Jude Saucier, Capt. Kevin Donnelly, Ron Thiel,"Uncle Dave" Lang, Guy Thisdelle, "Apache" Pat Davis, Frank Darlington, Dave FitzGerald, Sandra Tara Balduf (Ane Palmo), Herb Moeller, Kelly O'Dell, Bruce Devenne, Ken Thomson, and all of the many others for whom the cure came too late.

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0: Administrivia

0.00 Copyright

This is a document whose development is in progress. Please make comments to help improve it. Please send suggestions for additions, corrections, or changes privately to Joan King at info@hepcbc.ca.
If you want your contribution to be anonymous, please state so.

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HEPV-L is a list devoted to people with chronic hepatitis, and related liver diseases. Its address is *HEPV-L@listserv.icors.org*; HepCBC can be reached through *www.hepcbc.ca*.
Subscribe by addressing a message to: *listserv@listserv.icors.org* and in the body of the message, on the first line, type: SUB HEPV-L FIRSTNAME LASTNAME (substituting your name for the first and last name). Any questions, or problems signing on—or off—the list, please contact one of the listowners at *HEPV-L-request@listserv.icors.org*

HepCBC (www.hepcbc.ca) is an association of independent grassroots organizations in British Columbia, Canada, and beyond, dedicated to education and prevention of hepatitis C. It is the home of the *hepc.bull*.

0.01 INTRODUCTION

This document answers frequently asked questions (FAQ) about the hepatitis C virus (HCV), its treatment, and related complications. We have made every effort to provide the most current and most accurate information.

This updated version (FAQ v10.0) reflects the international nature of the hepatitis C community. Although the home of the HEPV-L list is in the US, many of its members come from other parts of the globe. Patricia Johnson (Peppermint Patti), the original author of the FAQ had asked David Mazoff (squeeky), of the HCV Advocate in San Francisco, if he could take over the arduous task of revising and updating the FAQ, and he has passed the torch to Joan King. She lives in Canada, and so this version has quite a bit of information for Canadians. To make the FAQ more accessible to those from countries other than Canada, information relating specifically to Canada has been put in appendices at the end of the document.

Thanks to a grant from the Legal Services Society of British Columbia, we include information on Disability Benefits for residents of BC. Hopefully, this section will expand to include all of Canada. The reader will also note that there is no list of physicians in the US comparable to the list of Canadian physicians (Appendix D). Anyone wishing to compile this list is welcome to do so. Please contact the authors of the FAQ.

0.02 DISCLAIMER

The information presented in this document was written and developed by patients and members of the HEPV-L mailing list. It represents an informal catalogue of accumulated knowledge by people who for the most part are not medical professionals. As this file is developed further, we will include references and citations to document more of the statements that are made here. Much of the information contained in this FAQ was compiled from the varied and personal experiences and opinions on the HEPV-L and HepCAN mailing lists, and from original research published in the *hepc.bull*. As useful as this information may be, it must not be considered medical advice, and must not be used as a substitute for medical advice. And as always, don't forget to use your common sense. It is important that anyone who has, or thinks they may have, hepatitis should consult with a licensed health care practitioner who is familiar with liver disease and systemic disorders.

Thanks are due to the many contributors to this new official version of the FAQ. Below, in no particular order:

Alan Franciscus (HCV Advocate), Brad Kane (HepCBC), Andi Thomas (Hep-C-Alert), Anne Karim, Bruce Bennett, Bryce Brogan, Paul Harvey, Cindy Torchin, David Lang† (HEP Seattle), Frank Smith, Joe Shaw, Joan King (HepCBC), Kathryn Morse, Eileen Caldwell-Martin (FHCQ), Ken Benjamin†, Kevin, Kunga Palmo† (USHA), Sue Brown (Mid Island HepC), Capt. Kevin Donnelly†, Bruce Devenne† (HepCNS), Leslie Gibbenhuck (Children's Liver Alliance), Marjorie Harris (HepCure), Darlene Morrow (HepC VSG), Lucinda Porter, Pat Buchanan (LiverHope),**Peppermint Patti**, Sara Amber (HEP Seattle), Scott Warren (aka Reezer), C.D. Mazoff, aka "Squeeky" (HCV Advocate), Cheryl Reitz (HepCBC), Rivaud (Hepv-l), Sheree Martin (Hep B List), Sybil†, Smilin' Sandi, Marie Stern, Brian D. Klein (HAAC), John & Matti Kirk, Rick Crane, and our mothers for making us possible.

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PART I - THE BASICS

I.0.1 WHAT IS HEPATITIS?

Hepatitis is an inflammation of the liver. It is a symptom of many different diseases and conditions. Poisons, viruses, bacteria, parasites, auto-immune disorders, and drugs can all cause hepatitis.

Hepatitis A, B, and C are all forms of viral hepatitis. Although their names sound the same, they are actually very different viruses, causing different symptoms and requiring different treatments. Other viruses that cause hepatitis are hepatitis D, E, and G; these are less common, and were discovered more recently than hepatitis A, B and C.

Non-viral hepatitis can be caused by toxic agents or autoimmune disease. Autoimmune disease is the body attacking itself, treating its own tissues as foreign invaders. Toxic hepatitis is a deterioration of the liver cells caused by chemicals, alcohol, drugs, or industrial compounds. Toxic hepatitis is another way of saying liver inflammation due to poisoning. Alcohol abuse is one of the most common causes of toxic liver damage.

I.0.2 WHAT ARE THE DIFFERENT TYPES OF HEPATITIS?

The different types of VIRAL hepatitis are:
A (formerly called infectious hepatitis, or yellow jaundice)
B (serum hepatitis)
C (formerly called non-A, non-B hepatitis)
D (delta hepatitis)
E (transmitted through the feces of an infected person)
G (a virus transmitted through infected blood products)
CRYPTOGENIC (or Non-A,B,C,D,E,G)

More hepatitis viruses are being discovered, but may be less common. Other viruses, including Yellow Fever, Epstein-Barre virus, Cytomegalovirus, and parasites and bacteria, can cause hepatitis as a secondary effect.

Types of NON-VIRAL hepatitis include:
Autoimmune disease (the body attacking its own tissues)
Wilson's disease (a genetic disorder causing too much copper in the liver or brain)
Hemochromatosis (a genetic disorder causing too much iron in the bloodstream)
Drug, chemical, or alcohol induced hepatitis.

I.0.3 WHAT HAPPENS IN THE BODY?

Hepatitis infections enter the body in different ways. The hepatitis A and E viruses enter through the gut, whereas B, C, D, and G enter through the bloodstream. All forms of viral hepatitis attack the liver, and reproduce in the liver cells.

Hepatitis A and E thrive in unsanitary conditions. There is a vaccine for hepatitis A. It usually resolves itself, but can be fatal in children, the elderly, or the chronically ill. Hepatitis A can prove fatal to people with hepatitis C. Hepatitis E is found mainly in the third world. It also resolves itself, but it can pose a serious danger to pregnant women.

As hepatitis B, C, D, and G infect liver cells, the body fights them, which causes the liver to become inflamed. With hepatitis B, the liver usually repairs itself, leaving behind antibodies. Antibodies are proteins produced by the body as a part of its defense against viruses. If you have only the antibodies for a disease it means that you either have it now, or have had it at one time and have gotten over it.
Recent studies show that hepatitis B may resurface many years later in individuals who have supposedly cleared the virus, much like the "post-polio syndrome." Up to 90% of those infected with hepatitis B will clear the virus. There is a vaccine for hepatitis B.

There is no vaccine for hepatitis C. For people who get hepatitis C, the immune system doesn't defeat the virus. More often than not, the antibodies fail to identify the hepatitis C virus properly, and infection remains long-term. In fact, most infected people don't know they have it. This is because, for some people, there will be no symptoms, and for others, symptoms may take 13 years or more to develop. Some people may have hepatitis C for over 20 years before they find out they have it. Hepatitis C affects different people different ways.
From what we know, if 100 people catch hepatitis C:

- 15-20 will have an acute infection. These people will recover from the virus the same way a person recovers from the flu.
- 80-85 will get a chronic infection. This infection doesn't go away without treatment.

Of those 80-85 people with chronic infections:

- 60 will never show more than a moderate level of liver damage, if they show any at all.
- 20-25 will progress to serious liver disease.

Of those 20-25 who progress to serious liver disease:

- 10 will remain stable
- 15 will progress to liver failure or liver cancer about 5 years after developing serious liver disease. According to an article in *Gut* 2000; 47:131-136, the 5 year rate for progression to hepatocellular cancer is 13.4% and the 5 year rate for progression to death is 15.3%.

Nevertheless, hepatitis C infection doesn't always make people sick. When someone does get sick, symptoms take a long time to develop (approximately 13 years). Even when a person is showing symptoms, the pattern changes so much from person to person, the condition may be mistaken for something else. People often don't get tested until they are showing symptoms of end-stage liver disease, so it is important to get tested if you have **any** reason to believe that you **ever** had blood-to-blood contact with another person. **Everyone should take precautions to prevent the spread of hepatitis C, even people who think they don't have it.**
Studies that follow the progress of the disease are few, include relatively few subjects, and only follow people over a short period of time. Generally, they only track those people whose date of infection can

be well documented, (e.g., blood transfusion recipients and victims of accidental needle sticks). From what we know so far, the progress of the disease appears to differ according to geography, alcohol use, virus characteristics, (e.g., genotype, viral load), co-infection with other viruses, age, age at infection, gender, weight, and other unexplained factors. - *(National Institutes of Health Statement on Hepatitis C 1997 and* Gut *2004; 53:451-455).*

I.0.4 WHAT IS THE INCUBATION PERIOD?

The time it takes for symptoms to appear varies amongst the different types of hepatitis. People with hepatitis A and E may start to develop symptoms as soon as 2 weeks after exposure, but it usually takes four weeks for symptoms to become noticeable. For hepatitis B and C it tends to take much longer. The average time for the onset of symptoms with hepatitis B is 2-3 months. In experiments on chimpanzees, hepatitis D symptoms appeared two to ten weeks after infection.

One to three weeks after the initial exposure, HCV RNA can be detected in blood. Virtually all patients develop liver cell injury within 15-150 days (50 days is the average). Liver damage is detected by looking for an elevation of serum alanine aminotransferase (ALT is an enzyme which leaks out of the damaged cells into the bloodstream). The majority of people are aosymptomatic (don't show symptoms) and anicteric (whites of the eyes are clear). Only 25-35% of people develop discomfort, weakness, or anorexia, and some develop jaundice in the whites of their eyes. Rapid onset liver failure following HCV infection has been reported but is a rare occurrence. Antibodies to HCV (anti-HCV) almost invariably become detectable during the course of illness. HCV antibodies can be detected in 50-70% of people at the onset of symptoms and in approximately 90% of people in 3 months after onset of infection. When a disease goes away without treatment, it is called self-limited; HCV is self-limited in 15% of cases. Recovery is characterized by disappearance of HCV RNA from blood and return of liver enzymes to normal. – *(National Institutes of Health Statement on Hepatitis C 1997*).

I.0.5 HOW DOES HEPATITIS C USUALLY BEGIN?

Different people have different reactions to HCV. For a few people, the illness begins suddenly, as though they had come down with the flu, except that this "flu" doesn't seem to get completely better.
Symptoms may include fatigue, low-grade fever, headaches, slight sore throat, loss of appetite, nausea, vomiting, sensitivity to light, and stiff or aching joints. Many people develop a pain in the right side, over the liver area. Urine may become dark brown, and feces may be pale. In severe acute infections, people may develop jaundice, where the skin and whites of the eyes become yellowish.
The severity of symptoms can differ widely among people, and will also vary over time for the same individual. It can range from getting unusually fatigued following stressful events, to being totally bedridden and completely disabled. The symptoms have a tendency to wax and wane over time.

I.0.6 WHAT IS THE FUNCTION OF THE LIVER?

The liver has many functions, including:

- storing iron reserves, as well as vitamins and minerals.
- detoxifying poisonous chemicals, including alcohol and drugs (prescribed and over-the-counter medicines as well as illegal substances), and acting as a filter to convert them to substances that can be used or excreted from the body.
- converting the food we eat into stored energy and chemicals necessary for life and growth.
- making blood products.
- manufacturing new proteins.
- making clotting factors to help blood clot.
- manufacturing bile, an enzyme used in breaking down fats and in waste disposal.

I.0.7 HEPATITIS C VIRUS (HCV)

Hepatitis C is a form of hepatitis caused by an RNA virus of the Flaviviridae family that targets the liver. HCV accounts for the majority of the hepatitis cases previously referred to as non-A, non-B hepatitis, and is responsible for 150,000 to 250,000 new cases of hepatitis each year.
Those infected with the virus can show symptoms such as fatigue, nausea, loss of appetite, dark urine, and jaundice. If left untreated it can lead to liver failure, liver cancer and death. HCV is also a trigger for a host of autoimmune disorders and various other diseases, such as diabetes, non-Hodgkin's lymphoma, retinal complications and thyroiditis (inflammation of the thyroid gland). According to recent reports by the National Institutes of Health, over three million individuals in the U.S. are infected with HCV. The reports also noted that the disease kills about 15,000 people in the US yearly, and is the leading cause of death in those co-infected with HIV. Treatment of the disease with current drugs is much more effective and more easily tolerated than those in the past. It is feared that, without treatment, the *number of deaths could triple over 10-20 years. (www.ncbi.nlm.nih.gov/books/NBK11903/ and*

www.ncbi.nlm.nih.gov/books/NBK115347/)

I.0.8 WHEN WAS THE HEPATITIS C VIRUS DISCOVERED?

In 1987, Michael Houghton and colleagues at Chiron Corporation in California discovered part of the genetic material of HCV using molecular recombinant technology. This discovery allowed the development of tests to detect specific antibodies. The first enzyme immunoassay (EIA) test made available in 1989 employed only a single recombinant protein to detect antibodies and produced a significant proportion of both false positive and false negative results. An antibody test that could be used to increase the safety of the blood supply and of transplantable organs and tissues was available by 1990.

In mid-1995 the hepatitis C virus was seen for the first time ever by scientists with the aid of an electron microscope. It is a linear, single-strand RNA (ribonucleic acid) virus 40-50 nanometers in size, covered with a lipid envelope and encased with glycoprotein peplomers or "spikes".

According to the late Bruce Devenne of Hepatitis Nova Scotia, governments and medical communities had knowledge of hepatitis C well before 1987, and could have done much to prevent the deaths of thousands, but they chose to save money and not test blood used for transfusions. Consider the poisoning of those in Ireland and France with HCV infected blood, where court cases clearly found criminal liability on the part of blood merchants and governments. Consider also the history of blood safety in Canada, and the current Arkansas Blood Trail scandal (See Appendix E, below).

I.0.9 WHO GETS HEPATITIS?

People should be tested for hepatitis C if they were born between 1945 and 1965 or if they have ever:

- received a blood transfusion or blood products before screening was introduced (1986 in the US, 1990 in Canada).
- shared injecting equipment for drugs.
- were tattooed or had body piercing.
- had a needle stick injury or performed "exposure-prone procedures."

People with abnormal liver function tests with no apparent cause would also benefit from having a hepatitis C antibody test. HepCBC also recommend that anyone who has had dental procedures where blood was present, or who has had manicures or pedicures be tested. People undergoing hemodialysis are infected at a rate of about 10% in the US, and 70% in underdeveloped countries and are still at risk, as are many former and current cancer patients. (*www.hindawi.com/journals/isrn/2013/159760/*)

There were approximately 17,000 new cases of hepatitis C in the US in 2010--down from previous rates of 150,000 and 250,000. Hemophiliacs and intravenous drug users are at the greatest risk, but anyone, of any status or age, and of any walk of life, is at risk for acquiring the hepatitis C virus. Researchers have found about half of the people infected with hepatitis C don't even know it. Twenty to forty percent of patients in inner-city hospitals are infected, as are 80 % of intravenous drug users.
(http://us.milliman.com/uploadedFiles/insight/2013/convergence-of-risk-and-opportunity.pdf)

I.1.0 HOW IS IT TRANSMITTED?

"Relax...you have cooties...but they aren't as bad as you are imagining." - *Cindy Torchin: cindyt@cpcug.org Listowner HEPV-L*

Most people with hepatitis C contracted it through either a contaminated blood transfusion or a blood product (plasma, gamma globulin, etc.) or by sharing contaminated needles. Prior to 1990, the official line was that blood in Canada could not be screened for HCV (*see, Appendix E: History of Blood Safety).* Thanks to HCV testing with modern methods, the risk of acquiring hepatitis C from blood transfusion is now less than 1%. See **HCV AND BLOOD TRANSFUSIONS**.

The virus enters through a break in the skin or mucous membrane. Therefore, there are other ways people acquire hepatitis C. For example, health care and laboratory workers may get stuck with an infected needle or instrument. People can also be infected by receiving medical/dental procedures, undergoing hemodialysis, body piercing, sharing razors, toothbrushes, nail clippers or having tattoos or manicures performed with poorly sterilized equipment. Infected mothers can pass the virus to the fetus in utero. Statistics for transmission from mother to child are approximately 5%, however, it may occur more readily if the mother is also infected with the human immunodeficiency virus (HIV) that causes AIDS--16% rate. See **MOTHER-TO-CHILD**

Cases of hepatitis C with no evidence of exposure through blood transfusions, needle sticks or needle sharing are called "sporadic." How these individuals became infected is unknown. As early as 1956 the *Merck Manual* stated that Non-A/Non-B hepatitis could be spread through the use of glass syringes and

other then current medical testing and mass vaccination devices.

Forty percent of all cases of hepatitis C were contracted through unknown means by people who are in no current risk category.
What this means is that **all people** are at risk for contracting hepatitis C.

1.1.1 HOW HCV IS NOT TRANSMITTED

There can be misconceptions about how HCV is transmitted. To clarify, HCV is NOT airborne. It is NOT spread by:

- sneezing and coughing.
- holding hands.
- kissing (unless there is deep-kissing and open sores present).
- using the same toilet.
- eating food prepared by someone with HCV.
- holding a child in your arms.
- swimming in the same pool.

I.1.2 HCV AND BLOOD TRANSFUSIONS

Anyone who received a blood transfusion or a blood product before 1992 is considered to be in a high risk group. Blood banks began screening donors for certain markers as early as 1986, but contaminated blood still found its way through to people. In May 1990, screening tests for the hepatitis C virus came into use, and the risk is now thought to be 1 per 2 million units of blood *(www.cdc.gov)* for the typical recipient of a transfusion. A typical recipient is one who does not have other conditions that would make it more likely for them to catch the virus (like HIV infection). - *California at Berkeley Wellness Letter, May 1993.* See **Appendix E: History of Blood Safety**. HCV acquired through blood transfusion tends to be more severe than through other modes of transmission.

I.1.3 HCV AND INTRAVENOUS DRUG USE

Investigators at Johns Hopkins report that injection drug users are at high risk for contracting hepatitis B and C, and that many contract hepatitis B or C within the first year of IV drug use.

Dr. David Vlahov and colleagues studied 716 volunteers who had been injecting for six years or less. Seventy-seven percent of them were infected with HCV and 65.7% were infected with HBV. Roughly 20% were HIV-positive. Hepatitis C was more prevalent among those who reported injection drug use for less than four months than among those who reported injecting drugs for 9 to 12 months. *(Am J Pub Health 1996; 86:642-646).*

Studies in British Columbia (1999) showed that 90% of the male prison population is infected with HCV. Rates of infection among young IV drug users is rising, with as many as 45% infected in the US, excluding those institutionalized. *(http://blog.aids.gov/2013/06/hepatitis-c-infection-among-young-injection-drug-users-addressing-an-emerging-trend.html)*

I.1.4 HCV AND IV IMMUNOGLOBULIN (also called GAMMAGARD/POLYGAM/FACTOR D)

Contaminated batches of Gammagard and Polygam, drugs used in intravenous immunoglobulin therapy, may have caused thousands of people across the U.S. to contract the hepatitis C virus. Many of those infected by Gammagard were children. Gammagard is primarily used to boost a person's immune system. Many women in Ireland were infected through the use of contaminated Factor D after childbirth.

Therefore, people who received immunoglobulin therapy should contact their doctor immediately to have liver function tests performed. These products are still made from human plasma, but the donors are carefully screened and the tests for viruses are much more sensitive now than they were in the past.

I.1.5 MOTHER-TO-CHILD TRANSFER OF HCV

The greatest risk of infecting a baby from mother to child (vertical transmission) depends on the amount of virus in the mother's body (viral load). The IL28B allele doesn't affect the risk, but having the CC type is associated with spontaneous clearance in infected GT1 children.
(www.natap.org/2011/HCV/052311_02.htm)

Reducing the Risk of Transmission During and After Pregnancy
(From the HepCBC pamphlet "HCV & Pregnancy")

A woman living with Hep C who wishes to become pregnant may be worried about the health of her baby. The chance of the virus being transmitted to the baby is 1.1-10.7%, but higher in persons who have HIV (4.2-28.5%) or use IV drugs. *(http://natap.org/2014/HCV/011915_07.htm)* If a mother also

has AIDS, the chances can increase up to 36 in 100. The risk may be even greater in mothers who are infected with both Hep B and Hep C.

Viral Load and Mother-to-Baby Transmission *(See also* ***PREGNANCY AND BREASTFEEDING)***
Viral load is the amount of Hep C in the blood. If a woman with Hep C has low viral load (less than 1 million copies/mL), it is less likely that the virus will be passed to her baby than if she has high viral load, but there is still a chance that Hep C will be transmitted. If the mother has no virus, the baby will not be infected.

There are indications that a female baby is twice as likely to be infected as a male baby.
(www.medicalpost.com/mpcontent/article.jsp?content=20060115_181536_2940 January 17, 2006 Volume 42 Issue 02)

Transmission to the baby can happen before or during birth.
Present information shows that transmission may be slightly more likely in infants born to mothers with genotype 1, one of the six major strains of the virus.

Most doctors and midwives will be helpful and supportive to a woman with Hep C who wants a child. Pregnancy with Hep C is not officially discouraged, however, a woman may wish to take treatment for hepatitis C before becoming pregnant. **RIBAVIRIN CAUSES BIRTH DEFECTS**, so if you have taken it, wait at least 6 months after stopping treatment before getting pregnant, to avoid birth defects. Infected men on ribavirin treatment should use birth control during, and for at least 6 months after treatment for the same reason.

Birth by Caesarian section does not usually reduce the risk of transmission. However, it is possible that if a woman has an acute case of Hep C or is co-infected with HIV, there is a higher risk of her baby being infected.

Breastfeeding
There has been no documented case of infection through breast feeding. Generally, women with Hep C are encouraged to breast feed unless their nipples are cracked or bleeding--just in case the virus could be transmitted this way. Two studies published in the *Journal of Infectious Diseases* concluded that breastfeeding is safe. One was a European study involving 1,479 mother-and-child pairs, and the other, a US study which followed 244 infants born to HCV+ mothers.
(www.medicalpost.com/mpcontent/article.jsp?content=20060115_181536_2940 January 17, 2006 Volume 42 Issue 02) (See also ***PREGNANCY AND BREASTFEEDING)***

Children with Hep C *(See also* ***HOW DOES HCV AFFECT CHILDREN****?)*
In children, viral infection is usually silent, although children as young as 8 years old can become quite ill from HCV.
Children are less likely than adults to have symptoms of infection with Hepatitis C, and thus may be able to transmit the virus unknowingly.
Having hepatitis C does not seem to affect a child's growth. (It may be associated with increased insulin resistance and lower rates of total cholesterol).
All children, with or without hepatitis C, should be taught proper hygiene.

Children and Advanced Liver Disease
Chronic hepatitis C eventually causes cirrhosis or cancer. However, it can take 10 to 20 years or more before cirrhosis may occur. Liver cancer rarely occurs in children.
Worldwide, there are an estimated 11 million people under the age of 15 who are infected with HCV.

Treatment in Children
The AASLD recommends:

1. Diagnosis, testing, and liver biopsy of children thought to have HCV. A Fibroscan is safer than a biopsy for everyone, including children, and it's painless, but children may need an S2 probe, which has a thinner tip than those for adults. Sometimes they are hard to find, and adult probes (M probes) are used on children. You can inquire at info@liverscan.ca or 416-268-0150. *(www.liverscan.ca/#!faq/c1mhs)*
2. Because of the high spontaneous clearance rate during the first year of life, children of HCV-infected mothers should be tested at 18 months or later.
3. Healthy children with HCV ages 3-17 may be given interferon alpha-2b and ribavirin by specialists in treating children. (Note: This FAQ uses "alpha," although some companies use the term "alfa" with their interferon products, and have them patented this way).
4. Children under the age of 3 should not be treated.

The CDC recommends:

1. Testing after 12 months of age.
2. Earlier testing, if required, should be nucleic acid-based for the virus (HCV RNA) at age1-2

months (not just the antibodies).
3. If positive, children should be evaluated for liver disease, sent to a specialist, and followed up for presence of the virus or antibodies at 18 months.
4. Follow-up tests aren't needed when anti-HCV is negative.
(http://natap.org/2014/HCV/011915_06.htm)

There are still many questions about hepatitis C in children. More studies are necessary to learn more about how the disease progresses and about different treatments. Clinical trials are presently being done in a few children age 3 and up: Telaprevir+pegIFN/RBV, Sovaldi + RBV, and a Phase III trial of Ledipasvir/Sovaldi ("**Harvoni**"). (*www.clinicaltrials.gov*) (WARNING: Do not take Amiodarone with Sovaldi or Harvoni).

Talking to Health Care Workers

Doctors and midwives can be helpful and supportive to a woman with Hep C who wants a child. It can be very hard for a woman with Hep C to tell her health care workers she is or wants to be, if she suspects they will try to change her mind. Health Care workers with experience in helping women who have Hep C are likely to be the best informed and most supportive.

I.1.6 OTHER MEANS OF HCV TRANSMISSION

Like hepatitis B, hepatitis C is spread through exposure to blood from an infected person, such as through a blood transfusion or sharing needles. There is no evidence that the hepatitis C virus can be transmitted by casual contact, through foods or by coughing or sneezing.

I.1.7 SEXUAL TRANSMISSION

Is HCV transmitted sexually? Studies are still being done. We picked three interesting studies, one studying heterosexual couples and two more, studying homosexual men.

A 2012 study interviewed 500 HCV+/HIV-long-term, monogamous heterosexual couples, separately, about risk factors for HCV, such as sexual practices and sharing grooming items. Blood was analyzed to see if the couple's viruses matched. It was found that 4% of the partners had HCV. Of those, 9 couples had the same genotype and serotype. It was found that 3 couples among the 500 interviewed had viruses that indicated possible transmission from one partner to the other, so sexual transmission was 0.07% per year. There was no obvious sexual practice that was especially dangerous.

The second report, from England, indicated an increase of STDs among men who have sex with men (MSM), probably due to not using condoms or to unsafe injection practices. Those risky practices may be the reason for the recent spread of HCV among the MSM community there. Most studies have looked at MSMs who are HIV/HCV co-infected. To find out if HCV appears in HIV-negative MSM, they looked for those patients at the clinics and found 44 such patients between 2010 and 2014. Half were classified as having had up to 2 partners. The other half had more than two. The most common risk factor was not using condoms. They also found that the riskiest behavior was receptive, unprotected anal intercourse, About 50% disclosed use of injected or inhaled drugs.

Many seemed to think that when they were screened for HIV, they were also screened for HCV, which usually was not the case. The researchers concluded that "…more research needs to be done to assess the extent of the spread of HCV among HIV-negative MSM not only in London but in other cities and countries." *(www.medscape.com/viewarticle/775549)*

Health Canada says, "Long-term monogamous couples should decide for themselves about routine condom/dental dam use." (*www.phac-aspc.gc.ca/hepc/faq-eng.php#a4)*

A report on February 19, 2015, says that the Kaiser Permanente San Francisco Medical Centre discovered two probable cases of sexually-transmitted hepatitis C among 485 MSM who tested negative for HIV and were using PrEP (pre-exposure prophylaxis, such as Truvada [tenofovir/emtricitabine]). Both were infected with syphilis, gonorrhea and chlamydia, and one had unprotected sex with multiple partners. *(www.aidsmeds.com/articles/sexual_acquisition_HCV_1667_26831.shtml)*

Practicing safer sex is always a good idea for people with multiple partners. People who engage in high-risk sexual behaviour have a greater risk of contracting STDs, which can cause open sores and lesions. Open sores and lesions mean a greater risk of blood-to-blood contact and a higher risk of contracting hepatitis C. If you have herpes, you are at a greater risk of catching hepatitis C. It might be possible that HCV piggybacks on the genital herpes virus through genital lesions. If you have multiple partners, use condoms. People with acute HCV or with compromised immune systems, should be more careful, as these conditions can raise the level of virus in the bloodstream, and can mean a greater risk of infection. Sex during menstruation should be avoided. Also see: **DISCLOSURE**
(www.ncbi.nlm.nih.gov/pubmed/23175457)

I.1.8 OCCUPATIONAL EXPOSURE (NEEDLESTICKS, ETC)

The general consensus is that HCV is a greater threat to healthcare workers than HIV. The risk that healthcare workers will become infected with hepatitis C virus (HCV) following an accidental needlestick injury is 20 to 40 times greater than their risk of HIV infection. (According to data presented at the International Conference on Emerging Infectious Disease, Sponsored by the US Centers for Disease Control and Prevention and the American Society for Microbiology in July 2000.

HCV exposure is possible in any occupation that could involve contact with infected blood, (i.e., nurses, phlebotomists, emergency medical technicians, firemen, and police to name a few). The risk of HCV infection following a needlestick injury with HCV-contaminated blood may be as high as 10%. Nonetheless, the risk of occupational transmission of HCV to Health Care Workers is far less than that of HBV. Current recommendations are that "both private and public health providers be made aware of the risk, and above all that all source patient providers be tested for hepatitis C." *(Dr. Robert T. Ball www.hepnet.com/hepc/news072000.html)*

If you are exposed to the blood of a person who might be infected with HCV:

1. Wash the area with soap and water
2. Flush eyes, nose or mouth with water or other sterile liquids in case of splashes
3. Report the event to the supervisor. Have the source person tested.
4. See a doctor immediately to have baseline testing done.
5. Get follow-up testing done after 4-6 weeks.

(www.cdc.gov/niosh/topics/bbp/emergnedl.html)

Remember that only about 1.8% of exposures transmit HCV. There is no treatment given immediately after exposure, but early diagnosis and treatment can improve response rates in case of infection. *(http://nccc.ucsf.edu/clinical-resources/pep-resources/pep-quick-guide/)*

I.1.9 TOOTHBRUSHES/RAZORS/NAIL CLIPPERS

It is possible for toothbrushes, razors, nail clippers, tweezers, and similar personal care items to come in contact with infected blood. It is safer not to share personal items, especially for people infected with hepatitis C. Recently concern was expressed over the sharing of electric razors in a VA hospital and in prisons. A study in *Hepatology* showed that 19% of veterans tested in a VA hospital in San Francisco were infected with HCV.

I.1.10 HEMODIALYSIS

Patients on hemodialysis have higher rates of hepatitis C viral infection. It is vital that hospitals stick to strict infection control practices and that hemodialysis patients be tested regularly for HBV and HCV. *(Minerva Urol Nefrol. 2005 Sep;57(3):175-97).*

I.2.0 HIGHLY SPECULATIVE MODES OF TRANSMISSION OF HCV

The following few sections discuss highly speculative ways of getting Hep C, because there have either been no studies, or conflicting studies. There may be reason to believe this is not a mode of transmission, but still no conclusive study to rule it out.

I.2.1 TEARS, SALIVA, URINE, AND OTHER BODY FLUIDS

"The presence of the RNA in the tear fluid was independent of the severity of the hepatitis and of the viral load as measured by the branched DNA assay…These findings suggest that tear fluid may transmit HCV but the source of HCV RNA in this fluid needs to be better understood." *(Med Virol. 1997 Mar; 51(3):231-3).*

HCV has been found in all body fluids, but not in all patients, and in varying amounts. The question remains as to whether or not the virus can be spread through these fluids. Blood in the fluids can definitely spread the disease, as with saliva from patients with bleeding gums. Another factor may be whether or not there are HCV-receptor cells in the mouth lining, and whether or not the body's immune system fights off the virus in these quantities. *(Oral Dis. 2005 Jul; 11(4):230-5).*

A report suggests that a health care worker contracted HCV and HIV from a patient. The worker had chapped hands, did not use gloves, and was in frequent contact with the patient's urine and feces. *(Am J Infect Control. 2003 May; 31(3):168-75).*

I.2.2 CAT SCRATCHES

It is unknown if the hepatitis C virus can be transmitted via cat's claws if the cat scratches one person and immediately scratches another.

I.2.3 MOSQUITOES

Researchers have determined that the hepatitis C virus is not transmitted by mosquitoes. There is a lack of epidemiological or physical evidence that it is mosquito-borne and experiments to see any HCV replication in mosquito cells have failed. See more here:
www.researchgate.net/post/Can_hepatitis_B_and_hepatitis_C_be_transmitted_by_mosquito_bite

There are two ways that mosquitoes can transmit illness to humans. One way is "mechanical transmission," where a small amount of blood may be present on the mosquito's feeding spike. This type of transmission does not occur with serious human diseases such as HCV, HBV, or HIV. The second way mosquitoes transmit disease is called "biological" transmission. Studies show that mosquitoes can swallow viruses into their middle gut, but once there the virus dies and is digested in the same way we digest food - by breaking it down using acid.

I.2.4 ALTERNATIVE MEDICAL PROCEDURES

Alternative medical procedures involving invasive medical procedures, particularly those performed in non-medical settings *(i.e., acupuncture)*, or involving autologous blood (such as the ozone-enrichment of blood) may transmit the hepatitis C virus. *("Transmission of Hepatitis C by Ozone Enrichment of Autologous Blood," Lancet, 1996; 347:541*). A cross sectional survey in Japan found an increased risk of hepatitis C associated with acupuncture *(BMJ 2000;320:513, 19 February).*

I.2.5 HOUSEHOLD TRANSMISSION

Household transmission of hepatitis C is rare. It can occur where blood-to-blood contact happens. This could involve a person's blood coming into contact with someone else's open cut, or to a lesser extent, the sharing of razor blades, toothbrushes and sharp personal grooming aids. It is advisable to wipe up blood spills with paper towels and bleach, and to keep razors and toothbrushes separate from those belonging to other family members. Wiping a surface with isopropyl alcohol and leaving it to air dry will also kill the virus. *(See I.1.7c Cleaning Up Blood Spills)*

A person cannot spread the virus through hugging, touching, sneezing, coughing, or sharing food, dishes, or bathrooms.

I.2.6 UNKNOWN CAUSES

A proportion of HCV infected individuals do not fall into any currently recognized risk group. It is thought that **some** of these cases may have had exposure to injected drugs or shared cocaine paraphernalia many years ago which they have forgotten or are unwilling to discuss. It is possible that many persons were infected in the early 50s during mass vaccination programs in schools and camps. As well, programs for the poor often used cost cutting measures which included the recycling of medical devices (syringes, needles) which should have been thrown away. Furthermore, blood products have been used in the making of many vaccines and in the 50s and 60s these products were not screened for HCV.

I.3.0 IS HCV ANYTHING LIKE HIV?

Both HIV and HCV are RNA viruses. Their genetic code is carried in RNA strands instead of DNA, like some other viruses. HCV is more like HIV than some other forms of hepatitis, but they are from completely different families. They have completely different strategies for replication and for survival.
HIV is a retrovirus, and once the virus is in a human cell it copies itself to DNA and migrates into the cell nucleus and integrates into the host genome and is then copied every time the cell copies its own DNA. Retro means that the virus reverts to a DNA virus once it is in the cell. Other retroviruses are HTLV viruses like some types of leukemia.

HCV is a flavivirus. It is related to yellow fever and dengue fever viruses. It replicates by making positive and negative RNA strands and does not make DNA or integrate into the host genome.
There are lots of other structural and envelope differences between these two, but the main point is that HIV and HCV are NOT very similar at all but for two exceptions. One, they both completely mess up the immune system, and two, there is no known cure.

I.4.0 PREVENTION

Prevention: avoid risky behaviors. Shots of gamma globulin (now hopefully safe) after a person has been stuck with a needle do not seem to work. There are no current HCV vaccines. With screening of the blood supply, the risk of HCV infection from a transfusion has dropped from 10% (1970's) to less than 1%. *("Prevention, Diagnosis, and Management of Viral Hepatitis," AMA)*

I.4.1 WHEN, AND FOR HOW LONG, IS A PERSON ABLE TO SPREAD THE HEPATITIS C VIRUS?

Before the cure, eighty-five to ninety percent of all HCV carriers would have Hep C for life. There no longer seems to be a debate over whether people who have had a sustained viral response after treatment are cured or not. All carriers of HCV can transmit the disease to others via blood until they are cured. The disease may occur in the acute form and be followed by recovery, but the majority of the cases become chronic and cause symptoms for years.

A study at the Center for Disease Control and Prevention, Atlanta, suggests that HCV in dried blood may survive on environmental surfaces at room temperature at least 16 hours but not longer than 4 days. (*www.hepatitisresources-calif.org/news* Krawczynski, K. et al, Centers for Disease Control and Prevention, *Environmental stability of hepatitis C virus (HCV): Viability of dried/stored HCV in chimpanzee infectivity studies. 11/25/2003)*

I.4.2 HOW CAN THE SPREAD OF HEPATITIS C BE PREVENTED?

People who have hepatitis C should remain aware that their blood, and possibly other body fluids, are potentially infective, even when the person carrying the virus is asymptomatic. Care should be taken to avoid blood exposure to others by sharing toothbrushes, razors, needles, etc. Infected people must not donate blood, plasma or semen, and should inform their dental or medical health providers so that proper precautions can be followed. Of course, the best way to not spread the disease is by getting cured. Luckily, the new treatments are expected to be short (4-8 weeks), all oral, and with few, if any, side effects.

I.4.3 CLEANING UP BLOOD SPILLS

A 10% bleach solution (soak for 30 minutes) should be used on all contaminated surfaces. There is no proof that this KILLS everything, but you can't autoclave the world. There are also chemical disinfectants containing phenols and other very expensive ingredients, but for home use, bleach is the best we have. Bleach can be **very, very** corrosive on some surfaces, so be careful what you use it on. For cleaning up blood on the skin, use isopropyl (rubbing) alcohol.

Dispatch Hospital Cleanser Disinfectant with Bleach (www.caltechind.com/dispatch/index.asp) and Spartan Chemical's HDQ NEUTRAL7 (www.spartanchemical.com) both claim to kill HCV.

From the* hepc.bull *Dec 1999, Issue 18.

"BLOOD SPILLS: DO YOU KNOW HOW TO SAFELY CLEAN UP A SPILL OF BLOOD OR BODY FLUID? THIS ARTICLE WILL TELL YOU HOW", by Mark Bigham, MD, FRCPC, British Columbia Centre for Disease Control

Hepatitis C virus (HCV) is transmitted mainly by exposure to HCV-contaminated blood. HCV infection is not generally associated with exposure to other body fluids, such as saliva, urine, feces or vomit, but if HCV-contaminated blood is present in these or other body fluids, then the risk of infection will be greater. Therefore, it's important to treat any environmental contamination of blood or body fluid as potentially infectious. The simple principles of cleaning and disinfecting, which are effective against HCV, are also very effective against other micro-organisms.

Viruses can only reproduce inside cells and HCV will not survive very long outside the human body (usually no more than a few hours). Survival of HCV in the environment is limited by such factors as lower temperature and dryness. HCV is also readily killed by standard household products, such as 5% household bleach or 70% isopropyl alcohol.

If you encounter a spill of blood or body fluid, the most important infection control principle is to avoid direct contact. This is easily and effectively achieved by wearing rubber gloves—preferably single use, disposable vinyl gloves, or even household rubber gloves. Litter, such as broken glass should be picked up first. Try not to handle broken glass that could tear the gloves. Pieces of stiff cardboard or newspaper folded over can be used to pick up glass. When disposing of glass, wrap it in a newspaper before throwing it in the garbage bag, to protect municipal waste disposal workers from being cut when handling the bag.

Next, clean up the visible blood or body fluid with plain water and disposable paper towel. Using water will dilute the spill, reduce its infectivity, and facilitate wiping up the spill. Cleaning the visible spill will also remove organic matter that can reduce the effectiveness of disinfectants. The used paper towel can be put in a plastic bag (double bag if very wet and dripping) and disposed of in the regular household garbage.

A disinfectant should then be used. Regular 5.25% household bleach is an excellent disinfectant choice—it is inexpensive; has low toxicity and is not usually irritating to the skin; is fast acting; and is very effective not only against HCV, but also other blood-borne viruses (e.g., HIV, Hepatitis B virus), bacteria and fungi. It can be diluted with water to make a 1:10 to 1:100 bleach solution. The diluted solution should be prepared fresh, since bleach degrades over time when exposed to air or light. It can be wiped onto the surface with a towel and left to air dry, or poured onto the affected area and then

wiped up with disposable paper towels after 10 minutes. An effective, alternative disinfectant for use on colour-sensitive fabrics or materials is 70% isopropyl alcohol, full strength, and applied in the same manner as described for bleach.

Gloves can then be carefully removed and disposed of in the regular household garbage along with the used paper towels. Reusable gloves can be rinsed in water and dipped or wiped in disinfectant and allowed to air dry. Finally, don't forget to wash your hands.

I.5.0 WHOM SHOULD I TELL? HOW DO I TELL?

If you have hepatitis C, you are under no legal obligation to tell others. However, the law may change. Right now, it is up to you to decide whether to tell anyone of your hepatitis C status. Some people (and unfortunately some health care providers, also) may have judgmental attitudes or unnecessarily exaggerated fears of infection. People should carefully consider whom they inform, in the light of possible discrimination. How people might have caught the virus is not important. Those who have the hepatitis C virus should be covered by anti-discrimination laws. If in doubt, get legal advice.

Cases where patients have been infected by physicians have raised the ethical issue of whether or not infected physicians should be banned from performing invasive procedures. Some hospitals are now insisting that their surgeons be tested and that those infected get immediate treatment. (*www.macleans.ca/society/health/when-a-doctor-has-hep-c/)* Surgeons infected with HCV in Germany are allowed to perform surgery with approval of a committee of experts which takes into account the individual's situation, such as his or her viral load. *(www.ncbi.nlm.nih.gov/pubmed/15205780)*

DISCLOSURE: "Under public health law in some provinces and territories, people have a legal obligation to not pass on infections like HCV—in other words, to protect sex partners from becoming infected through sex. That is why Public Health (or physicians and nurses working in cooperation with Public Health) often counsel people living with hepatitis C to disclose their HCV infection to sex partners and to practice safer sex, including using condoms for intercourse."
(www.catie.ca/en/practical-guides/hepc-in-depth/faq/when-person-legally-required-tell-other-people-)

HOW DO I TELL?

If you've decided to tell your employer and/or co-workers, a good way may be to print pamphlets to give them which speak of how the disease is and isn't transmitted. It can come in handy for them to know, in case you're involved in some sort of accident at work, for example.

What about a potential or present sexual partner? With a spouse or former partner, you may have the excuse that you didn't know, so there is no fault in not telling earlier. If you are searching for a partner, don't worry; just because you've been diagnosed with Hep C doesn't mean you can't have a partner. But how do you tell? It can be scary, so practice first. How much will you say? When will you say it? Practicing can help you get over feeling nervous. Write out a speech. Record yourself. Try your speech with a trustworthy friend or therapist. Ask how he or she would react. Is there anything that makes him or her feel uncomfortable? What could work better?

It might be best not to tell on a first date. Let your prospective partner get to know YOU. If you're asked a personal, direct question, deal with it as such, and say you're not ready to discuss certain topics until you get to know him or her better. Some people suggest telling by the fourth date, so neither of you has invested too much time. Be prepared to be turned down. You may not always be successful. Tell before you get involved enough to be hurt; if you wait until the other person is emotionally involved, then he or she might feel you were dishonest.

Definitely plan on telling before sleeping with the person, and DON'T leave it until you're in bed or in the hotel room…or in the back seat. If the topic of sex comes up, that might be a perfect time to discuss the matter of both of you getting tested for sexually transmitted diseases. (No, Hep C is not an STD, but there is still the possibility of contracting it through unprotected sex if blood is involved*).* Or, if you can work it into the conversation somehow, such as talking about your volunteer work, or the movie "Deal With It," it's better than having a talk just about Hep C. Consider having a pamphlet handy. Give your friend the important facts, but don't overdo it. You will earn "brownie points" by suggesting he or she speak with a doctor. You can truthfully tell the other person that there is less than a 3 percent chance of transmitting Hep C, even during unprotected sex.

If you are met with uncertainty, it might be a good thing to say that you understand that he or she needs time to think, and invite your new friend to call you in a day or two. If you haven't heard back after about 3 days, consider calling to say you're still thinking of him/her, but frankly, if the person won't accept you with Hep C, the person is probably not worth your time. Hep C can be a blessing in disguise. A caring person who is interested in you will go to the trouble of investigating the disease, and will be intelligent enough to see it really doesn't matter. It's an excellent way to weed out the duds! But if you really don't want this great opportunity to find a quality mate….get treated. Get cured! *(From the hepc.bull Feb. 2015)*

I.6.0 CAN YOU GET HEPATITIS MORE THAN ONCE?

Once you completely recover from hepatitis A or B you can't get it again, although in some people the condition becomes chronic and can last their whole lives. Nevertheless, since there are at least five different viruses that cause hepatitis, you can get one of the others (though not D if you are immune to B). Becoming infected with B and C at the same time may actually cause a much more severe, dangerous case of hepatitis. A person who has recovered from a case of viral hepatitis could also develop hepatitis again due to other causes, such as alcohol or drugs.

If you have had hepatitis C and clear the virus, you **can** become infected with it again, or you can become co-infected with more than one genotype. Because there are so many different genotypes of hepatitis C, and because the virus mutates so rapidly, natural immunity is not developed. Studies have shown chimpanzees that have recovered from acute hepatitis C became sick again when re-exposed to the same strain of the virus. *(www.bloodjournal.org/content/bloodjournal/85/7/1681.full.pdf?sso-checked=true)*

PART II - MEDICAL ISSUES

II.0.1 HOW DO I FIND GOOD MEDICAL CARE FOR HEPATITIS?

It is very important to find a health practitioner who is familiar with this illness. The symptoms of hepatitis can be mimicked by other illnesses, such as autoimmune illnesses, cancer, chronic fatigue syndrome, lupus, arthritis, etc... If you in fact have another illness that is not properly diagnosed, you may be losing out on getting treatment that might be effective for you.

It is still an uphill struggle to find a doctor who is experienced in diagnosing and treating hepatitis C. A hepatologist specializes in diseases of the liver, and is the best choice, followed by a gastroenterologist (a digestive disease specialist), or an infectious disease specialist. If there is a hepatitis support group nearby, it could be an excellent resource for identifying local doctors who may be familiar with hepatitis. You can also contact the American Liver Foundation (ALF), the HEP project in Seattle, the Hepatitis C Support Project in San Francisco, HepCBC in Victoria, British Columbia, or a host of other hepatitis C organizations for a list of doctors near you who are experienced in treating Hep C. If there are no hepatitis specialists in your area, you may want to go out-of-town, and your local hepatitis C organization may be able to help you. For a list of hepatitis C organizations in your area see Part XII of the FAQ.

If your own doctor is sympathetic but doesn't have a lot of experience with Hep C, you might gather together some medical articles on hepatitis and hepatitis treatments and encourage your doctor to study them. You can also give him or her a copy of the FAQ.

See Appendix D for a list of Hepatologists and Gastroenterologists in Canada and possible places offering clinical trials.

II.0.2 WHAT IS THE DIFFERENCE BETWEEN A GASTROENTEROLOGIST AND A HEPATOLOGIST?

A hepatologist specializes in treating liver disease. A gastroenterologist specializes in the gut. Hepatologists are more likely to be on top of the latest information concerning treatment of hepatitis C. Unfortunately, hepatologists are few and far between, especially in Canada.

II.1.0 HOW IS IT DIAGNOSED?

There are 2 major blood tests for HCV.

1) An antibody test (EIA or RIBA--blood tests) or a quick screening test called OraQuick (20 minutes—one drop of blood)
2) The HCV RNA test (Qualitative: Detects if the virus is still present and/or Quantatitive, which measures the amount of virus circulating in a person's blood stream).

While the newer HCV antibody tests screening tests are better than before, the test shows exposure to the virus, but doesn't say if you still have the virus. Further testing should be used to confirm a positive antibody test. Abnormal liver function tests (LFTs) suggest chronic disease, but there is no correlation between the level of the liver function tests and how severe the disease is. Many physicians (especially primary care physicians) still assume that people with low LFT's do not have severe disease, and this has led to complications and even death because of misdiagnosis. Studies show that testing for enzyme level elevation is not an accurate diagnostic for the presence of hepatitis C *(Digestive Disease Week 2000)*.

Before 1990 doctors could diagnose HCV only by ruling out other possibilities (thus the old name for HCV was "non-A, non-B hepatitis").

Hepatitis C antibodies may not develop for two to six months after infection, so not all patients who go to the doctor with possible hepatitis C infection can be diagnosed immediately with blood tests. Diagnosis may have to exclude other possible reasons for symptoms such as HAV, HBV, cytomegalovirus, Epstein-Barre virus infection, as well as non-viral liver problems such as fatty liver, or alcohol or drug-related diseases.

Follow-up blood tests are very important in order to determine if the disease has become chronic. The blood tests for antibodies are usually repeated three and six months after the original diagnosis.

II.1.1 ANTIBODY TESTS

Antibody tests indicate whether the body has been exposed to the virus and has produced antibodies to fight it. They do not determine whether or not someone still has the virus, or how long they've been infected. Antibody tests are the most common method of diagnosing hepatitis C. However, the test can show a false positive reaction and therefore confirmation is necessary by finding evidence that the hepatitis C virus is actually in the blood using the polymerase chain reaction (PCR).

II.1.2 WHAT IS A PCR?

HCV Polymerase Chain Reaction (PCR) tests came onto the market in late 1994. HCV PCR tests look for the presence of the virus. Information gained from the HCV PCR can be useful in interpreting unclear antibody test results. The HCV PCR cannot tell how long someone has been infected. A tiny amount of your blood sample is separated into parts and cleaned. Some of the viral RNA is pulled out. This goes through the process of PCR. Part of the RNA specific to hepatitis C is pulled apart by heating it, and new copies are made of this area. This is done millions of times in just a couple of hours. Your sample can then be analyzed through many different methods, including being seen under a UV light, producing that pretty sheet of stripes that you see in forensic crime shows, Maury Povich and the OJ trial. *(Viola Vatter, Victoria, BC)*

There are at least three sets: two are the controls--a known HCV-positive sample and an HCV-negative sample; the other sample is you. If yours matches the positive sample, you have the virus.

II.1.2a WHAT IS A GENOTYPE?

A genotype (GT) is the "family" to which our specific virus belongs. Our genotype does not change, but we can be re-infected with a different genotype. The most common genotypes are: 1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, and 5. GT3a has the highest response rate to interferon. People with this genotype are generally younger in age, and usually have been IV drug users. GT1 patients need longer treatment in order to respond to interferon, but are responding well to the 2nd generation direct-acting antivirals (DAA's)

II.1.2b The IL28b Test

This is a test, not yet approved in Canada, which tells whether or not you will respond to interferon-based treatment. Right now clinical trials are stratified into arms, sometimes according to genotype, sometimes according to viral load, sometimes according to status as a non-responder/null-responder/relapse, etc. Many researchers believe that patients should also be divided according to IL-28b genotype (C/C vs. non-C/C) before they are randomized to different arms. (This is a human, not a viral genotype). In a trial, it was shown that there could be a 10 to 20% difference in response rates especially at week 4, according to the patient's IL28b genotype. The difference may be even higher in non-white patients. It has been discovered that C/C GT1 patients have improved early responses, as shown in 3 hypothetical trials, where the researchers re-stratified results obtained in other trials. This stratification is especially important in the early phase trials.
(www.clinicaloptions.com/Hepatitis/Conference%20Coverage/AASLD%202010/Tracks/HCV%20Treatment/Capsules/810.aspx)

The good news is that the IL28b status doesn't seem to affect treatment response with the new DAA's.

II.1.2C WHAT IS A Q80K?

We have heard about the IL28b gene, part of our own immune system that we were born with, and we know that, if we could choose, we would want the kind of the gene that has the CC allele (a variant—a type of DNA coding, occupying a certain part of a chromosome), which can mean the virus might respond to IFN treatment more easily or even go away spontaneously, perhaps even before we are diagnosed. If you have the CT allele, you may or may not respond to treatment. But if you have inherited the TT allele, then it is very difficult for you to respond to conventional Hep C treatment with IFN. Luckily, the new DAAs don't care about what kind of IL28b gene we have. (Just think: A few years ago, they couldn't even find the virus, and now they're studying its genes!!)But now researchers have

discovered yet another stumbling block: Q80K.

Q80K is a polymorphism—a variation in the virus's NS3/4A protease enzyme that occurs naturally in up to 48% of patients with genotype 1a (GT1a). The GT1b virus rarely has this mutation.
Trials suggest that, even though simeprevir (formerly TMC435, now Olysio in the US and Galexos in Canada) cures 80% of treatment-naïve patients, those with the Q80K mutation should consider a different therapy, and not waste their money or time. ("Notably, no Q80K-related reductions in efficacy were observed during the pivotal trials of the previously approved NS3/4A protease inhibitors, telaprevir and boceprevir.")
(*http://livertree.easl.eu/easl/2014/international.liver.congress/49037/undefined*)

II.1.3 COULD THE TEST RESULTS BE WRONG?
Antibody tests are usually positive or negative, but sometimes they come back unclear. Tests that come back positive are redone to confirm that they are right. Unclear results are repeated and if still unclear, different types of blood tests are done. If you get a positive test result and have no risk background (for example, blood transfusions or drug use) it's a good idea to check with your doctor to make sure that the laboratory double checked the result by using confirmatory tests.

II.2.0 DO I NEED A BIOPSY?
Patients with chronic hepatitis often do not experience symptoms. On the other hand, others complain of excessive fatigue, weakness, and a reduced capacity for exercise.

Since liver damage may occur even in asymptomatic cases (no patient complaints), it is important to determine whether there is ongoing liver damage. As chronic hepatitis progresses, damage to liver cells may impair liver function. A biopsy of the damaged liver indicates the degree of cellular necrosis (death of liver cells), inflammation (cellular infiltration and swelling), and scarring (scar tissue beginning to replace functioning liver cells). - "Understanding Chronic Hepatitis" - Schering - 10/92 INH-001/17098403

Some specialists have invested in Fibroscan machines, which give results comparable to a biopsy, are safer, and don't involve pain. (See "What is a Fibroscan"**)**

II.2.0a WHAT IS A LIVER BIOPSY?
A liver biopsy is a diagnostic procedure used to obtain a small amount of liver tissue, which can be examined under a microscope to help identify the cause or stage of liver disease. The most common way a liver sample is obtained is by inserting a needle into the liver for a fraction of a second. This can be done in the hospital with a local anesthetic, and the patient may be sent home within 3-6 hours if there are no complications. The physician determines the best site, depth, and angle of the needle puncture by physical examination or ultrasound. The skin and area under the skin is anaesthetized, and a needle is passed quickly into and out of the liver. Approximately half of individuals have no pain afterwards, while another half will experience brief localized pain that may spread to the right shoulder. Some persons, however, have had to be hospitalized afterwards due to extreme pain, shock or puncture of another organ.

Many patients have commented that taking Ativan, a tranquilizer, before the procedure helped reduce the pain, since this drug will relax the internal muscles and prevent spasms.

Patients are monitored for several hours after a biopsy to make sure serious bleeding has not occurred. Some patients occasionally have a sudden drop in blood pressure after a biopsy that is caused by a vagal reflex and not by blood loss; this is caused by sudden irritation of the peritoneal membrane. The characteristics that distinguish this from a bleeding event are: 1) slow pulse rather than rapid, 2) sweating, and 3) nausea.

II.2.0b WHAT ARE THE DANGERS OF LIVER BIOPSY?
The risk of a liver biopsy is minimal. The primary risk is bleeding from the site of needle entry into the liver, although this occurs in less than 1% of patients. Other possible complications include the puncture of other organs, such as the kidney, lung or colon. Biopsy, by mistake, of the gallbladder rather than the liver may be associated with leakage of bile into the abdominal cavity, causing peritonitis. Fortunately, the risk of death from liver biopsy is extremely low, ranging from 0.01% to 0.1%.

A biopsy should not be done if: 1) you have taken aspirin in the last 5-7 days, 2) the hemoglobin is below 9-10 grams/dl, 3) the platelets are below 50,000-60,000, or 4) the prothrombin time INR is above 1.4. Those with bleeding disorders such as hemophilia, which can be temporarily corrected with transfused clotting factors, can safely have a biopsy, or they may be able to have a transjugular biopsy.

II.2.0c WILL IT HURT?
Most doctors will not do percutaneous needle liver biopsies under anesthesia. This is because the liver is directly under the diaphragm and moves as you breathe. When the needle is inserted through the skin and body wall, the liver must not be moving or else there is danger of a laceration. To keep the liver from moving, the patient has to stop breathing momentarily. Doctors prefer to have you alert and able to follow directions, but if you are very anxious, you may want to ask for a sedative to help you relax. The injections of local anesthetic, and the actual puncture of the liver capsule, itself can be a little painful for some people, but it only takes a second and is over very quickly. Other people feel no pain at all, and don't realize it's happened until the doctor tells them they're finished.

Occasionally there will be a small to moderate amount of pain afterwards. If you find that you are uncomfortable, your doctor will generally prescribe a light painkiller immediately after the biopsy. The pain may be far away from the biopsy site, possibly in the pit of your stomach or typically in the right shoulder. Be aware that some doctors are hesitant to give pain killers to those with hepatitis C. It is advisable to discuss this matter with your doctor before hand to avoid unnecessary discomfort. The liver itself has no pain-sensing nerve fibers, but a small amount of blood in the abdominal cavity or up under the diaphragm can be irritating and painful. Very occasionally, small adhesions (scar tissue) may form at or near the biopsy site, and can cause a chronic pain that persists near the liver area after the biopsy.

There are blood tests that can give a fairly accurate idea of the amount of fibrosis in the liver. One such test, the Fibrometer, combines the platelet count, the AST, the prothrombin index, α2-macroglobulin, blood urea nitrogen, HA, and age, which can indicate the stage of fibrosis relative to the METAVIR system, or as the percentage of scarring (fibrosis) in the liver. Two of the similar tests are the APRI and the FibroTest. Combining one of these tests with the results of a FibroScan produces a very accurate and safe way of knowing what's going on in the liver.
(www.ncbi.nlm.nih.gov/pmc/articles/PMC3961992/)
(http://hepatitiscnewdrugresearch.com/liver-biopsynoninvasive-tests.html)

II.2.0d WHAT IS A FIBROSCAN?
FibroScan® is a procedure that can measure scarring (fibrosis) of the liver by testing the stiffness of the tissue. It was approved in April 2013 by the US Food and Drug Administration, stating "FibroScan® is indicated for the measurement of shear wave speed in the liver. The shear wave speed may be used as an aid to clinical management of patients with liver disease."

FibroScan® is painless, and takes only about 15 minutes. It is useful to judge the severity of damage to the liver and is often approved for treatment instead of biopsy. There is no danger of infection or death, and it is not invasive. Having a FibroScan is much like having an ultrasound, but with a "thumpy" feel to it, caused by the "shear waves." They measure how elastic the liver is, by using Vibration-Controlled Transient Elastography (VCTE). The higher the number, the more advanced is the fibrosis (scarring). The significance of the levels varies depending on the type of liver disease. When deciding whether or not the patient has cirrhosis, for example, the maximum level is lower with Hep C than for alcoholic liver disease.

Fibroscan is not as accurate as a biopsy for patients with mid-level liver disease, those with ascites, or those who are morbidly obese. (www.hcvadvocate.org/hcsp/articles/bonacini_2_fibroscan.html)

II.2.1 CHRONIC PERSISTENT OR CHRONIC ACTIVE - WHAT'S THE DIFFERENCE?
Hepatitis C is considered to be "chronic" if it has persisted for longer than 6 months. The term "Chronic Persistent" used to be used to define hepatitis which persisted for longer than 6 months, but which was not currently causing active damage to the liver. The term "Chronic Active" was used to define hepatitis which persisted for longer than 6 months, and which was actively destroying the liver. The distinction between "persistent" and "active" is not commonly used any more, with the assumption being that if the virus is present, it is causing damage.

About 85% of HCV-infected individuals fail to clear the virus by 6 months, and develop chronic hepatitis with persistent, although sometimes intermittent, viremia. This capacity to produce chronic hepatitis is one of the most striking features of HCV infection. The majority of patients with chronic infection have abnormalities in ALT levels that can fluctuate widely. About one-third of HCV patients with chronic infection have persistently normal serum ALT levels. Antibodies to HCV or circulating viral RNA can be demonstrated in virtually all patients with chronic HCV hepatitis.

Chronic HCV is typically an insidious process, progressing, if at all, at a slow rate without symptoms or physical signs in the majority of patients during the first two decades after infection.
A small proportion of patients with chronic HCV hepatitis - perhaps less than 20 percent - develop non-specific symptoms, including mild intermittent fatigue and malaise. Symptoms first appear in many

patients with chronic HCV hepatitis at the time of development of advanced liver disease. If by advanced we mean cirrhosis, then this is most definitely not the case. Symptoms can occur well before cirrhosis occurs.

Although patients with HCV infection and normal ALT levels have been referred to as "healthy" HCV carriers, liver biopsies can show histological evidence of chronic hepatitis in many of these patients. - *National Institutes of Health Consensus Statement on Hepatitis C 1997*

It is thus possible to have low enzyme levels and few if any symptoms and yet have dangerously advanced liver disease. The problem with this scenario is that the carrier does not know he or she is ill, and does not make modifications to his or her behavior—alcohol consumption, sexual protection, fatty foods, and so forth.

II.2.2 WHAT ARE THE MAIN SYMPTOMS OF HEPATITIS C?

Acute hepatitis C is almost indistinguishable from acute hepatitis B infection. Patients with acute hepatitis C are frequently asymptomatic (meaning that they have no symptoms), even when liver tests are abnormal. - "Hepatitis C & E: how much of a threat?" Special Issue: *Emerging Infectious Diseases*, Brown, Edwin A., May 15 1994, v28, n9, p105(8).

Soon after contracting the infection many people have a flu-like illness with fatigue, fever, muscular aches and pain, nausea and vomiting. About 10% of patients become jaundiced (their skin turns yellow). Generally these symptoms resolve and the patient has no symptoms of liver disease for many years. Symptoms may occur from two weeks to six months after exposure but usually within two months.

The symptoms of chronic infection range from no symptoms at all, to gradually progressive fatigue and lack of energy, to complete debility. The effects of the virus vary widely between individuals.

The symptoms of cirrhosis include progressive fatigue, jaundice (yellow skin), icterus (yellow eyes), dark urine (the color of cola), abdominal swelling, muscle wasting, itching, disorientation and confusion, loss of appetite, and easy "bruisability".

In an informal survey of hepatitis C symptoms, Scott Warren swarren@idir.net polled 50 people on the HEPV-L list and compiled the following results:

FATIGUE, WEAKNESS, TIREDNESS - 72%
JOINT, MUSCLE PAINS - 52%
MEMORY LOSS, MENTAL CONFUSION - 50%
SKIN PROBLEMS-DRY\ITCHY\RASHES\SPOTS - 44%
DEPRESSION, ANXIETY, IRRITABILITY, ETC - 44%
INDIGESTION, NAUSEA, VOMITING, GAS - 34%
SLEEP DISTURBANCES - 32%
PAIN OR DISCOMFORT IN ABDOMEN - 32%
CHILLS, SWEATING, HOT \ COLD FLASHES - 26%
EYE OR EYESIGHT PROBLEMS - 24%
SENSITIVITY TO HEAT OR COLD - 22%
NO SYMPTOMS - 20%
VERTIGO, DIZZINESS, COORDINATION - 18%
FLU LIKE SYMPTOMS - 18%
HEADACHES - 18%
URINARY PROBLEMS, ODOR, COLORATION - 16%
FEVER - 16%
SLOW HEALING AND RECOVERY - 14%
SUSCEPTIBLENESS TO ILLNESS \ FLU - 14%
WEIGHT GAIN, WATER RETENTION - 10%
MENSTRUAL PROBLEMS - 10%
APPETITE \ WEIGHT LOSS - 8%
SWELLING OF STOMACH, LEGS OR FEET - 8%
ORAL, OR MOUTH SORES \ PROBLEMS - 8%
EXCESSIVE BLEEDING - 4%

II.2.2a FATIGUE

The main symptom of most people with hepatitis C is chronic fatigue, ranging from simply getting tired easily to extreme, debilitating fatigue. The fatigue is often not recognized as such. Many people suffering from this "fatigue" do not have a desire to sleep because they are tired. Rather, they are suffering a very low level muscle pain (which often they do not recognize) that just wears them down. Taking a nap really helps. "It took me years to figure out that it was pain. When nurses would say to

me, "You look tired," I wouldn't know what they meant. I did not always want to go to sleep. Now much of that has changed. I do get sleepy-tired and must nap often." *(squeeky).*

A study by Goh J, Coughlan B, Quinn J, O'Keane JC, Crowe J Department of Hepatology, Mater Misericordiae Hospital and University College Dublin, Ireland found that fatigue does not correlate with the degree of hepatitis or the presence of autoimmune disorders in chronic hepatitis C infection. The doctors concluded that the perceived functional impact of fatigue on quality of life is significantly higher in patients with chronic HCV genotype 1b infection compared to healthy controls. However, it is unrelated to the degree of hepatitis and cannot be accounted for by the co-existence of autoimmune disorders alone. *Eur J Gastroenterol Hepatol* 1999 Aug;11(8):833-8

II.2.2b UPPER RIGHT QUADRANT (URQ) PAIN (SIDE PAIN)

Even though the liver itself contains no nerve endings, and does not feel pain, many people with HCV experience a pain on the upper right side of their body, just beneath the ribs. It varies from a dull ache and bruised feeling, to sharp stabbing pain which is quite different from "gas pains."

This is thought by some to be "referred pain" from the swelling of the liver capsule due to the disease process. This pain may also be referred to the right shoulder or to the back between the shoulder blades.

II.2.2c LOSS OF LIBIDO

Many hepatitis C patients find that they are no longer interested in sex. This tends to be especially true for those undergoing interferon treatments. This is not necessarily directly related to the hepatitis, but is most likely due to the stress, discomfort and exhaustion caused by the struggle with a chronic illness. It's good to know that many people say they recover their sex drive after treatment.

II.2.2d RED PALMS

Red palms can occur in any chronic liver disease and are not specifically caused by the virus. The cause for the redness is unknown, but it's speculated that it may involve upset hormone metabolism or microcirculatory changes.

II.2.2e NAUSEA

A few of the more popular nausea remedies are chewing candied ginger, putting a (small) drop of peppermint oil on the end of your tongue, eating small frequent meals, dry crackers and weak tea, and sucking on popsicles. Sometimes the nausea is caused by disturbances to the inner ear, in which case your doctor might be able to prescribe treatment. Many persons on the list have developed autoimmune inner ear disease as a complication of hepatitis C.

II.2.2f BRAIN FOG

This is the mental fuzziness and forgetfulness that some people experience. It's not the same as encephalopathy, and seems to occur in all stages of the illness. Some people have found taking CoEnzyme Q10, also known as CoQ10, to be helpful (two 30 mg capsules per day). Another listmember recommends taking Gingko Biloba.

II.2.2g ITCHING

The build-up of bilirubin in the skin may cause itching.

Itching can be treated with antihistamines, or cholestyramine (which binds bile in the intestines). Actigall and Questran are two drugs reported to help with this problem.

Recently many of our members have taken to using "bag balm," an antibacterial ointment used on cow's udders. It is apparently effective and harmless. It can be obtained from any equestrian or farm supply store, and sometimes in the better pharmacies.

II.2.2h VISION PROBLEMS

Some hepatitis patients complain of blurring vision, and dry eyes. This can be especially true while undergoing interferon treatment. Interferon treatment can and does trigger retinal complications in some people, such as hemorrhages, as well as vitreous detachments, cotton wool spots, cataracts and even strokes (infarcts). Be sure to get your eyes tested before beginning treatment. There are products to counteract dry eyes. If you are on treatment, use sunglasses outdoors

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II.2.2i DIZZINESS

Some people have found that wearing "Sea Bands" helps with their dizziness. Sea Bands are elastic

bands that can be bought, usually in sporting goods stores, which press against pressure points in the wrist. They were designed for use in seasickness.

Hepatitis C is becoming increasingly associated with a host of autoimmune disorders. Some of these disorders affect the inner ear. The inner ear regulates balance. Symptoms of autoimmune inner ear disease are dizziness, ringing in the ears (tinnitus) and hearing loss.

II.2.2j DRY MOUTH
There are some products (mouthwash, toothpaste, etc.) by the name of Biotene, which are designed to help with the problem of a dry mouth and gum problems resulting from medication use. Several listmembers have reported great relief by using these products. The pharmacies often don't carry the products, but can order them.

II.3.0 IT'S NOT ALL IN YOUR HEAD!
Some doctors (but thankfully fewer than there used to be) insist on believing that HCV usually has no symptoms, and dismiss the patient's complaints as being "all in their head."
Some HCV+ patients have been treated for depression for many years before their actual diagnosis of HCV was uncovered. Much is still unknown about the hepatitis C virus, and many physicians have not had much experience treating it. Many doctors are not yet familiar with the research which legitimizes the various symptoms which go along with this virus.
Emerging illnesses such as HCV typically go through a period of many years before they are accepted by the medical community, and during that interim time patients who have these new, unproven symptoms are all too often dismissed as being "psychiatric cases." This has been the experience with HCV as well.

II.3.1 WHAT IS THE PROGRESSION OF THE DISEASE?
Over fifty-nine percent of people infected with hepatitis C will remain infected for life, but among those with genotype 1b, that figure zooms up to 92%. Up to half of those people will develop cirrhosis, scarring of the liver, and up to 10,000 will die this year, say doctors and disease trackers meeting in San Diego. The latest findings are sobering because about 1.4% of the U.S. population is infected with the virus - "Hepatitis C Chronic 75% of the Time", *USA Today*, 05-15-1995
Approximately 85% of people infected with HCV will develop chronic hepatitis; ultimately, 20-30% of those will progress to cirrhosis. (*JAMA* Vol. 284 No. 4, July 26, 2000). Another 20-30% may develop chronic HCV infection without abnormal elevations of liver enzymes in the blood. - "Prevention, Diagnosis, and Management of Viral Hepatitis", AMA
Progression of the disease depends on several factors: mode of transmission (transfused victims usually progress faster), age at transmission (people infected older progress faster), gender (men usually progress faster than women) alcohol use, and coinfection with other viruses such as HBV, HAV or HIV.

Also see **EARLY TREATMENT**

II.4.0 WHAT OTHER MEDICAL PROBLEMS CAN BE RELATED TO HCV?
Chronic hepatitis C infection causes problems for parts of the body beyond the liver. The organs most often affected include the blood vessels, skin, joints, kidneys, thyroid gland, heart and brain. The virus itself has been found in the heart, muscles, nerves and lymphatic system. Many problems may arise from the cirrhosis, per se. Potential problems from cirrhosis include fluid accumulation in the abdomen, bleeding into the stomach, jaundice, confusion, poor blood clotting, coma, and susceptibility to infection.
During the last years many autoimmune manifestations have been correlated with HCV infection, namely, sicca syndrome, chronic polyarthritis, polydermatomyositis, fibromyalgia, autoimmune thyroiditis, lung fibrosis, and diabetes mellitus. (*Curr Opin Rheumatol* 2000 Jan;12(1):53-60)
Hepatitis has so many symptoms that it's easy to ascribe all new anomalies to this disease. But HCV patients are not also immune to other diseases; therefore it is important to regularly monitor your health and to consult with your doctor about the changes as they progress.

Hep C Illness - Outside the Liver
By Paul Harvey
In considering the possible impact of hepatitis C on our health, we should first question our definition of good health. Some clinicians suggest that good health is not so much a specific state such as "absence of disease or illness". They believe that good health is an overall approach: one that accommodates a certain level of illness as normal and has people working positively towards overcoming the physical and emotional problems caused by disease (Lorig et al.). This is quite a useful approach when considering that most people will develop some type of chronic illness in their life.

Our complex biological system
An additional issue before examining the possible impact of hepatitis C on health is consideration of the

incredibly complex biological nature of our bodies. Modern technologies are forever changing our world but they remain crude in comparison to the fantastic interaction of electrical, chemical and biological processes that exist within us. Given this level of complex interactions, it is not unusual that a disease most noticeably causing illness in one major organ or body system will have some level of impact on other parts of the body.

Non-liver HCV illness
Studies suggest that hepatitis C related fatigue is not primarily related to actual liver disease but is linked either to disorders of the immune system (*Eur J Gastro Hept* 1999 Aug;11(8):833-8) and (*Am J Gastro* 1999 May;94(5):1355-60), or to altered neurotransmission (brain tissue) function (*Lancet* 1999 Jul 31;354(9176:397).

The most commonly reported symptom of hepatitis C is fatigue. Clinicians are yet to confirm if this is an extrahepatic condition (an illness affecting parts of the body other than in the liver), or if it is related to actual liver damage (see p16). Aside from fatigue and possible complications of actual liver damage, hepatitis C infection has comparatively little impact on the rest of our body - although several conditions have been observed. Of the range of other health conditions linked to hepatitis C, some have been observed and well documented by clinicians (see below), while the occurrence of many others have been noted in only a small number of cases and may yet be explained as simple coincidence.

The publication *Hepatitis C: a management guide for general practitioners* (*Aust Family Physician* 1999;28 SI:27-31) recently listed a range of HCV extrahepatic conditions (below). Many of these are reported in *The Hep C Review*, ED30, September 2000, by Dr Bryan Speed (page 12), Dr Tony Jones (page 16), Doug Mellors (page 29), Dr Ed Gane (page 30) and Tina Pirola (page 34).

Arthralgia
Cyroglobulinaemia
Diabetes melitis
Glomerulonephritis
Lichen planus
Non-Hodgkin's lymphoma
Peripheral neuropathy
Porphyria cutanea tarda
Sicca syndrome
Sjogren's syndrome
Thrombocytopaenia
Thyroid disorders
Vasculitis

Summary
The majority of all people in our culture experience chronic illness at some point in their life. So although it's great to have good health, it's probably unreasonable to expect to have perfect health. In a small number of cases, hepatitis C can cause imbalance and illness in various parts of the body other than the liver. Given the complexity of our bodies, the fact that such extra hepatic HCV conditions can occur should not be seen as abnormal. These "extra hepatic conditions" are not necessarily serious and properly diagnosed and treated, they should not cause alarm if they occur. Certainly, they do not warrant unnecessary anxiety.

If anyone suspects they may be experiencing extra-hepatic conditions, they should consult their GP and if necessary, ask for referral to a hepatologist or other hepatitis specialist. Prior to such consultation, people should do a "work up" with their doctor, i.e., noting the frequency of possible symptoms and having any relevant blood tests done.
* Paul Harvey is Special Projects Officer with the Hepatitis C Council of NSW, Australia.
Source: *The Hep C Review*, Ed30, September 2000

II.4.0a CRYOGLOBULINEMIA
One-third to one-half of people with chronic hepatitis C infection has cryoglobulinemia. Cryoglobulinemia is a condition where antibodies which are attached to the hepatitis C virus solidify when cold. Hepatitis C is recognized as the most common cause of mixed cryoglobulinemia.
Most of the people with cryoglobulinemia from hepatitis C have had their hepatitis for a long time or have cirrhosis. People with higher concentrations of hepatitis C RNA in their blood do not seem to have a higher risk of having cryoglobulinemia. Usually the cryoglobulins are in low concentration and cause no symptoms.

About 20% of people with hepatitis C and cryoglobulinemia have symptoms. Symptoms most often associated with cryoglobulinemia include mild fatigue, joint pains, or itching.
Occasionally, people with cryoglobulinemia develop vasculitis (inflammation of the blood vessels) which

can cause purpura (purple skin lesions), Raynaud's phenomenon (the hands turn white, then blue, and then red from constriction and subsequent dilation of the blood vessels), or numbness in the hands and feet. The presence of cryoglobulinemia does not affect people's response to interferon.
In fact, some people with vasculitis have improvement in the vasculitis as their liver tests improve on interferon.

II.4.0b THYROID AND AUTOIMMUNE PROBLEMS
Chronic hepatitis C infection is also associated with many autoimmune diseases (where the body develops antibodies which attack parts of itself). For example, about one-tenth of people with chronic hepatitis C infection (more often in women and older people) have antibodies to the thyroid gland, one-half of whom may develop hypothyroidism (an underactive thyroid gland).
Additionally, interferon therapy causes hypothyroidism or hyperthyroidism (an overactive thyroid gland) in about one-tenth of those treated.

People with hypothyroidism may suffer from fatigue, poor memory, weakness, constipation, weight gain, muscle cramps, intolerance to cold, hoarse voice, coarse skin, and brittle hair. People with hyperthyroidism may suffer from anxiety, insomnia, weakness, diarrhea, weight loss, intolerance to heat, velvet-like skin, and brittle nails. Hypothyroidism can be treated with thyroid hormone pills.
Hyperthyroidism can be treated with pills that block the creation of the thyroid hormones. If the thyroid gland dysfunction is from interferon treatment and is caught early, the thyroid gland will return to normal once interferon is stopped.

II.4.0c RHEUMATOID ARTHRITIS-LIKE SYMPTOMS
Hepatitis C infection can mirror rheumatoid arthritis symptoms. The predominant clinical findings include palmar tenosynovitis: small joint synovitis, and carpal tunnel syndrome. Risk factors such as transfusions and IV drug abuse or a history of hepatitis or jaundice should be included in the history of present illness of any patient with acute or chronic polyarthritis or unexplained positive RF. In such patients, gammaglutamyl aminotransferase, serologic studies for hepatitis C, and other tests appropriate for chronic liver disease should be performed. - *Journal of Rheumatology*, June 1996;23(6):979-983; *Rev Med Chil* 1998 Jun;126(6):725-6.

II.4.0d FIBROMYALGIA
Fibromyalgia is the name for a condition that typically includes widespread muscle pain, fatigue and abnormal sleep patterns. Until a few years ago, doctors called the condition fibrositis, or muscular rheumatism, and believed mostly that the condition was "all in the patient's head". Today, fibromyalgia is recognized by medical organizations as a genuine and serious problem.
The symptoms of fibromyalgia typically include pain in many muscles, and around ligaments and tendons, persistent fatigue, waking up feeling tired even after a full night's sleep, headaches, bouts of constipation and diarrhea, abdominal pain, painful menstrual periods, sensitivity to cold, numbness or tingling, and difficulty exercising.

Symptoms vary widely among patients and tend to wax and wane over time. An illness, injury, cold weather or emotional stress may trigger a fibromyalgia episode or make ongoing symptoms worse.
A study at the Oregon Health Sciences University and Portland Adventist Hospital suggests hepatitis C may trigger fibromyalgia *("Fibromyalgia: A prominent feature in patients with musculoskeletal problems in chronic hepatitis C, A report of 12 patients," by A. Barkhuizen, G.S. Schoepflin, and R.M. Bennett, Journal of Clinical Rheumatology, Vol. 2, No. 4, August 1996)*. This study is the first to show a link between the two illnesses. A more recent study *(Curr Opin Rheumatol 2000 Jan;12(1):53-60)* suggests that a causative role of HCV seems to be likely in the development of fibromyalgia.

It was determined that the relationship between the hepatitis C virus and fibromyalgia followed three distinct patterns:
In nine patients, fibromyalgia developed as a long-term complication of the hepatitis, arising on average 13.4 years after the virus was acquired.
In two patients, fibromyalgia arose simultaneously with the hepatitis C infection.
In one patient, pre-existing fibromyalgia was significantly worsened by the hepatitis C.
It is unknown why the hepatitis C virus and fibromyalgia may be linked, but the authors suggest that hepatitis C causes chronic activation of the immune system that leads to muscle aching, fatigue, mental changes, sleep abnormalities, and alterations of the neuroendocrine system.
The patients with both hepatitis C and fibromyalgia could be distinguished from most other patients with fibromyalgia alone because they had symptoms unusual to fibromyalgia. These symptoms included synovitis (inflammation of the membrane around a joint, bursa, or tendon) and vasculitis (inflammation of a blood or lymph vessel).
In addition, laboratory findings pointed to a disease process other than fibromyalgia.

II.4.0e DERMATOLOGICAL MANIFESTATIONS

The main dermatological disorders in HCV infection include (1) vasculitis (mainly cryoglobulin-associated vasculitis, the cause of which is HCV in most cases, and, possibly, some cases of polyarteritis nodosa); (2) sporadic porphyria cutanea tarda; (3) cutaneous and/or mucosal lichen planus; and (4) salivary gland lesions, characterized by lymphocytic capillaritis, sometimes associated with lymphocytic sialadenitis resembling that of Sjogren's syndrome.

Numerous extrahepatic disorders have been recognised in association with HCV infection among which dermatological diseases occupy a central part. Cutaneous necrotising vasculitis, mixed cryoglobulinemia, porphyria cutanea tarda and lichen planus are the major skin diseases frequently associated with HCV infection, but other skin disorders, such as Adamantiadis-Behcet syndrome, erythema multiforme and nodosum, malacoplakia, urticaria and pruritus, may also be linked to hepatitis C. Further studies are necessary to establish or refute an aetiopathogenetic role of HCV in these conditions. Skin manifestations are also part of the clinical picture of other extrahepatic disorders associated with HCV infection, such as thyroid dysfunction and HCV-related thrombocytopenia. The response to interferon alpha (alpha-IFN) therapy in skin diseases is unpredictable with some patients ameliorating, others remaining stationary and others deteriorating. (*J Eur Acad Dermatol Venereol* 1998 Jan;10(1):12-21).

Hepatitis C virus is the cause of, or is associated with, various dermatological disorders. In patients with such disorders, HCV infection must be sought routinely because antiviral therapy may be beneficial in some of them. – (*Arch Dermatol. 1995; 131:1185-1193).*

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II.4.0f PORPHYRIA CUTANEA TARDA (PCT)

Porphyrins are a group of compounds that are mainly synthesized in the bone marrow. They play an important role in many chemical reactions in the body, e.g., with proteins to build hemoglobin. They are later converted to bile pigments mainly in the liver. Porphyrinuria (increase of porphyrins in the urine) may be caused by chronic liver diseases. Hepatitis C is a major cause of porphyria throughout the world and may cause many symptoms, including excess blood iron - important in conjunction with an interferon therapy (since elevated blood iron seems to reduce the effect of interferon).

Porphyria cutanea tarda is a rare deficiency of a liver enzyme essential for cellular metabolism. The enzyme deficiency may cause sun exposed skin to blister, ulcerate, turn dark, or bruise. Hair may increase on the forehead, cheeks, or forearms, and the urine may turn pink or brown. It now appears that hepatitis C is the most common trigger of porphyria in people who are predisposed.
Topical sunscreens do not prevent the skin lesions. Avoidance of alcohol and removal of iron by repeated phlebotomy (blood removal) or taking medication that binds to iron sometimes helps. Chloroquine (an anti-malaria drug), which removes a toxic by-product of the enzyme deficiency, may help, as well.

II.4.0g LICHEN PLANUS

Occasionally, people with chronic hepatitis C develop a skin condition called lichen planus. It is a grouping of small, itchy, irregular, flat-topped reddened bumps. The bumps often have a network of very fine gray lines on their tops. The bumps show up most often on the wrists, shins, lower back, or genitals. Lichen planus also frequently occurs in the mouth, where it looks like a white, net-like plaque. It sometimes shows up as mouth ulcers and can be treated with a steroid mouth rinse called Dexamethasone Elixir or Nystatin tablets.

II.4.0h PERIPHERAL NEUROPATHY

Often people with HCV suffer from peripheral neuropathy. Peripheral neuropathy refers to an inflammatory disease (-pathy) of the nerves (neuro-) and "peripheral" refers to the extremities: hands and feet. The problem may be related to many illnesses or disorders, such as diabetes, Sjogren's syndrome, vasculitis, rheumatoid arthritis, and especially to cryoglobulinemia in hepatitis C patients. It can be hereditary, or can be an autoimmune problem. It can be caused by compression (carpal tunnel), or can be caused by some drugs, but the inflammatory kind is the kind usually related to hepatitis C. The symptoms are numbness, pain and/or tingling in the feet or hands. It is the most common symptom in HCV patients who have mixed cryoglobulinemia. The cryo often responds to IFN treatment, but it doesn't always help the neuropathy.

Peripheral neuropathy may have the same cause as encephalopathy, which is also caused by inflammation of the small blood vessels, but in the brain. Some doctors believe that HCV causes our immune system to produce rheumatoid factors, which are deposited in the capillaries, causing inflammation called vasculitis and may lead to a kidney disease called glomerulonephritis, or to arthralgias or skin lesions, and of course, neuropathy. Peripheral neuropathy can cause weakness and loss of productivity, even if the liver is not seriously damaged.

Diagnosis can be as simple as a doctor testing the patient's reflexes, or testing the feet for sensibility. Other tests can be done to confirm the diagnosis, such as blood tests, a nerve biopsy, urinalysis for glomerular injury, and a nerve conduction test.

What can be done? Try to get rid of the cause, rather than just treat symptoms. Standard Hep C treatment helps some patients, so it may be worth a try. Others, however, develop the problem while on treatment, in which case, treatment may have to be stopped. Steroids may help some people, but may increase HCV viral load. Plasma exchange was used successfully in one patient with a serious case.

If you have pain because of neuropathy, remember that most pain remedies can damage the liver, and eventually make the situation worse. Having said that, sometimes you just have to deal with the pain. Start out by talking to your doctor. He may recommend vitamin B. You may, with your doctor's approval, wish to start with alternative therapies, such as magnets, acupuncture, massage, visualization or biofeedback. A healthy diet and exercise may delay symptoms and prevent progression. TENS (transcutaneous electrical nerve stimulation) won't hurt your liver. A simple remedy for pain is Tylenol or aspirin (not too much). You can try Capsaicin, from chili peppers, in a cream form. Neurontin has been used for the pain, with good results, but it has quite a list of side-effects, and is not good for people with kidney problems. Antidepressants such as Elavil, and anti-seizure medications, such as Tegretol may help the pain. If necessary, a nerve block may be considered.

Here are some things you can do:

- Check your feet every day for blisters, calluses or cuts.
- Throw away those tight shoes and socks.
- Use a hoop from the medical supply store to keep sheets and covers off your sensitive feet.
- Don't smoke
- Massage your hands and feet
- Don't cross your knees or lean on your elbows

Remember, if you go to a podiatrist for the care of your feet, take your own pedicure tools to avoid getting other people's infections, or spreading your own.
(http://millercenter.uchicago.edu/learnaboutpn/typesofpn/inflammatory/index.shtml
http://www.med.ucla.edu/modules/wfsection/article.php?articleid=46)

II.5.0 CYCLES AND FLARE-UPS

Hepatitis flare-ups tend to occur in cycles, where for a while you may feel pretty good, then bad (maybe days to weeks for each period), then good again. It can be frustrating to obtain some relief, but then not know whether you have recovered or if you are merely between cycles. Some people claim that they begin to feel better in the Spring, then start to feel worse again in August/September, with a low point usually around November/December.

II.6.0 SHOULD I BE VACCINATED AGAINST OTHER TYPES OF HEPATITIS?

All persons with hepatitis C should be vaccinated against hepatitis A and B. An editorial in the *New England Journal of Medicine* warned that fulminant hepatitis is associated with hepatitis A virus superinfection in patients With chronic hepatitis C. What this means is that persons with hepatitis C who get hepatitis A are at significant risk for fulminant hepatitis and death. From June 1990 to July 1997, the scientists examined 163 adults with chronic hepatitis B and 432 patients with chronic hepatitis C who were seronegative for HAV antibodies; tests were conducted every four months for serum IgM and IgG antibodies to HAV. Over the course of the study, 10 patients with HBV infections and 17 with HCV infections acquired HAV superinfection. Of these patients, fulminant hepatic failure developed in seven of the HCV-infected individuals, six of whom died. All but one of the HBV patients who developed HAV had uncomplicated courses. Since HAV infection rarely has a fulminant course and is usually non-fatal, the scientists note that "the high mortality rate among our patients with chronic hepatitis C and HAV superinfection (35 percent) is thus surprising, as is the even higher percentage of such patients with fulminant hepatitis (41 percent)." The authors suggest, therefore, that individuals with chronic HCV infection be vaccinated against the hepatitis A virus. *(Vento, Sandro, et al. New England Journal of Medicine 01/29/98 Vol. 338, No. 5, P. 286)*

Patients with chronic hepatitis C who are at risk for hepatitis B should be offered vaccination during their first contact with healthcare professionals, according to a report from Great Britain's University of Cambridge. *("Prospective Study of Hepatitis B Vaccination in Patients with Chronic Hepatitis C," British Medical Journal, May 25, 1996;312:1336-1337).*

Chronic hepatitis C (HCV) infection is estimated to occur in between 70 and 92 percent of intravenous drug users. These IV drug users are also at risk for parenterally or sexually transmitted hepatitis B. Coinfection with hepatitis B virus (HBV) may accelerate underlying liver damage due to hepatitis C.

II.7.0 HCV AND WOMEN'S CONCERNS

Women can be affected by hepatitis C differently than men. This is possibly due to hormonal effects and liver damage. A study presented at the 3rd International Conference on Therapies for Viral Hepatitis, December 12-16, 1999; Maui, USA and Antiviral Therapy 1999; 4 (Supplement 4), 38, suggested that pre-menopausal women have better response rates to alpha interferon for chronic hepatitis C. Interestingly, menstruation protects women from organ damage until after menopause. This is thought to be caused by the protective effects of estrogen and the lower amounts of iron in the blood in pre-menopausal women.

MENSTRUATION: The hormonal effects of HCV can involve menstrual irregularities, particularly if you are experiencing significant hepatitis C symptoms. It is important that your general health is checked as well as your hepatitis C monitored. Tampons and sanitary napkins should be secured in plastic bags before going into the trash.
BIRTH CONTROL: If you are experiencing significant hepatitis symptoms, using the estrogen-based contraceptive pill may be inadvisable.
In these cases, the progesterone-only pill or Depo-Provera may be preferable.
HORMONE REPLACEMENT THERAPY: If you have severe hepatitis symptoms you may need to discuss with your doctor whether hormones should be used for menopausal symptoms. If this is the case, external vaginal creams and skin patches are probably better than pills. Beware: Recent studies show that hormone replacement therapy can cause breast cancer.

Dysfunctional uterine bleeding and premature menopause, and most any other sort of hormonal aberration is pretty common with chronic liver disease. The liver processes these hormones, and they tend to not get processed properly when the liver is damaged.

While on interferon therapy, many women find that they come down with one yeast infection after another, due to the immunosuppression.

Waste paper products (napkins and tampons) that have been exposed to blood should be securely wrapped and disposed of in a safe manner. A 10% bleach solution (soak for 30 minutes) should be used on all contaminated surfaces, and in the laundry for clothing and linens which have been exposed to blood.

Sexual intercourse during your period is **not** safe.

II.7.1 PREGNANCY AND BREASTFEEDING

(Also see **Mother-to-Child Transmission**)
If a baby is born to an HCV+ mother and its blood were tested at birth for hepatitis C antibodies, the test would come back positive. This is because the baby has some of its mother's antibodies. The antibodies clear naturally over time. A test at 12 months usually confirms whether or not a toddler has the virus.
About one third of babies test positive for the virus when tested at the age of 3 days. Method of delivery made little or no difference. The rate of fetal infections in HCV+ can be zero and up to 10%. The rate goes up if the mother is co-infected with HIV. Present information shows that transmission may be more likely in infants born to mothers with genotype 1. *(Obstet Gynecol Surv. 2005 Sep;60(9):572-574)*

Any woman, or partner of a man, who has taken ribavirin must wait 6 months after the end of treatment before becoming pregnant to avoid birth defects. See this fact sheet about the safety of other Hep C treatments during pregnancy: *www.hcvadvocate.org/hepatitis/factsheets_pdf/Treat_pregcat.pdf*

BREASTFEEDING: There has been no documented case of HCV being transmitted by breastfeeding, and the rates of infant infection are identical in both breastfed and bottle-fed infants. There are many advantages to breastfeeding. Breastfeeding mothers should check their nipples before each feed and avoid breastfeeding if they are cracked or bleeding. They may want to consider using breast shields.
It is not known if interferon or ribavirin is passed on to the baby through breast milk.

Circulating HCV RNA does not increase pregnancy complications. A high viral rate, however, increased the baby's chance of infection before birth.

Many pregnant women with hepatitis C virus infection have circulating HCV RNA, even when they are asymptomatic, however, these women do not have an increased risk of obstetric complications and pregnancy does not appear to induce symptomatic liver disease. "There is no risk to the outcome of pregnancy in an anti-HCV positive pregnant mother. The majority of pregnant women has normal transaminase levels during the course of pregnancy, although a substantial proportion has circulating HCV RNA. Pregnancy does not induce a deterioration of liver disease, and HCV infection does not increase the risk of obstetric complications." ("HCV Infection in Pregnancy," *British Journal of Obstetrics*

and Gynecology, 1996;103:325-329)

There is a high mortality rate among pregnant patients infected with hepatitis E, which sometimes accompanies hepatitis C. There have been no studies on pregnant women taking interferon.

II.8.0 HOW DOES HCV AFFECT CHILDREN?
*(See also **Children with Hep C**)*
Children with chronic hepatitis cannot be treated simply like miniature adults. Specific issues and questions need to be addressed when dealing with the pediatric age group. Pediatric patients are less likely than adults to have symptoms of infection with hepatitis C, leaving the viruses undetected and possibly unknowingly spread. According to information available on the natural history of HCV, children have a higher rate of spontaneous viral clearance than adults, and generally a slower progression rate during the first 20 years of infection. Children who are chronic carriers of HCV have normal growth patterns.

In 16 HCV children followed for up to 14 years, encephalopathy (mental confusion), ascites (swollen stomach), or bleeding did not develop. The lack of cirrhosis in children with HCV is consistent with the fact that a time period of 10 to 20 years or more is required for cirrhosis to occur. Hepatocellular carcinoma occurs very rarely in the pediatric group.

A study (2005) conducted by HELIOS Children's Hospital Wuppertal in Germany demonstrated that treatment with peginterferon-alpha-2b and ribavirin is a well-tolerated and effective therapy for children with HCV genotype 2 or 3. The level of sustained viral response among patients varied, dependent upon the HCV genotype, liver enzyme levels, and the mode of infection. While receiving the therapy, 64 percent of patients had no detectable level of HCV RNA., and only five percent of patients relapsed during the follow-up period. The study also demonstrated the following:
• All children infected with genotype 2 or 3 achieved a sustained viral response; however, less than half of patients infected with genotype 1 had similar success
• Children infected by their mothers did not respond as well as non-vertically infected children
• Patients with normal liver enzyme levels before treatment responded better that those with above normal levels.
(Hepatology Volume 41, Issue 5, Date: May 2005, Pages: 1013-1018 Peginterferon alpha-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C,)
Children have surprisingly few side-effects from treatment, compared to adults.
Recommendations:
1. Diagnosis, testing, and liver biopsy of children thought to have HCV.
2. Because of the high spontaneous clearance rate during the first year of life, testing for children of HCV-infected mothers is recommended at 18 months or later.
3. Otherwise healthy children aged 3-17 may receive therapy with interferon alpha-2b and ribavirin, administered by specialists in treating children
4. Children under the age of 3 should not be treated.
(Doris B. Strader, DB, et al, HEPATOLOGY, April 2004 AASLD PRACTICE GUIDELINE, Diagnosis, Management, and Treatment of Hepatitis C p 1157-1158)

Clinical trials are presently being done in a few children age 3 and up: Telaprevir+pegIFN/RBV, Sovaldi + RBV, and a Phase III trial of Ledipasvir/Sovaldi ("Harvoni"). (*www.clinicaltrials.gov*) (WARNING: Do not take Amiodarone with Sovaldi or Harvoni).

II.9.0 WHAT ARE THE DIFFERENT CLINICAL INDICATIONS OF HCV?
The most often reported clinical symptoms are: fatigue, abdominal pain, loss of appetite, intermittent nausea, vomiting and, sometimes, jaundice (CDC).

Often doctors incorrectly assume that hepatitis C is a liver disease and that the only "real" symptoms of hepatitis C are related to liver disease and liver dysfunction

The virus itself has been found in the nervous system, the lymphatic system, the muscles and the heart where it causes direct inflammation. Many physicians, unfortunately, do not take this other activity and the stress it subjects us to into account. Rather than relying on the latest tests and literature to help form a diagnosis, they often mistakenly assume that hepatitis C is only a liver disease, and that, unless the patient has obvious cirrhosis, the complaints are psychosomatic

Just as HIV often causes death by AIDS-related pneumonia, even though HIV is not a lung disease, hepatitis C often causes death through liver failure or liver cancer, but it is not a liver disease. Hepatitis C is a virus that lives in and attacks many other organs of the body. It is also an active virus which engages the immune system to the point of exhaustion. The high viral activity is called viremia.

When your body is under attack from a hepatitis C viral flare-up, the immune system mounts a defense

which produces symptoms much like that of having the flu. The primary symptoms are aches, tiredness, fogginess and maybe a slight fever. These symptoms are the result of the immune system's response to the hepatitis C virus.

For a list of common reported symptoms of hepatitis C see the survey above.

II.9.1 ELEVATED LIVER ENZYMES

There are two general categories of "liver enzymes." The first group includes the alanine aminotransferase (ALT) and the aspartate aminotransferase (AST), sometimes referred to as the SGPT and SGOT. These are enzymes that are indicators of liver cell damage. The other frequently used liver enzymes are the alkaline phosphatase and gamma-glutamyltranspeptidase (GGT and GGTP) that indicate obstruction to the biliary system, either within the liver or in the larger bile channels outside the liver.
The ALT and AST are enzymes that are located in liver cells and leak out and make their way into the general circulation when liver cells are injured. The ALT is thought to be a more specific indicator of liver inflammation, since the AST may be elevated in diseases of other organs such as heart disease or muscle disease. ALT and AST are often used to monitor the course of chronic hepatitis and the response to treatments, such as prednisone and interferon.

The alkaline phosphatase and the GGT are elevated in a large number of disorders that affect the drainage of bile, such as a gallstone or tumor blocking the common bile duct, or alcoholic liver disease or drug-induced hepatitis, blocking the flow of bile in smaller bile channels within the liver. The alkaline phosphatase is also found in other organs, such as bone, placenta, and intestine.
For this reason, the GGT is utilized as a supplementary test to be sure that the elevation of alkaline phosphatase is indeed coming from the liver or the biliary tract. In contrast to the alkaline phosphatase, the GGT tends not to be elevated in diseases of bone, placenta, or intestine. Mild or moderate elevation of GGT in the presence of a normal alkaline phosphatase is difficult to interpret and often caused by changes in the liver cell enzymes induced by alcohol or medications, but without causing injury to the liver.

For some reason many physicians continue to assume that if the enzyme levels are low or near normal, that there is no cause for worry or need for treatment. However, the studies which show that **THERE IS NO NECESSARY CORRELATION BETWEEN ENZYME LEVELS IN THE BLOOD AND THE EXTENT OF LIVER DAMAGE** are too numerous to mention. Several individuals had to insist on a liver biopsy, only to find out that despite the low enzymes, they had grade 2 and grade 3 liver damage. One is dead; another is Joan King. You may post her at jking.hepcbc@gmail.com and she will tell you her story.

HEP C AND ALT'S - WHAT IS NORMAL?

Alan Franciscus

Twenty to thirty percent of people with HCV have persistently normal alanine aminotransferase (ALT) levels. It is currently recommended that HCV+ individuals with normal ALT levels should not be treated with antiviral medications and followed simply by measuring their ALT levels. However, emerging data suggests that it may not be this simple. What does this mean for the patient that has persistently normal ALT counts? Should they be biopsied and treated? This is a 'hot' area of research and some recent findings are changing the way the medical profession views this group of HCV+ patients.
We know that most HCV+ individuals with persistently normal ALT levels have a less serious disease progression and milder disease. The National Institutes of Health (NIH) and European consensus conferences recommended no liver biopsy or antiviral therapy in patients with persistently normal ALT levels outside of clinical trials due to the assumed mild disease progression and low response rates to current antiviral therapy. Some medical professionals dismiss this group as healthy 'carriers' and offer minimal medical follow-up. However, some of these patients with normal ALT's do not fit so neatly into this category and researchers are finding that a small percentage of these patients may have moderate to severe liver damage.

Alanine aminotransferease (ALT's – formally called SGPT) is produced in the liver in response to liver injury or cell death. This injury is not specific to HCV inflammation, but can come from a variety of agents such as alcohol, medications and other substances that can produce liver injury. This is usually, but not always, the first indication that someone may be infected with HCV. Normal values: 0-48 IU/L
It should be noted that many experts believe the normal ALT range value for women should be lower than the range value for men. In fact, women populate a large part of this 'normal group'. The lower ALT levels in women might be explained by the production of estrogen which is believed to lower ALT levels.

Biopsy

In a recent study by Edmund J Bini and others (AASLD abstract #485) 43 patients with persistently normal ALT levels and 96 with abnormal ALT levels were followed. Normal levels were defined by 3

normal ALT readings taken at least 1 month apart. The researchers found that the abnormal ALT levels group had significantly more advanced liver disease than patients with normal ALT's. However, 28% of the patients with normal ALT's had advanced liver disease, which led the researchers to recommend that all patients with normal ALT's undergo a liver biopsy for disease staging.

In a different study by Luis Balart, MD and others, over 300 patients with persistently normal ALT levels defined as 3 normal ALT levels readings taken 6 weeks apart for a period of 6 months were studied. It was found that most of these patients had mild liver disease, but a small percentage had more advanced disease, and some patients were found to have cirrhosis. Based on his study, Dr. Balart recommended that other factors should be considered when evaluating these patients and a biopsy should be considered. [Note: **FibroScans** are generally used now, where available, instead of biopsies. They are safer and painless.]

Treatment

This is a much more complex issue. In a recent study conducted by Dr. Mitchell L. Shiffman and colleagues, it was found that response to interferon monotherapy was similar in both normal (58 patients) and abnormal (37 patients) ALT level groups. The researchers concluded that persons with persistently normal ALTs should undergo a liver biopsy and considered for treatment if the liver is damaged. These findings have been collaborated by previous studies.

However, some evidence suggests that antiviral treatment for a small segment of this group could be counterproductive. Some patients do not respond to treatment, but develop elevated ALT levels that continue to be elevated after treatment is stopped. The big question is if antiviral treatment for this subset of patients makes the disease worse. This is a very important, controversial issue. This area of research is expanding and deserves more attention. It is hoped that a patient with normal ALT values will at the very least be offered additional liver function tests and a liver biopsy if necessary to establish if severe disease is present and given the option for antiviral treatment.

Common tests used to measure liver function:

Liver function tests include a variety of tests to help gauge the health of the liver. Measuring ALT's does not give a complete picture of liver health. A list of the more common liver function tests follow with the normal values listed. It is important to remember that 'normal values' vary from lab-to-lab and can be influenced by the way the blood samples are handled. Treatment decisions should never be made based on one test and always consult with a medical professional to accurately interpret test results.

- **Albumin** is a blood protein produced by the liver. It is responsible for keeping fluids and salts within blood vessels. If the liver does not produce enough albumin, water retention in the form of swelling occurs usually in the feet and ankles. **Normal values: 3.2-5.0g**
- **Alanine Aminotransferase (ALT –formerly called SGPT)** is an enzyme found in the blood, mostly in the liver, but also in the kidneys, pancreas, heart and muscles. The test indicates whether or not the liver is damaged. If there is damage, ALT is released into the blood and discovered in the tests. **Normal values: 7-56 IU/L.**
- **Alkaline Phosphatase (AP)** is an enzyme mainly found in the liver and is responsible for phosphorus metabolism, which delivers energy to the cell. Elevated levels of AP along with elevated GGT indicate that something is wrong in the liver. **Normal values: 35-115 IU/L**
- **Aspartate Aminotransferase (AST – formerly called SGOT)** is a liver enzyme used for amino acid metabolism. Elevated levels indicate liver injury. Tests for this enzyme and ALT are the most frequently used blood tests to watch changes in liver inflammation. **Normal values: 0-42 IU/L**
- **Bilirubin** is a waste product produced by the liver. A healthy liver will convert these bile salts into water-soluble substances that are excreted by the body. When the liver is damaged it is unable to convert these bile salts into a water-soluble substances leading into a buildup of toxic yellowish liquid which produces jaundice (yellowing of the skin). This is seen in some acute cases of hepatitis C and in end stage liver disease. **Normal values: 0-1.3mg**
- **Gamma-Glutamyltranspepidase (GGT)** is a liver enzyme used in metabolizing glutamate (an amino acid). High levels of GGT may indicate blockage and damage to bile ducts. **Normal values: 30-60 IU/L**
- **Platelets** are blood cells that help the blood to clot. Low platelet counts indicate liver damage. Platelets counts are also followed closely during interferon therapy**. Normal values: 130-400 thousand/MCL**

(HCV Advocate – http://www.hcvadvocate.org/)

This information is provided by the Hepatitis C Support Project. Reprint permission is granted and encouraged with credit to the Hepatitis C Support Project.

[Note: Normal values may vary from one lab to another.

II.9.1a ELEVATED ALPHA-FETOPROTEIN LEVELS

It is fairly common for alpha-fetoprotein markers to be elevated in patients with hepatitis C. Alpha-fetoprotein is a marker for tumors, but unless your numbers are extremely high, (in the hundreds) there is no need for alarm. Your doctor will probably want to perform further studies, such as an ultrasound or CT scan, just to be on the safe side. In fact a recent study cautions that in anti-HCV positive patients, AFP level is not a good single reference for diagnosis of HCC. Anti-HCV positive patients should be routinely screened for HCC by image studies along with serum AFP level. Keep copies of your AFP tests, and discuss the results with your doctor if the numbers rise. (*Hepatogastroenterology* 1999 Nov-Dec;46(30):3208-11)
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II.9.2 JAUNDICE

Jaundice (yellow skin) may appear as a symptom occasionally, but is most common during an acute attack. Jaundice is caused by the buildup of bile pigment that is passed by the liver into the intestines. This same bile buildup can also cause intense itching.

II.9.3 HEPATOMEGALY, SPLENOMEGALY

Some people experience a swelling of the liver (hepatomegaly) or the spleen (splenomegaly) as a result of hepatitis.

II.9.4 SPIDER NEVI

Spider nevi are small capillaries that are seen on the surface of your skin. Branches form (grow) from the one capillary and it can either look like a small red spider or a splat (kind of like a squashed spider). They are also referred to as spider angiomas. If you have less than 10 it can be considered normal, but more than that and it's an indication of chronic liver disease. They can be found only above the waist, usually on the chest, upper arms, shoulders, face, neck and upper back.

II.9.5 ASCITES

Occurring in cirrhosis, the accumulation of fluid in the abdominal cavity, or ascites, is related to portal hypertension, significant reduction in serum albumin, and renal retention of sodium. The volume of abdominal ascites in adults with cirrhosis may reach levels as great as 10 to 12 litres (10.6 to 12.7 quarts).

Ascitic fluid may accumulate in the scrotum and in the chest cavity, where its presence, combined with the upward pressure on the diaphragm from the abdominal fluid, may severely affect breathing. Appetite also is often reduced by the abdominal distension. Ascites is treated by the removal of enough fluid directly from the abdomen by needle puncture to ease discomfort and breathing.
Patients are placed on diets low in salt, and they are given diuretic drugs to increase the output of water by the kidneys. If these measures do not control massive ascites, ascites can be drained internally into the general venous blood system by running a plastic tube from the abdominal cavity, under the skin of the chest, into the right internal jugular vein of the neck (peritoneovenous shunt of LeVeen).

II.9.6 PORTAL HYPERTENSION / VARICES

Sometimes occurring in cirrhosis, portal hypertension is the increased pressure in the portal vein and its tributaries resulting from blockages to the blood flow into the liver. It is usually caused by the scarring processes of cirrhosis. The increased pressure causes varices, or dilations of the veins leading into the portal vein. When varices are located in superficial tissues, they may rupture and bleed profusely. Two such locations are the lower esophagus and the perianal region.

Esophageal varices are likely to bleed most heavily, and this bleeding is frequently associated with the onset of hepatic encephalopathy or coma. Because of their location at the lower end of the esophagus, or the upper portion of the stomach, bleeding from varices is often difficult to control. If variceal bleeding persists, surgical formation of a shunt, or artificial passageway, from the portal vein to an abdominal vein may be done.

II.9.7 HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy refers to the changes in the brain that occur in patients with advanced acute or chronic liver disease. If liver cells are damaged, certain substances that are normally cleansed from the blood by the healthy liver are not removed (mainly ammonia, or possibly certain fatty acids). A patient with chronic hepatic encephalopathy may develop progressive loss of memory, disorientation, untidiness, and muscular tremors, leading to a form of chronic dementia. The ingestion of protein invariably aggravates these symptoms.

The treatment of hepatic encephalopathy involves, first, the removal of all drugs that require

detoxification in the liver and, second, the reduction of the intake of protein. Restricting the amount of protein in the diet will generally lower the levels of amino acids and ammonia in the bloodstream and brain. Most physicians advise their patients with this condition to eat only about 40 grams of protein a day, and will prescribe lactulose or neomycin to lower amino acid production. Non-meat proteins, such as those found in vegetables and milk, are also recommended. Certain amino acids are used in treatment, since they are considered less likely to cause mental impairment. A dietary supplement rich in these amino acids is used at many liver treatment centers.

II.9.8 CIRRHOSIS

When chronic diseases cause the liver to become permanently injured and scarred, the condition is called cirrhosis. The scar tissue that forms in cirrhosis harms the structure of the liver, blocking the flow of blood through the organ. The loss of normal liver tissue slows the processing of nutrients, hormones, drugs, and toxins by the liver. Also slowed is production of proteins and other substances made by the liver. People with liver cirrhosis may develop many problems beyond the liver. When the liver is scarred the blood cannot easily get through, and backs up under higher than normal pressure (portal hypertension). This often causes ascites, which is yellow fluid that leaks out of the bloodstream into the abdominal cavity.

If the ascites becomes tense, it can cause an umbilical hernia (a protruding belly button). The backed-up blood also often creates varices, in which the pressure causes the blood vessels around the esophagus to burst causing significant blood loss. Varices can be treated with beta blockers, using endoscopically-placed rubber bands to obliterate them, or by injections of liquid that cause the varices to scar. If endoscopy fails to stop bleeding, TIPS (transjugular intrahepatic portosystemic shunt) can be created by inserting a short metal mesh tube through a neck vein into the liver and connecting the portal vein in the liver to a regular vein in the liver. Another alternative is to surgically redirect some of the blood flow around the liver.

People with cirrhosis sometimes may develop jaundice (a yellowing of the whites of the eyes or the skin) due to an accumulation of bilirubin in the blood. If the bilirubin is excreted in the urine, the urine may turn dark.

People with cirrhosis are also at risk for hepatic encephalopathy, which is fatigue or confusion caused by ammonia and other products of protein digestion which are inadequately cleared from the bloodstream by the liver.

People with cirrhosis often bruise easily because the liver manufactures reduced amounts of clotting factors. Additionally, platelets may be lower than normal in the circulation if the spleen is enlarged.
A spleen enlarged from portal hypertension may hold onto too many platelets.

Chronic HCV infection leads to cirrhosis in at least 20 percent of patients within 2 decades of the onset of infection. Cirrhosis and end-stage liver disease may occasionally develop rapidly, especially among patients with concomitant alcohol use. *(National Institutes of Health Consensus Statement on Hepatitis C 1997)*

"Nearly 80 percent of chronic hepatitis C sufferers who have the disease for several decades will develop cirrhosis or end-stage liver disease later in life," according to a trial done on Asian patients infected for probably more than 60 years. (*Clin Gastroenterol Hepatology* 2005;3:910-917).

II.9.9 FULMINANT HEPATITIS

In very rare cases hepatitis symptoms develop quickly and become very severe. This less common form of hepatitis is called fulminant hepatitis, or fast-progressing hepatitis, and it requires prompt medical attention. It can be fatal in up to 80% of cases. The kidneys may fail, and the liver shrinks as cells are killed. The person may fall into a coma and die. Fulminant liver failure following HCV infection has been reported but is a rare occurrence.

II.9.10 DOES HCV INCREASE THE LIKELIHOOD OF CANCER?

Chronic infection by HCV is associated with an increased risk of liver cancer. The prevailing concept is that hepatocellular carcinoma (HCC) occurs against a background of inflammation and regeneration associated with chronic hepatitis over the course of approximately 3 or more decades. Most cases of HCV-related HCC occur in the presence of cirrhosis. Earlier statistics put the risk for a person with chronic HCV hepatitis developing HCC at 1-5 percent after 20 years, with striking variations in rates in different geographic areas of the world. Once cirrhosis is established, the rate of development of HCC is 1-4 percent per year. (*National Institutes of Health Consensus Statement on Hepatitis C 1997)*

Later studies, however, put the risk for those with advanced liver disease of developing HCC at 13.4% (*Gut 2000;47:131-136*). Cirrhosis is NOT a necessary precursor to HCC: it can develop at any time, as

the study below shows:
"Chronic infection with hepatitis C virus (HCV) is regarded as a risk factor for hepatocellular cancer, mostly in patients with liver cirrhosis. We looked for HCV genomes in the livers of patients with hepatocellular cancer who did not have cirrhosis to see whether HCV was directly oncogenic. Cancerous and non-cancerous liver tissue and serum samples from 19 patients negative for hepatitis B surface antigen were analysed by polymerase chain reaction for the presence of HCV genome, HCV replication, HCV genotyping, and HBV genome. 13 of 19 patients were HCV RNA-positive in cancerous and non-cancerous liver tissue; 8 of 17 tested were anti-HCV positive."

"Among the 13 HCV RNA-positive patients, 11 had genotype 1b and 2 had genotype 2a. 7 of 13 serum samples were HCV RNA positive."

"7 of 19 patients were HBV DNA positive in cancerous and non-cancerous liver tissue, 5 of them anti-HBc positive. 4 patients were both HCV RNA and HBV DNA positive and 3 were both HCV RNA and HBV DNA negative. The results provide evidence for the association of HCV, mostly genotype 1b, with hepatocellular cancer without the intermediate step of cirrhosis." *(De Mitri MS, et al. Lancet 345: 413-5, 1995, "HCV-associated liver cancer without cirrhosis")*

"Previously, we reported the high prevalence of hepatitis C virus (HCV) infection in patients with **oral cancer** or oral lichen planus in Kyushu, Japan. We now report a 61-year-old man with chronic hepatitis C and no oral lesions who developed oral cancer 6 months after interferon therapy (interferon alpha, 6 million units (MU) daily for 2 weeks and then 3 times a week for 14 weeks). This case emphasizes the need for periodic oral cavity examinations of hepatitis C patients and contributed to the investigation of oral cancer and HCV." (*"Oral cancer and hepatitis C virus [HCV]: can HCV alone cause oral cancer?--a case report." Kurume Medical Journal, 1996 Vol 1, Issue 43, pp 97-100)*

An association between chronic hepatitis C infection and non-Hodgkin's lymphoma has been reported. ("HCV Infection and Extrahepatic Malignancies," *Journal of Clinical Gastroenterology* 1997 Mar;24(2):87-89)
The statistics are worse for those with HCV who smoke.

Researchers studying the Swedish HCV population looked at whether or not people with HCV were at greater risk for different types of cancer other than liver cancer. Of all the different types they looked at, they found that the danger of non-Hodgkin's lymphoma and multiple myeloma were higher than for people without HCV—for non-Hodgkin's lymphoma, 1.99 times higher, and for multiple myeloma, 2.54 times higher. The bulk of the people with HCV having one of the above cancers were estimated to have had HCV for greater than 15 years. Researchers propose that the danger for HCV-related cancers goes up with the length of time one is infected with HCV. *(Ann-Sofi Duberg, et al, Hepatology; 41:3; March 2005, "Non-Hodgkin's Lymphoma and Other Nonhepatic Malignancies in Swedish Patients With Hepatitis C Virus Infection,")*

A study from Japan followed 75 patients, 38 with SVR, and 37 who normalized their ALT but still had detectable HCV, for 12 years. After 12 years, there were still 15 patients available for testing in each group. Four of the SVRs developed liver cancer, found 1 month to 5 ½ years after treatment. None of the non-SVR group did. = *"SVR Can Last for Years, Doctors Claim"* (*John C. Martin, Hepatitis Neighborhood 11-24-04, http://www.hepatitisneighborhood.com/content/in_the_news/archive_2152.aspx)*

II.10.0 HOW MANY OF US ARE THERE?
(Thanks to Cheryl Reitz, HepCBC, for this update, April 2015.)
How many people have hepatitis C? Who has it? Where do they live? We at HepCBC went through the latest statistics about hepatitis C in BC, in Canada, and the World. They're not perfect because not everyone who has hepatitis C has been tested, and not all cases are reported, especially in less-developed countries. But with a cure now available and the eventual eradication of hepatitis C an achievable goal, governments are starting to collect better data allowing them to better target their resources. Here is a summary of the most recent statistics:
IN THE WORLD *(from European Assn. for Study of the Liver [EASL] –2014 vol. 61 j S45–S57*):
115 million people now living in the world (1.6% of the population) have been exposed to hepatitis C virus (have HCV antibodies), of whom 80 million have chronic hepatitis C (CHC).
The top-ten countries in order from greatest to least number of people with CHC are China, Pakistan, Nigeria, Egypt, India, Russia, USA, Brazil, Congo, and Japan. NOTE: Egypt, with 15% of its population suffering from CHC, has the highest prevalence of any country. However, because its total population is so much smaller than China, China has far more infected individuals than Egypt.
The top-ten regions in order of the percentage of their population which has CHC (prevalence) are
Sub-Saharan Africa, West; Sub-Saharan Africa, Central; Eastern Europe; Central Asia; North Africa/Middle East; "Other"; Latin America, Tropical; Central Europe; Australasia; and South Asia.

The top-ten regions in order of the total number of people with CHC (followed by the % prevalence) are:

- South Asia (15.2 million, 0.9%);
- Sub-Saharan Africa, West (14.9 million, 4.1%);
- East Asia (10 million, 0.7%);
- North Africa/Middle East (9.7 million, 2.1%);
- Eastern Europe (4.7 million, 2.3%);
- SE Asia (4.2 million, 0.7%);
- North America (2.8 million, 0.8%);
- Sub-Saharan Africa, Central (2.6 million, 2.6%);
- Western Europe (2.6 million, 0.6%);
- Sub-Saharan Africa, East (2.4 million, 0.6%)

NOTE: If we add together the three Sub-Saharan African regions above plus Sub-Saharan Africa South (0.7 million, 0.9%) the total, 20.6 million, puts Sub-Saharan Africa into the top position.

The genotypes are found in this distribution in the world:
Genotypes 1a and 1b = 46%; Genotype 2 = 22%; Genotype 3 = 13%; Genotype 4 = 13%; and
Genotypes 5 and 6 together = 6%. For maps, see link below.
Source: www.journal-of-hepatology.eu/article/S0168-8278(14)00526-1/pdf

IN CANADA *(from Public Health Agency of Canada [PHAC], Canada Communicable Disease Report [CCDR] Volume 40-19, Dec. 18, 2014 and Canadian Liver Foundation)*:

Depending on whom you talk to, the number of people with chronic hepatitis C (CHC) in Canada can be anywhere from 220,000 to approximately twice that number. The Canadian Liver Foundation estimates 300,000 Canadians are currently infected with the virus, but that number could include those who test positive but have cleared the disease, either on their own (generally in the first six months of infection) or through treatment. The percentage of the population living with CHC (prevalence), and the percentage of this population which does not realize they have CHC (undiagnosed) can vary widely as well. A 2013 Canadian Health Measures Survey (PHAC, 2013) was strongly criticized because data from several provinces was missing and members of key populations such as intravenous drug users, immigrants from countries with high HCV prevalence, the homeless, aboriginal people and prisoners were under-represented. This new report tries to address the limitations of the previous survey by using statistical methods such as a "back-calculation model" (for more details on this see link below). The results were quite fascinating!

2014 PHAC study concluded between 0.64% and 0.71% of Canada's population were living with CHC in 2011. This is 220,697 people, and 44% of them were undiagnosed.

Birth cohorts most affected by CHC (followed by prevalence in %): 1950-1954 (1.25%); 1955-1969 (1.5%); 1960-1964 (1.2%); 1965-1969 (1.1%); and 1970-1974 (0.8%).

NOTE: The prevalence in cohorts previous to 1950 has actually declined to below the national average. The author assumes this is likely due to deaths which could be related to CHC in this aging population. Though the 1945-1950 cohort may now contain lower than average prevalence, those with CHC remaining in this cohort are the most in danger of dying from this disease. The sooner we find and treat them, the more cases of liver cancer and liver failure will be averted and the more quality years of life these people will be able to have. (On a personal note: the author of this article is a person born in 1948 who was recently cured of hepatitis C with the new DAA drugs, and feels incredibly fortunate and grateful for this extra lease on life!)

Who has hepatitis C in Canada? Nine groups in order of the total number of people with CHC (followed by the percentage of prevalence) are the following:

- Foreign-born, ages 14-79 (116,428 - 1.9%);
- Former IDU, ages 14-79 (75,602, - 28.5%);
- Current IDU (66,000 - 66%);
- Non-aboriginal, non-foreign-born, non-IDU ages 14-79 (39,711 – 0.2%);
- Provincial inmates, including youth (9,287 – 23.25%);
- Residents of nursing homes & long-term care hospitals (8,832 – 2.95%);
- Aboriginal, non IDU (6,115 – 0.5%);
- Homeless, non IDU (4,072 – 2.25%);
- Federal inmates, including youth (3,493 - 24%).

NOTE 1: The foreign-born statistic should be split into those who are from countries or regions with high prevalence versus those who are not. This would show a far higher % prevalence among those from certain countries (see previous "WORLD" section).

NOTE 2: Many of those who are foreign-born, former IDU, aboriginal, homeless, or residents of nursing homes are also "Baby Boomers." One-time-only testing of "Baby Boomers" would locate approximately 67% - 75% of all those with hepatitis C, including those from all of the groups above.

What % of the CHC population remains un-diagnosed? Various studies have looked at specific groups and found that of those who have CHC, the following % of each group did not know they had CHC until they were diagnosed:

- Drug users = 20% to 43% undiagnosed;
- Hospital patients = 56% undiagnosed;
- Inmates = 28% - 50% undiagnosed;
- First-time blood donors = 48% - 58% undiagnosed;
- Males who have Sex with Males = 44% - 75% undiagnosed;
- US Population = 50.3% undiagnosed;
- Canadian household, population ages 14 – 79 = 70% undiagnosed. *(Canadian Health Measures Survey – CHMS: Health Reports 2013; 24 11): 3-13)*

Sources:
www.phac-aspc.gc.ca/publicat/ccdr-rmtc/14vol40/dr-rm40-19/surveillance-b-eng.php and
www.liver.ca/support-liver-foundation/advocate/clf-position-statements/hepatitis_C_testing.aspx

IN BC *(from BC Centre for Disease Control, PHAC, Statistics Canada, and BC Centre for Excellence in HIV/AIDS):*

There are approximately 80,000 people with HCV in British Columbia. BC has one of the highest (perhaps the highest) rate of new cases per year (incidence). There appears to be approximately the same proportions of infected people in the categories described above for Canada as a whole. Recently BC Centre for Disease Control released a new table titled "HCV Cases among Immigrants BC & Canada". Based on published "2013: HCV Rates" data published by Statistics Canada, this graph showed that the prevalence among immigrants in both Canada and BC is approximately 3%. It showed that approximately 18,883 of the 80,000 cases of hepatitis C in BC are among immigrants from Eastern Asia, SE Asia, and Southern Asia – those represented include (in order of number) people from China, India, Philippines, Taiwan, and Vietnam. While Vietnam has only an estimated 1608 HCV+ people, it has the highest rate of prevalence among immigrants (6.1%).

Sources: www.cfenet.ubc.ca/sites/default/files/uploads/HCV%20Fact%20Sheet.pdf
www.phac-aspc.gc.ca/sti-its-surv-epi/hepc/pdf/hepc-2010-eng.pdf and
BC Centre for Disease Control Power Point slide – permission given by author and available on request to HepCBC

II.11.0 LONG TERM PROGNOSIS (WILL I EVER GET CURED? AM I GOING TO DIE?)

Current studies indicate that most (80%) people infected with hepatitis C will develop a chronic state of infection if they aren't treated. About 30% those with chronic, untreated infection will go on to develop cirrhosis of the liver. The percentage increases with advancing age. The disease appears to progress slowly; symptoms often do not appear for ten or twenty years.

After an average follow-up of 18 years, a prospective study of patients who received blood transfusions showed no difference in overall mortality between HCV-infected cases and non-infected controls. Liver-related mortality, though rare, was twice as high in the cases (3.2 percent vs. 1.5 percent). A European study showed survival among HCV patients with compensated cirrhosis was 91 percent at 5 years and 79 percent after 10 years. Among patients developing decompensated cirrhosis, however, 5-year survival was only 50 percent. - (*National Institutes of Health Statement on Hepatitis C 1997)*

Hepatocellular carcinoma…liver cancer, or HCC, now ranks 3rd in cancer-related deaths. There were 30,640 new diagnoses of HCC and 21,670 deaths expected in 2013 in the US from HCV-related HCC.
An article in the July 2000 issue of *Gut* about HCV+ untreated cirrhotic patients reveals that '"of the 416 patients, 60 developed HCC with a 5-year rate of 13.4%...and 83 died (including 34 with HCC), with a 5-year death rate of 15.3%.' According to the authors, these results contrast with previous studies, which cite 5-year mortality rates of 9%, and HCC rates of 5% or 7%."
(*www.ncbi.nlm.nih.gov/pubmed/10861275*)

The overall severity of chronic hepatitis C is controversial. There is no question that HCV can lead to cirrhosis and hepatocellular carcinoma (HCC) and that end-stage chronic hepatitis C is the leading indication for liver transplantation. At question is how frequently and how soon these serious consequences occur.

A controlled prospective study (Seeff) has shown that after 20 years of follow-up, patients with transfusion-associated hepatitis C had no increase in overall mortality and only a slight increase in liver-related mortality compared to controls who did not develop hepatitis. Another prospective study

(Koretz) has shown that the probability of developing clinical cirrhosis or liver related mortality was 20% and 5%, respectively after 16 years; comparable values were 24% and 3% in the NIH series. The paradox between the relatively benign mortality figures and the observed fatal outcomes resides in the indolent nature of progressive HCV infection.

Progression in the untreated patient is generally measured in decades and most subjects acquiring infection in mid-life or later will succumb to their underlying disease or old age before they develop end-stage chronic hepatitis C. By inference, it appears that the HCV mortality risk is approximately 4% in the first two decades and the risk will increase over time in those that do not succumb to other events. *("Natural History and Clinical Aspects of HCV Infection." H.J. Alter. Department of Transfusion Medicine, National Institutes of Health, Bethesda, Maryland. Cancer Biotechnology Weekly, 01-29-1996, pp 20).*

Some researchers in Japan studied the progression rate of 21 Hep C patients with high ALTs who each had at least 2 biopsies a year apart. All the patients were untreated. They found that the ALT "was an independent variable correlating with fibrosis progression." The progression of fibrosis was found mostly in patients who had continuously elevated ALTs even for a short period of time. In patients with an ALT over 70, fibrosis could progress as much as one stage in 4 or 5 years (Stage 4 is cirrhosis). *(www.ncbi.nlm.nih.gov/pubmed/18600393?ordinalpos=8&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum Epub Jul 4. 2008)*

So how long can you live if you already have cirrhosis? These researchers used data from an older study of patients with advanced fibrosis, who took IFN-based treatment between 1990-2003. Survival was compared in 530 patients, taking into account age and sex. Follow-up was completed in 86% of them. 192 (36%) achieved SVR. 13 with SVR died (10 year survival rate 91.1%). 100 patients who didn't achieve SVR died (10 year survival rate 74%) *(www.natap.org/2014/HCV/120314_01.htm)*

Also see: Is treatment worth it?

PART III - TREATMENT (Conventional Medicine)

Special thanks to Joan King of HepCBC, to Viola Vatter of Victoria, BC, and to Alp of Vancouver, BC for their help with Parts III and IV. Thanks to HCVAdvocate for providing some of data and charts! (http://hcvdrugs.com/Approved_meds.html)

APPROVED TREATMENT OPTIONS

BRAND NAME	GENERIC NAME	FUNCTION	COMPANY	GT/SVR
Intron-A	interferon-alfa-2b	interferon	Merck	13%
Copegus/Rebetol	ribavirin	nucleoside analog	Genentech, Merck, Kadmon	(not used alone)
Pegintron	peginterferon alfa-2b	pegylated interferon	Merck	GT1 (14%) GT2-3 (47%)
Pegasys	peginterferon alfa-2a	pegylated interferon	Genentech	GT1 (28%) GT2-3 (56%)
*Victrelis/pegIFN/RBV	boceprevir/pegIFN/RBV	protease inhibitor	Merck	GT1 (66%)

Galexos (Olysio) pegIFN/RBV	**simeprevir/pegIFN RBV**	**protease inhibitor**	**Janssen**	**GT1 (up to 92%) GT4 (92%)**
Sovaldi/RBV	**sofosbuvir/RBV**	**nucleotide polymerase inhibitor**	**Gilead**	**GT2 (up to 100%) GT 3 (up to 91%)**
Sovaldi/Galexos /RBV	**sofosbuvir/simeprevir /RBV**	**nucleotide polymerase/ protease inhibitor**	**Gilead**	**GT1 (up to 92%)**
Harvoni	**sofosbuvir/ledipasivir**	**nucleotide polymerase/ NS5A inhibitor**	**Gilead**	**GT1 (up to 100%)**
Holkira Pak	**ombitasvir/ paritaprevir+ritonavir/ dasabuvir w/wo RBV**	**NS5A/boosted protease/ non-nuc polymerase inhibitors**	**AbbVIE**	**GT1 (up to 100%)**
Daklinza/Sovaldi	**daclatasvir/sofosbuvir (Approved in Europe)**	**NS5A inhibitor**	**Bristol-Myers Squibb**	**GT1,2,3,4 (up to 100%)**

***Victrelis is being discontinued.**

III.1.0 STANDARD TREATMENT

III.1.1 Pegylated Interferon, Ribavirin and a Protease Inhibitor Combined

At first, we had only interferon (IFN) as treatment, and then the "combo treatment"--interferon plus ribavirin--became standard therapy, until pegylated interferon appeared on the scene. Until May 2011, standard therapy for hepatitis C has been pegylated interferon (either Merck's Peg-Intron or Roche's Pegasys) along with ribavirin (Merck's Rebetrol or Roche's Copegus).

This has changed, and standard treatment in the US now includes a protease inhibitor. The 1st generation protease inhibitors boceprevir (Merck) and telaprevir (Vertex) were approved for use with IFN/RBV in 2011, and are covered by insurance in Canada. Both have been discontinued since the newer drugs were approved. The 2nd generation DAAs, Sovaldi (sofosbuvir) and Galexos/Olysio (simeprevir) are now approved for use combined with pegIFN/RBV, and is covered by some insurance companies. Harvoni (Sovaldi + ledipasvir) is approved (as of 2014) for use without IFN/RBV. (It is suspected that Sovaldi may be used with simeprevir off-label without IFN/RBV, due to the success rates of that combination, as shown in clinical trials).
(www.ottawacitizen.com/health/Drugs+cure+hepatitis+coming+soon+afford+them/9760578/story.html)
(www.ncbi.nlm.nih.gov/pubmed/24677184)

Recommendations for GENOTYPE 1 PATIENTS in Canada (Oct 2014):
1. CDEC (Canada Drug Expert Committee) recommends the DAA simeprevir (Olysio or Galexos) daily for 12 weeks, in combination with PR (pegylated interferon + ribavirin) for 24 to 48 weeks, as the protease inhibitor of choice for treatment-naive patients or for treatment-experienced patients with prior relapse.
2. No definitive recommendation regarding the place in therapy for the DAA Sovaldi (sofosbuvir) (relative to available protease inhibitors, can be made by CDEC at this time. WARNING: Do not take Amiodarone with Sovaldi or Harvoni.
3. CDEC recommends that a DAA (direct-acting antiviral) plus PR treatment should be offered only to persons with CHC who have fibrosis stages F2, F3, or F4.

4. CDEC recommends that persons in whom a DAA plus PR regimen has failed not be re-treated with another DAA plus PR regimen.

Reasons for Recommendation 3:
1. No liver-related morbidity is expected in the short-term for patients with no fibrosis or a low fibrosis stage (stages F0 and F1).
2. In all analyses, treatment of patients with higher stages of fibrosis was more cost-effective.
(www.cadth.ca/media/pdf/TR0007_HepC_RecsReport_e.pdf)

Interferons are types of naturally-occurring proteins produced by our own immune system. They direct our immune system to attack viruses, bacteria, tumours and other foreign substances that may invade the body. Virtually all interferons used in HCV treatment today are obtained from bacteria that have had slight man-made DNA modifications. In general, genetic material from human leucocytes (white blood cells) is spliced into the genetic material of bacteria, and the bacteria are allowed to reproduce and grow. The inserted genetic material causes the bacteria to produce interferon.

Pegylated interferon (PegIFN) is a type of interferon with a large polyethylene glycol molecule attached to it, so that it stays in the body for a longer time, and we can inject it just once a week, rather than 3 times a week, like we did in the past. Side effects are similar to or slightly less unpleasant than those experienced with non-pegylated interferon.

The two available pegylated interferons, Peg-Intron and Pegasys have been compared. The two substances differ basically in the size of the molecule involved, (about 60 kilodalton for Pegasys, 31 kilodalton for Peg-Intron). Pegasys has a longer half-life. Some studies show that SVR rates (Sustained Viral Response, or loosely, "cure rates") for Peg-Intron or Pegasys are slightly different, with one being higher than the other, or showing little difference at all.

Ribavirin (RBV) is an antiviral discovered over 30 years ago. No one knows for sure how it works, but when combined with pegIFN, these two drugs have drastically improved the response rates. The dosages of RBV are weight-based, so the more the patient weighs, the higher the dosage of both medications. Generally SVR rates when combined with either pegylated interferon were about 40-50% for genotype 1 (G1) patients (the most difficult to treat), and about 80% or higher for genotype 2 and 3.

The Ribavirin Solution in Canada:

Montreal-based Pendopharm has received a priority review designation from Health Canada for the first stand-alone ribavirin (RBV) tablet. RBV is already part of the current standard of care for treating hepatitis C, and stand-alone RBV is required for some new IFN-free treatments, but it is currently only approved by Health Canada when co-packaged with pegIFN. Gilead's Sovaldi (sofosbuvir), for example, can be used in combination with RBV alone for HCV patients with GT 2 and 3. Harvoni (Sovaldi + Ledipasvir) is the first new all-oral treatment regimen that eliminates IFN entirely. Pendopharm's RBV can bring IFN-free HCV treatment regimens to patients with GT 2 and 3, who make up approximately 30% of HCV cases in Canada. WARNING: Do not take Amiodarone with Sovaldi or Harvoni. (*www.newswire.ca/en/story/1331397/pendopharm-announces-priority-review-of-new-therapy-to-support-treatment-of-patients-with-hepatitis-c*)

Protease Inhibitors PI's are part of our arsenal of approved drugs in Canada and many other countries. The protease is a part of the virus that is needed for it to reproduce. Once HCV enters a liver cell, its genes guide the production of proteins that will become the inner core and surface coat of new viral units. First of all, the HCV makes an immature protein—a kind of unfinished sheet of material, which the Hep C protease cuts into the finished proteins, which then become the virus's outer cloak. Scientists have designed protease inhibitors which stick specifically to HCV protease to stop its scissor-like function.

There is much hope for these protease inhibitors. Where the 40-50% of G1 patients achieved an SVR with PegIFN and RBV, numbers for protease inhibitors show about 75% of treatment naive patients may achieve SVR with treatment with the triple combo. Those who responded to previous therapy but relapsed have a better than 80% chance of SVR. Those who responded but did not clear have about a 60% chance of SVR. Non-responders and null-responders have a 30-40% chance of SVR. (These numbers are based mostly on telaprevir data and may vary depending on the study).
(www.clinicaloptions.com/Hepatitis/Conference%20Coverage/Berlin%202011/Tracks/From%20Podium%20to%20Practice/Capsules/5.aspx)

Protease inhibitors often cut treatment time in half. On the other hand, they are used only for non-cirrhotic genotype 1 patients, and they can cause more side effects and are more difficult to take (more pills, exact timing, dietary requirements…) In cases of non-response, they can cause resistance. *(www.medscape.org/viewarticle/760746)*

- **Victrelis (Boceprevir)**

Victrelis is Merck's protease inhibitor, previously known as boceprevir. It was approved and covered for use with pegylated interferon and ribavirin since 2011. Merck is voluntarily discontinuing Victrelis in the US as of December 2015. It has been discontinued in Japan.

A Phase III study of the drug combined with PegIFN/RBV in G1 patients, with a 4-week lead-in of SOC alone (high-dose RBV 600-1400 mg/day), resulted in SVRs up to 66%. There were some serious side-effects. *(EASL 2011)*

- **Incivek (telaprevir or VX-950)**
  Telaprevir is Vertex's oral protease inhibitor, and was approved for sale in 2011, but as of October 2014, Vertex no longer sells the drug, and has stopped all hepatitis C research, due to reduced demand. The company has ceded its rights to sell telaprevir (protease inhibitor) in Europe to Janssen. The treatment has lost a lot of its popularity because it has to be combined with interferon injections. *(www.hepmag.com/articles/vertex_ends_hepatitis_c_investment_2831_25553.shtml)*

Second Generation Direct-Acting Antivirals
"Second generation" refers to anything after Boceprevir and Incivek. DAAs can be divided into 3 groups: protease inhibitors, with drug names ending in "previr", like simeprevir; NS5A inhibitors, with names ending in "asvir," like daclatasvir; and polymerase inhibitors, with names ending in "buvir", like sofosbuvir.
(www.hepatitiscnewdrugresearch.com/2014---treatment-of-hepatitis-c-in-the-near-future.html)

Second generation DAAs, have now been approved by Health Canada for use with pegIFN/RBV, or with just RBV alone. There is some talk of the use of the two drugs together, off label, without IFN or RBV, since the clinical trial results seem to compare favourably. The drugs are being reviewed and considered for Pharmacare coverage.
(www.newswire.ca/en/story/1264711/new-treatment-for-hepatitis-c-approved-by-health-canada-priority-review-gives-physicians-and-patients-an-effective-and-tolerable-treatment-choice and www.ncbi.nlm.nih.gov/pubmed/24677184)

- **Simeprevir (Galexos in Canada, Olysio in the US, formerly TMC435)** *(Thanks to Cheryl Reitz, HepCBC)*
  As of October 29, 2014 Janssen's protease inhibitor simeprevir will be reimbursed by BC PharmaCare. Since it is covered, BC's patients most in need of this treatment will be able to afford it. It will probably replace two drugs with significant side-effects, boceprevir (VICTRELIS) and telaprevir (INCIVEK), no longer being sold. As of January 30, 2015 simeprevir can be combined with sofosbuvir rather than with PegIFN/RBV.
  A downside is the very restrictive list of access criteria:
  •Genotype 1 ONLY
  •No de-compensated cirrhosis
  •Fibrosis stage F2 or greater on Metavir scale, determined through biopsy, Fibroscan, or serum biomarker panel (such as APRI).
  •No prior treatment with a HCV protease inhibitor (such as boceprevir or telaprevir)
  •No current treatment with an NS5A/NS5B inhibitor (e.g., daclatasvir, sofosbuvir, ombitasvir, PPI-668, or ledipasvir).
  More details: *http://hepcbc.ca/treatment-criteriasimeprevir-galexos-british-columbia/.*

III.1.2 DAA TREATMENT

- **Harvoni** (**Sovaldi + ledipasvir** in one pill) is approved (2014) for use without IFN/RBV, but coverage of the drug is sporadic. The cost for this and for Sovaldi and Olysio (simeprevir) are threatening to bankrupt the insurance companies, so some are discussing restricting coverage for all but advanced cases of liver damage. Gilead's newly approved Harvoni is changing the hepatitis C landscape. One tablet a day can treat most of the Hep C genotype (GT) 1 and 4 patients, both treatment naïve and experienced, even those with compensated cirrhosis. The tablet combines ledipasvir (LDV), an NS5A inhibitor, with the nucleotide polymerase inhibitor sofosbuvir (SOF), also called Sovaldi. Harvoni is taken for as little as 8 weeks by treatment-naïve GT1 patients without cirrhosis. Other patients take it for 12 or 24 weeks, according to their grade of cirrhosis and their treatment history. Those with GT 1 or 4 with advanced cirrhosis and cirrhotic GT3 patients who are prior non-responders are advised to take Harvoni plus ribavirin for 24 weeks. Patients co-infected with HIV can take Harvoni.

  The guidelines for Harvoni treatment are based on data from the three ION trials. Patients who have non-detectable virus at 12 weeks post treatment (SVR12) are considered CURED. In the non-RBV arms, results showed 94-99% of patients were cured.

  There have also been trials for late-stage cirrhotics, post-liver transplant patients, for previous non-responders, and for HIV/HCV co-infected patients. Complete results are not yet available, but appear

to range between 90 and 98%. Genotype 3 patients appear to be achieving 100% SVR12 rates by taking Harvoni with ribavirin for 12 weeks, but they had more cases of headache and fatigue. (*www.gilead.com/news/press-releases/ Nov 18, 2014)* WARNING: Do not take Amiodarone with Sovaldi or Harvoni.

- **Sovaldi (sofosbuvir, formerly PSI-7977, then GS-7977)**
  WARNING: Do not take Amiodarone with Sovaldi or Harvoni.

  Gilead's Sovaldi is a nucleotide analog NS5B polymerase inhibitor, originally discovered by Pharmasset and acquired by Gilead in January 2012. SVR12 rates up to 100% have been produced by combining Sovaldi with NS5A inhibitors like ledipasvir or daclatasvir, as shown in March 2013, at the 20th Conference on Retroviruses and Opportunistic Infections, where researchers had combined those drugs and ribavirin. The trial included not only treatment-naïve subjects, but also GT1 nonresponders to prior treatment. Similar trials without RBV led to FDA approval on October 10, 2014 of the combination of ledipasvir 90 mg/Sovaldi 400 mg called Harvoni. Sovaldi combined with ribavirin has produced a 100% SVR24 in treatment-naïve GT2 and 3 patients. It is recommended by the AASLD for use on GT1-6, combined with RBV or pegIFN/RBV. (*http://en.wikipedia.org/wiki/Sofosbuvir)*

  Phase III studies FISSION, FUSION and POSITRON, retreated GT2 or 3 NR patients with 12 or 16 weeks of Sovaldi (SOV) and ribavirin (RBV) for either 12 weeks of SOV/RBV/peg-IFN, or SOV+RBV without IFN for 24 weeks (36% of the patients had cirrhosis). SVR12 data showed 63% of those on the 24-week SOV+RBV arm and 92% of those on the 12-week SOV/RBV/peg-IFN arm achieved SVR12.
  (*http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol*-news&nyo=0)

  Gilead is allowing generic-drug makers in India to produce a new version of Sovaldi, thanks to a patent loophole. Sovaldi will soon about one-tenth the price in India than what Gilead charges in the U.S. Gilead is also exploring possibilities of reducing the cost of its drugs in Europe.
  (www.bloomberg.com/news/2015-01-26/gilead-expands-generic-sovaldi-pact-to-add-investigational-pill.html) (www.pmlive.com/pharma_news/gilead_cuts_hepatitis_c_drug_prices_in_germany_637978)

- **Ledipasvir (GS-5885)**
  Ledipasvir is an NS5A inhibitor. It drew attention for its potent *in vitro* activity, and has been tested and shown to be effective and safe in both treatment-naïve and treatment–experienced patients. The results of a Phase I 3-day trial were presented at the EASL 2011 conference in Berlin. It was found effective with once-a-day use. During its 3-day Phase I clinical trial, GT1 patients experienced reductions in viral load ranging from 2.3 to 3.3 $\log_{10}$. It was more effective in GT1b than in GT1a patients. The drug is now part of the approved Harvoni treatment. Ledipasvir is currently being tested in several combos, such as **Vedroprevir/Ledipasvir/Sovaldi +RBV** and **Sovaldi/Ledipasvir with GS-9669 or Vedroprevir** and **Vedroprevir/Ledipasvir** *(www.natap.org/2012/HCV/021312_01.htm)*
  WARNING: Do not take Amiodarone with Sovaldi or Harvoni.

- **Holkira™ Pak** (Canada) or the **Viekira™ Pak** (US), produced by AbbVIE, was approved for sale in the US and Canada in December 2014. The treatment is what was previously called the 3D combo, consisting of paritaprevir (boosted with ritonavir), ombitasvir and dasabuvir (ABT-450/r, ABT 267, and ABT-333… now called Exviera) In Phase III clinical trials, HOLKIRA PAK (with or without ribavirin) cured an overall 97% of GT1 HCV patients; additionally, 98 percent of patients completed treatment
  HOLKIRA PAK was evaluated in more than 2,300 patients in over 25 countries, demonstrating consistently high cure rates across a large and diverse patient population

  Recommended treatment:
  - •GT 1a, without cirrhosis: Holkira PAK + RBV for 12 weeks
  - •GT 1b, without cirrhosis: Holkira PAK for 12 weeks
  - •GT 1a and 1b, with cirrhosis: Holkira PAK + RBV for 12 weeks*

  *24 weeks of HOLKIRA PAK + RBV is recommended for those with GT1a-infection with cirrhosis and previous null response to pegIFN/RBV.
  Holkira PAK with RBV is recommended in patients with an unknown GT1 subtype or with mixed GT1 infection.

- **Paritaprevir (ABT-450/r previously Veruprevir)**
  Paritaprevir was discovered during a search for an effective protease inhibitor by AbbVie and Enanta Pharmaceuticals. In 2013, Abbott decided to divide the company into Abbott and AbbVie Inc. AbbVie took over the hepatitis research and development, including paritaprevir, which was developed by AbbVie to use with its investigational compounds for treating hepatitis C. Paritaprevir, boosted with ritonavir to make its effect stronger, is used in AbbVie's approved Holkira™ Pak. *(www.cnbc.com/id/102285823)*

- **Ombitasvir (ABT-267)**
  AbbVie's NS5A Inhibitor has been studied alone in clinical trials through Phase III, as well as in combos with the protease inhibitor paritaprevir (ABT-450r) and the non-nuc polymerase Exviera (dasabuvir) with or without RBV. It has been shown to be effective in genotype 1-6 in pre-clinical trials, and in GT1 and GT4 patients in combo trials. (*www.ncbi.nlm.nih.gov/pubmed/25347030*)
- **Exviera (dasabuvir or ABT-333)**
  Exviera is a non-nucleoside polymerase inhibitor produced by AbbVie, now part of the newly-approved Holkira Pak (Canada) or Viekira Pak (US). It seems to have been developed for use as a part of that drug combo. You can see just about everything there is to know about the drug here: *www.who.int/phi/implementation/ip_trade/dasabuvir_report_2014-09-02.pdf*
- **Daklinza (daclatasvir or BMS-790052)**
  Bristol-Myers Squibb's Daklinza is an NS5A replication complex inhibitor. NS5A is a protein of HCV used by the virus to replicate, and that protein also regulates the signaling pathways in the cell.

  Daclatasvir is approved in Japan, and as of August 2014, Daklinza has been approved by the European Commission for treating GT 1, 2, 3 and 4. The approval was based on clinical trials combined with Gilead's Sovaldi, where it produced SVR rates of up to 100% even in patients who failed previous treatment and those with advanced liver scarring. The drugs may be combined with pegIFN/RBV for some genotypes and higher grades of scarring. Treatment may last from 12 to 48 weeks, according to the patient's needs. Daklinza was approved earlier in 2014 in Japan, to be used together with Sunvepra, a protease inhibitor, in GT1 patients and patients with cirrhosis.
  (www.hcplive.com/product-news/EU-Approves-Daklinza-for-the-Treatment-of-Hepatitis-C)

DRAFT PROPOSED PROJECT SCOPE: **TREATMENT REGIMENS FOR CHRONIC HEPATITIS**.
The review from Canada's CADTH proposes looking at the following Interferon-Free Direct-Acting Antiviral (DAA) regimens, thanks to Cheryl Reitz of HepCBC:

Genotype 1	**simeprevir + sofosbuvir**
	sofosbuvir + ledipasvir
	paritaprevir/ritonavir + ombitasvir + dasabuvir
	daclatasvir + asunaprevir
	daclatasvir + sofosbuvir
	grazoprevir + elbasvir
	sofosbuvir + ribavirin
	daclatasvir + asunaprevir + beclabuvir
	sofosbuvir + GS-5816
Genotype 2	**sofosbuvir + ribavirin**
	sofosbuvir + GS-5816
	daclatasvir + sofosbuvir
Genotype 3	**sofosbuvir + ribavirin**
	sofosbuvir + ledipasvir
	daclatasvir + sofosbuvir
	sofosbuvir + GS-5816
	paritaprevir/ritonavir + ABT-530
Genotype 4	**sofosbuvir + ribavirin**
	sofosbuvir + ledipasvir
Genotype 5	**daclatasvir + sofosbuvir**
	sofosbuvir + GS-5816

	grazoprevir + elbasvir
Genotype 6	**sofosbuvir + ribavirin**
	daclatasvir + sofosbuvir
	sofosbuvir + ledipasvir
	sofosbuvir + GS-5816
	grazoprevir + elbasvir

III.1.3 Is treatment worth it?
We used to think our goal was an SVR (Sustained Viral Response), but the goal now is a CURE. A cure means we can't spread the disease to our loved ones. We must not forget that an important long-term goal is to prevent Hep-C related death or disability.

"Among patients with chronic HCV infection and bridging fibrosis or cirrhosis, attaining SVR was associated with survival comparable with that of the general population, whereas not attaining SVR was associated with reduced survival." (*www.natap.org/2014/HCV/120314_01.htm)*

Five hepatology centres in Canada and Europe analized data from 530 patients' treatment with IFN regimens between 1990 and 2003. 193 patients had SVR, and of those, 13 died. 91.1% of the patients survived 10 years—a rate comparable to the non-HCV+ population. On the other hand, of 100 patients who didn't respond with an SVR, the rate of 10-year survival was 74%. We will have to wait a while for the 10-year survival rate for those who have been cured with the new drugs.
(www.jwatch.org/na36305/2014/11/19/effective-hcv-treatment-prolongs-survival#sthash.uC3e6NDp.dpuf)

The word "cure" was, until recently, controversial. In patients who achieve SVR, which means that the virus can't be detected 6 months after the last dose of treatment, a trace of the virus can remain and reappear in 1 to 2% of them during those 6 months. It is very unlikely for the virus to reappear after that time, and after a year of remaining virus-free, doctors are confident enough to stop checking. Re-infections can occur, though. And even though the virus disappears, the antibodies remain, but they don't make you immune to future infections.

Studies have shown that the sooner one is treated after infection, the higher the chance of SVR. This is especially true if treatment starts within a few months of infection. See **EARLY TREATMENT**

HCV is usually not a life-threatening infection. It can take several years or even a decade or more before any signs of the disease become apparent. People infected may not even know they are ill. Of course different people will react differently. Some do not fare so well as others, therefore HCV infection should ALWAYS be monitored regardless of when it was contracted.

III.1.4 When is interferon treatment not indicated?
Many of the new treatments still include interferon, and interferon is sometimes used as a rescue therapy, but some patients can't take interferon because of other conditions, and many suffer uncomfortable and sometimes dangerous, side effects. The good news is that many patients who can't tolerate interferon can tolerate the new DAAs (Direct-Acting Antivirals).

Some patients have a genetic trait that seems to interfere with interferon treatment: the IL28b allele. These patients usually fare much better with non-IFN treatment.

Patients with chronic hepatitis B or C, with fluid in the abdomen (ascites), bleeding from dilated veins in the esophagus (variceal bleeding), mental confusion (encephalopathy), human immunodeficiency virus (HIV) infection or organ transplant recipients on prednisone, cyclosporine and FK-506 are usually treated only in a clinical trial. Others not suitable for treatment are those with symptomatic heart, lung or kidney disease, and patients on antidepressants or with a history of attempted suicide. Interferon should not be given to women considering pregnancy within six months after treatment, nor to the intended father.

"Treatment of HCV in current and former IDU within a multidisciplinary DOT program can be successfully undertaken, resulting in SVR similar to those in randomized controlled trials."
(www.blackwell-synergy.com/doi/abs/10.1111/j.1440-1746.2007.05032.x?cookieSet=1&journalCode=jgh Dr. Jason Greebly, Vancouver, BC)

In cirrhotic, genotype 2 and 3 patients who show a viral response to standard therapy at week 4, 24wks'

treatment resulted in SVR rates of more than 87%, the same as in non-cirrhotic pts. However, the response rates at week 4 are much lower in cirrhotic patients, indicating the necessity of earlier treatment. *(www.hcvadvocate.org/news/reports/DDW_2007/Abstracts/MondayAbstracts.htm)*

III.1.5 What if Treatment Doesn't Work?
Although treatment initially shows viral clearance in patients with chronic hepatitis C virus (HCV), many patients experience a relapse after treatment, breakthrough (relapse during treatment), or no response at all. This is less likely to happen with treatment involving DAAs (Direct-Acting Antivirals).

Relapse: This is said to occur when a patient who tested virus free during treatment becomes virus detectable sometime after treatment ends.

Breakthrough: Breakthrough can refer to the sudden emergence of a treatment-resistant strain or strains of the virus in a patient that has previously been responding well (viral load drop) to treatment, or to a sudden large increase in virus after a promising decline.
(www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed&uid=9759607&cmd=showdetailview&indexed=google)

Although recombinant interferon alpha (rIFN alpha 2) has initially been shown to normalize the aminotransferase levels in approximately 50% of patients with chronic hepatitis C virus (HCV), a few patients experience a relapse during the treatment, in spite of a complete initial response (breakthrough). Continued treatment with rIFN alpha 2, even at higher doses, did not restore the previous response in any patient. All of them were then switched to natural lymphoblastoid IFN, and this rapidly restored a complete response in all of the patients. - "Breakthrough during recombinant interferon alpha therapy in patients with chronic hepatitis C virus infection: prevalence, etiology, and management." *(Hepatology Vol. 21 no. 3 pp. 645-9, 1995 Mar).*

It may be that patients previously declared as having had a complete initial response followed by breakthrough may actually be non-responders, since the tests years ago were not sensitive enough to detect small amounts of virus that might not have been eradicated.

It has been found that many non-responders, including those who experience breakthrough or relapse, have unfavourable IL28b.

"The development of neutralizing antibodies to interferon is associated with Breakthrough in about half of the patients; other etiologic factors such as down-regulation of interferon receptors or development of virus resistance to interferon may be implicated in the remaining cases." Genotype does not seem to make a difference (*Ital J Gastroenterol Hepatol*. *1998 Jun;30[3]:333-7*).

Researchers (abstract #781) tried various combinations of therapies to treat relapse and breakthrough to IFN + ribavirin. 124 patients received Peg-IFN alpha-2a once a week for 48 weeks, combined with either ribavirin, Cellcept, amantadine, or a combination of ribavirin plus amantadine. The best response was 45.2% for the last group. – "*What Did We Learn About Hepatitis C From AASLD 2002?" (Alan Franciscus, HCVAdvocate)*

Non-Response: When a patient goes on standard treatment and does not achieve at least a 2 $\log_{10}$ drop in viral load by week 12 they are said to be non-responders. Non-responders have a much lower rate of successful treatment (SVR) than responders although some trial show longer treatment of treatment with higher doses can improve their odds.

III.1.6 Re-treatment
People who didn't have sustained viral response to interferon alpha/ribavirin are now often re-treated successfully with direct-acting antivirals, with or without pegIFN/RBV. But what about those unfortunate patients who develop multi-DAA-resistant strains of HCV? The ideal might be a combination of DAAs, but it may be necessary to use "QUAD therapy", consisting of pegIFN/RBV and 2 DAAs as a rescue therapy. *(www.sciencedirect.com/science/article/pii/S0166354214000394)*

III.1.7 Transplant and Post-transplant
When is a liver transplant necessary? This is a very complex issue and must be answered on a case-by-case basis. Anyone with hepatitis C should be referred to a gastroenterologist (specialist in digestive diseases and liver diseases), and followed by a physician regularly. If signs of progressive disease appear, the person needs to return to the gastroenterologist. Since hepatitis C is known to progress very slowly, it is not necessary to have a liver transplant until the disease has reached "end stage."

The United Network for Organ Sharing (UNOS) has developed a scoring system to determine which patients need a transplant. The scoring system is called Model for End-Stage Liver Disease, or MELD. The Pediatric End-Stage Liver Disease (PELD) is used for patients under the age of 18. The scores range

from Status 1 (those with less than 7 days to live without a transplant) on down, according to the MELD score (which uses creatinine, bilirubin and INR levels) or PELD score (uses albumin, bilirubin and INR levels). Both MELD and PELD scores range from 6 to 40. If scores are equally high in two or more patients most in need, then the doctors look at blood type, time waiting, and in the size of the available liver, in the case of minors. Also considered is where the liver is and where the patient is—the closer, the better.

People are denied livers if they are abusing alcohol or other substances that helped cause their liver damage, (2) if they have cancer in places other than the liver, (3) if they have heart or lung disease, (4) if they have a serious infection that threatens the operation, (4) if they have liver failure that has damaged the brain, or (5) if they have HIV.
(www.emedicinehealth.com/liver_transplant/page2_em.htm)

What are my chances with a liver transplant?

75% of liver transplant patients survive at least 5 years.
http://www.healthline.com/health-slideshow/liver-transplant#7

How long will a new liver last? No one knows how long a transplanted liver can last. The longest reported transplant survival is 36 years (*www.medscape.com/viewarticle/519810 2005*). Ten-year survival is commonplace. Hopefully improvements in techniques and medications that are continually occurring will allow most patients receiving liver transplants today to have long productive lives.

Will the hepatitis C be cured by a liver transplant*?* No. Hepatitis C can live in cells other than in the liver. Once the old liver is removed and the new one is connected the hepatitis spreads back into the liver within the first weeks to months after the transplant. If the patient has not responded to treatment before receiving a liver transplant, the virus almost always infects the new liver, since it lives in the blood, as well as other organs. Studies have been done treating patients with Sovaldi plus RBV for 48 weeks or until transplantation. This treatment was successful in 64% of subjects in a small study. There is no data yet for Harvoni pre-transplant, but some GT1 and 4 transplanted patients took Harvoni + RBV for 12-24 weeks, and 96-98% were cured. Of those treated later, after cirrhosis developed in the new liver, only 81% responded. *(www.hepmag.com/articles/2512_20529.shtml)*
WARNING: Do not take Amiodarone with Sovaldi or Harvoni.

Results were reported at the AASLD 2014 for a trial with daclatasvir + sofosbuvir or simeprevir with/without RBV for 24 weeks in 106 patients. Data after treatment was available for 30 of those patients. Treatment was started an average of 4 years after transplantation. All had GT1. All were taking anti-rejection drugs. 6 patients died. Of the 24 remaining, 79% were HCV- at end of treatment. Some results were not yet available. One patient relapsed, but was stable. There was no rejection. Researchers think this could be an effective therapy for patients with recurring HCV after transplant. *(www.natap.org/2014/AASLD/AASLD_80.htm)*

A liver transplant is a last resort. The best option is to take care of our liver and get rid of the virus, if possible. A transplant patient has to take very expensive anti-rejection medications for the rest of his/her lifetime, so that the body's immune system won't kill off the "foreign" liver. Strangely, though, in some cases, the Hep C virus may help the new liver to be accepted even more effectively than the anti-rejection drugs, since the virus itself suppresses the immune system in order to hide. The researchers think that HCV patients may be weaned off the antirejection drugs. Hopefully, with the new all-oral antiviral drugs, liver transplants for Hep C may no longer be needed.
(www.webmd.com/hepatitis/news/20140625/hepatitis-c-infection-may-have-silver-lining-for-transplant-patients)

Can I receive a transplant if I have hepatitis B and hepatitis C? Yes, some transplant centers are currently doing liver transplants for this indication.

Where do donated livers come from? Livers are donated, with the consent of the next of kin, from individuals who have brain death, usually as the result of a head injury or brain hemorrhage. There have also been real successes with living liver donors, where a part of the liver of the donor (still alive) is given to another family member.

How can I donate my organs? If you wish to be an organ donor, carry an organ donor card and place an organ donor sticker on your medical identification card. In Canada, it is permissible for HCV positive persons to donate their organs to other HCV positive persons.

Some Statistics:
United States--There were about 17,000 patients on the waiting list for livers at the end of 2014 *(http://optn.transplant.hrsa.gov/)*. There are about 6000 liver transplants done per year in the US.
(www.hopkinsmedicine.org/healthlibrary/conditions/liver_biliary_and_pancreatic_disorders/liver_transplantation_85,P00677/)

Canada--384 liver transplants were performed in 2012. 74 people were on the waiting list in 2012. *43 people died while waiting for a liver.*
(www.cihi.ca/CIHI-ext-portal/pdf/internet/REPORT_STATS2012_PDF_E)
The average waiting time for a liver transplant was 2.8-12.8 months in 2008.
(www.organsandtissues.ca/s/wp-content/uploads/2012/06/OTDT-INDX-final-C2A.pdf)
Canadian liver transplant 5-year survival rates are 80%.
(http://liver.ca/print/Treatment_and_Transplantation/Hepatitis_C_Treatment.aspx)

Survival rates in general are improving, probably due to more experience and better pre- and post-transplant treatment. Livers from live donors are now being used in many areas, and provide better results than cadaveric livers. Splitting livers from cadavers make it possible for more people to receive liver transplants, with a shorter waiting time.

III.1.8 SPONTANEOUS CLEARANCE
Past studies have shown that about 10% to 50% of those infected with HCV clear the virus with no treatment (average 25%). Unfortunately, determining the numbers is difficult since most people have no symptoms when they are infected. More women clear the virus than men. Spontaneous clearance is also higher in those who have symptoms of acute liver disease which are thought to indicate a strong immune system. Spontaneous clearance usually occurs within 4 months of infection, may take as many as 18 months, and in some cases may occur even later.

Two studies have provided more data. In the first, 67 HCV+ adults, 67% IVDU, were studied. 19% knew the source of their infection and 18% of that group reported high-risk sexual practices (sex before age 15, more than 6 partners, prostitution or sex with a prostitute, homosexual partners or partners who were IVDUs or HCV+). It was decided that those with acute infection were those who became HCV+ within a year of a previous negative test, or tested positive for antibodies with symptoms, or those infected through medical error (iatrogenic risk). Of these patients, 18% had cleared the virus with no treatment by the time they were re-tested at 6 months. 34% of the women cleared the virus compared to 3% of the men. The results were similar to those found among transfusion recipients.

In another study, 157 children found to be HCV+ between 1990 and 2001 (most infected through transfusions), were studied. Clearance was defined as having 2 or more positive HCV antibody tests but no HCV. In this study, 28% of the children cleared the virus with no treatment. The younger children had a higher clearance rate. The children infected at birth had a 25% clearance rate. Normal ALTs were related to clearance. *(www.hivandhepatitis.com/hep_c/news/2007/121107_b.html)*

DISCOVERY OF IFNL3

Researchers in Seattle have discovered that DNA changes on the IFNL3 (interferon lambda 3) gene on chromosome 19 are linked to spontaneous clearance of Hep C, or better treatment responses, and may be a good target for new pharmaceutical products. Until recently, they couldn't figure out the mechanism. When they noticed that Asians responded better than Africans, they started collecting data, hoping to find genes associated with SVRs.

They believe that two genetic variations on the IFNL3 gene found near an area that produces IL28b help fight HCV. Those with the T (which stands for thymidine) variant are unfortunate, while those with the G (which stands for guanosine) variant are luckier. They found that HCV can encourage liver cells to produce 2 microRNAs (silencers that stop "messengers" from sending info to form a protein from a gene like IFN lambda-3). Those 2 microRNAs are usually "sleeping" until HCV wakes them up and puts them to work. Usually they are used for bones and hearts, but the HCV hijacks them, thus becoming invisible to the immune system, except when the patient carries the "G" variant. But with this discovery, scientists can use the microRNAs as targets, so they can restore the patient's immune system. *See more:*
http://hepatitiscresearchandnewsupdates.blogspot.ca/2014/03/new-genetic-targets-ided-for-hcv.html#sthash.UWfN9xB4.dpuf
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III.2.0 WHAT ARE INTERFERONS?
Interferons are types of naturally-occurring proteins produced by cells of the immune system. Three classes of interferons have currently been identified: Alfa (also known as alpha), beta and gamma. Each class has different effects, though their activities overlap. Together, the interferons direct the immune system's attack on viruses, bacteria, tumours and other foreign substances that may invade the body.

Virtually all interferons used in HCV treatment today are obtained from recombinant bacterial sources (bacteria that have had slight man-made DNA modifications). In general, genetic material from human leucocytes is spliced into the genetic material of bacteria, and the bacteria are allowed to reproduce and

grow. The inserted genetic material causes the bacteria to produce interferon. Recombinant interferons of one type or another have been used to fight HCV since 1991.

III.2.1 Interferon Monotherapy
At one time, interferon alone was considered standard therapy.

III.2.2 Pegylated Interferon
Polyethylene glycol (PEG) is a substance with a high molecular weight that is easily excreted in the urine, due to being soluble in water. PEG attachment to interferon alpha leads to a longer half-life (the amount of time for given concentration of the drug in the body to drop by half). NOTE: Drugs may be metabolized or just excreted. Half-life covers both methods.

Comparisons of the two available pegylated interferons, Peg-Intron and Pegasys have been made. The two substances differ basically in the size of the molecule involved, (40 kilodalton for Pegasys, 12 kilodalton for Peg-Intron), Pegasys has a longer half-life and there are studies that say one or the other are more effective. Either of these drugs is considered part of standard therapy.

III.2.2a Pegylated Intron A (Peg-Intron A)
PEG-Intron A is a modified form of Merck's Intron A (interferon alpha-2b, recombinant), developed by Enzon, Inc., to have longer-acting properties than non-pegylated interferon. It is usually given along with ribavirin in the treatment of HCV. About 52% of genotype 1 patients achieve SVR on this combination therapy. 85% of genotype 2 and 78% of genotype 3 patients achieve SVR.
(www.hivandhepatitis.com/2005icr/aasld/docs/111405_j.html Nov 2005)

III.2.2b Peginterferon Alpha-2a (Pegasys)
Pegasys (peginterferon alpha-2a) is Hoffmann-La Roche's pegylated interferon. Studies have found that patients who do not achieve EVR (response at 12 weeks) have only a 3% chance of SVR. In patients with EVR, an average of 65% achieve SVR.
(http://hcvadvocate.org/hepatitis/About_Hepatitis_pdf/1.1.2_Training_Resources/PCP_web.pdf)
About 80% of genotype 2 and 3 patients achieve SVR with only 24 weeks of treatment, and almost 68% of genotype 4 patients achieve SVR. Of the approximately 16% of genotype 1 patients who achieve RVR, over 96% of those with a low viral load achieved SVR.*(From several posters at www.hcvadvocate.org/news/reports/AASLD_2007/Abstracts/Tuesday%20posters.htm)*

III.2.2c Other Approved Interferons

ViraferonPeg (Peginterferon alfa-2b)
This drug produced by Merck is now approved in India and the UK, as a result of their EPIC3 clinical study showing that certain non-responders even to prior pegylated treatments have successful re-treatment results. 1,336 patients were treated in the study. Of those who had undetectable virus at week 12 (EVR), which according to the rules of the study, qualified them to continue treatment for a total of 48 weeks, 57% achieved SVR in the non-pegylated arm and 47% in the pegylated arm. *(EASL 2009)*

Alferon (Human Leukocyte-Derived Natural Source Interferon Alpha-N3), developed by Interferon Sciences Inc., now owned by Hemispherix, is an injectable, natural-source, multi-species alpha interferon produced from human peripheral blood leukocytes. Alferon-N has been used recently (2014) in genotype 4 patients and in HIV/HCV co-infections in clinical trials, and is approved for use in Argentina.
(http://globenewswire.com/news-release/2014/01/07/600747/10063192/en/Hemispherx-Biopharma-Reports-Evidence-Based-Clinical-Potential-of-a-Natural-Interferon-IFN-Alpha-for-Infection-Control-and-Treatment-of-Drug-Resistant-H7N9-Influenza-Virus.html)

II.2.3a Interferons Not Yet Approved or Discontinued

- **Glycoferon** (glycol-engineered consensus IFN) **ACQUIRED BY JANSSEN**
  Alios BioPharma developed this pegylated interferon by changing the aminoacid sequence and introducing glycosylation sites into the protein, thus minimizing any disadvantages of the drug, without losing its potency. This is especially important, since non-responders are less likely to respond to re-treatment. Unfortunately, pegylation reduces the potency of the IFN, but it appears that the resulting product is 3 $\log_{10}$ more potent than pegIFN alpha 2a. Previous non-responders may, however, have more positive results if a more potent IFN is included in the combination treatment. *(www.natap.org/2008/EASL/EASL_46.htm)*

Janssen (Johnson & Johnson) acquired Alios in November 2014.
(http://connection.ebscohost.com/c/articles/98889484/oncore-biopharma-makes-acquisition-adds-hepatitis-trials)

- **PEG-interferon lambda (IL-29)** (BMS-914143) **DISCONTINUED**
  Bristol Myers-Squibb acquired ZymoGenetics in October 2010. A 3-year follow-up study is underway (2014-2018), recruiting patients who took part in the clinical trial.

  In August of 2014, BMS decided to discontinue the drug, saying, "We have concluded that given the very promising developments in HCV in terms of emerging all-oral therapeutic options, Lambda would no longer fulfill the unmet need that we had envisioned upon initiation of the clinical trials."
  (www.natap.org/2011/AASLD/AASLD_38.htm) (www.natap.org/2014/HCV/081514_02.htm)

- **Medusa IFN** (IFN alpha-2b XL) **NO NEWS**
  Flamel Technologies' IFN alpha-2b XL is a slow-release human IFN that uses the company's Medusa hydrogel technology. A Phase Ib study was done to prove the antiviral activity of two doses of the drug, given weekly, to 23 naïve patients (most with genotype 3) compared to Peg-IFN alpha 2b. The first dose showed similar activity in both drugs. The second dose, however, showed a 0.57 $\log_{10}$ reduction compared to only a 0.21 $\log_{10}$ reduction with the Peg-INF alpha 2b. The new drug was better tolerated. *(www.flamel.com/techAndProd/flamel-ifn-easl.pdf April 25, 2008)* The drug was in Phase IIa trials in France and Romania, starting March 2010, and ending in November 2013. There are no published results yet, as of January 2015.

- **Oral Interferon BANKRUPT (but may reorganize)**
  On October 31, 2013, Amarillo Biosciences filed for bankruptcy, and on May 23, 2014, a plan for reorganization was filed.
  (http://chapter11cases.com/2014/05/24/amarillo-biosciences-inc-bankruptcy-new-filing-alert-order-regarding-the-plan-of-reorganization/)

- **Consensus Interferon** (CIFN, Infergen, Interferon Alfacon-1) **LACK OF FUNDING**
  Further studies have been limited due to a lack of funding.
  http://hepatmon.com/24000.pdf **NO NEWS**

- **Omega Interferon NO NEWS**
  There seems to have been no more development since 2010.
  (http://clinicaltrials.gov/ct/show/NCT00519792;jsessionid=C5A138055F0E15830124F4D3BA63DC3A?order=41)

- **Belerofon NO NEWS**
  There has been no news on the Internet since its Phase I clinical trial in 2007.

- **Albuferon (Albinterferon),** developed by Human Genome Sciences and Novartis. **DISCONTINUED** in 2010. (*http://en.wikipedia.org/wiki/Albinterferon*)

- **Maxygen DISCONTINUED**
  Roche terminated development of Maxygen as of November 25, 2007.
  (www.maxygen.com/products-hep.php Nov 2007 and www.pharmatimes.com Nov 27, 2007)

- **Locteron (BLX-883) BANKRUPT**
  The company filed for bankruptcy July 5, 2012.
  (http://www.clinicaloptions.com/Hepatitis/Conference%20Coverage/AASLD%202010/Tracks/HCV%20Treatment/Capsules/821.aspx)

III.3.0 TREATMENT STRATEGIES FOR NON-RESPONDERS

So what can you do if you can't get rid of the virus? Watch your weight. Control any diabetes. Don't drink or smoke. Drink coffee, but in moderation. Stay away from alcohol, unnecessary drugs, and toxins.

In the pre-DAA days, the researchers would try adjusting the interferon dosage, using (1) high doses, (2) low dose maintenance doses to keep fibrosis from worsening, or (3) high-doses at the beginning of therapy (induction dosing). These strategies could hypothetically be used still today, with treatments that include interferon. Other approved interferons could be tried, as well.

Serious studies have shown that coffee, Vitamin D3 and Vitamin B12 each can improve treatment outcomes.
(www.sciencedirect.com/science/article/pii/S0016508511002733)
(www.ncbi.nlm.nih.gov/pubmed/20649944)
(http://gut.bmj.com/content/early/2012/06/28/gutjnl-2012-302344)

For **RESCUE THERAPY** *in cases of developing resistant strains of virus, see* **Re-treatment**
Be aware that you *may* be able to get compassionate access to drugs not yet approved, or approved in

other countries.

III.3.2 Early Treatment
HCV patients who are treated within a few months of being infected usually have a fast immune response, which helps eradicate the virus, according to Canadian research study published in the Journal of Virology. Only about 25% of patients get rid of the virus without treatment. Treatment is usually only effective in about 50% of cases, but those treated early have a 90% or more chance of getting rid of the virus. The research studied a group of IVDU before and after they were exposed to HCV. The results show how important it is to diagnose the disease quickly.
(www.upi.com/Health_News/2008/08/12/Early_treatment_key_to_treat_hepatitis_C/UPI-15141218575002/ Aug. 12, 2008)

Patients with little or no fibrosis (scarring) respond better to standard treatment than those with advanced fibrosis. *(EASL Conference 2009)*

Progression of fibrosis can start early. Doctors, patients and insurance companies need to know how fast hepatitis C can progress. Researchers did a study to find out what the progression rate is, from to infection to liver failure, and what can change that rate. To do this, they examined data from a database of 610,514 military veterans. They studied those who had an initial negative HCV-antibody test, and a later positive one, along with a positive test for the virus. They matched those 1840 veterans with a similar group (age, race, sex) of 1840 veterans with no Hep C. (Those co-infected with HBV or HIV, and those with liver cancer or cirrhosis at baseline were excluded). Cirrhosis was scored as anything greater than 3.5 fibrosis on a scale of 4.

The HCV+ group tended to be younger, with a lower body mass index. They abused drugs and alcohol more, and had higher liver enzymes, but fewer diagnoses of diabetes and blood pressure problems. Fibrosis started early in the HCV+ group, but slowed down after 5 years. At 5 years, 15% of HCV+ veterans had cirrhosis, compared to 5% of those without HCV. After 10 years, it was found that 18.4% of the HCV+ veterans were cirrhotic, compared to 6.1% of their HCV- counterparts. Liver failure was uncommon in those 10 years after diagnosis.

The researchers concluded that early treatment should slow or reverse the progression of fibrosis and delay the development of cirrhosis. They suggested that treating those with cirrhosis to avoid liver failure would work, but the number of those "saved" would be small. "Compared with HCV- persons, HCV+ persons had a significantly faster time to first hepatic decompensation event." "...[W]e found that among HCV+ persons the mean FIB-4 scores doubled in the first 4 years after infection and more than 18% of them developed cirrhosis within 10 years after infection." Early treatment seems to make more sense than waiting until a patient develops liver damage, according to this study.
(www.natap.org/2014/HCV/121214_01.htm)

III.3.3 Longer Treatment
Roche's REPEAT study of 950 non-responder patients showed that 72 weeks of Pegasys with Copegus is a promising option, and a viral response at 12 weeks usually predicts whether or not a patient will achieve a sustained virological response (SVR). All patients took Copegus (ribavirin). SVR was achieved in 16% of patients taking 360 mcg/week of Pegasys for 12 weeks (high dose induction therapy), followed by 180 mcg/week (standard therapy) for 60 weeks. 9% of patients receiving 180 mcg/week of Pegasys for 48 weeks achieved SVR. High dose induction therapy did not help. Longer dosing did help patients with a viral response at 12 weeks, with 57% of those patients achieving SVR. Relapsers were not included in this trial. They are easier to treat than non-responder patients. (*www.rocheusa.com November 2, 2007)*

The pharmaceutical companies have been working to shorten treatment and number of pills taken, using DAAs (direct-acting antivirals). Some experimental treatment regimens are lasting only 6-8 weeks now, with no injections in some cases. Longer treatments are used with patients with advanced liver scarring or difficult-to-treat previous non-responders to treatment.

III.4.0 Iron Reduction Therapy
The idea that iron reduction, through diet or bloodletting, could help improve response to interferon treatment was explored in the past. That it has not been widely adopted may be an indication of its effectiveness. Iron is required for replication of virtually all virulent micro-organisms. The role of iron influencing the natural history of viral hepatitis was reported in a study more than 15 years ago (Blumberg BS, Lustbader ED, Whitford PL. "Changes in serum iron levels due to infection with hepatitis B virus*." Proc Natl Acad Sci* USA 1981;78:3222-4). In this study it was observed that patients with hepatitis B viral infection with higher serum iron or ferritin levels had greater likelihood of development of chronic infections than those with lower levels, who more often resolved their infections

spontaneously.

Studies done since 1998 showed that phlebotomy (bloodletting), combined with IFN, reduces liver inflammation but not fibrosis. It seems to reduce the viral load, and may improve sustained response, but the results are not enough to be statistically important (*Journal of Hepatology* 1998; 28:369-374 and *Hepatology* 2000; 31:730-736). These studies were not done combining the interferon with ribavirin. Ribavirin tends to produce anemia.

PART IV: RESEARCH and CLINICAL TRIALS

The ideal goal of HCV research is to find a cure for everyone, which:

1) Has only one pill…no injections.
2) Has no side effects
3) Works for everyone and all genotypes.
4) Has a short treatment time. (i.e., 12 weeks)
5) Doesn't create resistance

As you read or search through the following drugs being tested in clinical trials, keep in mind that usually the intention of the researchers is to combine two or more types of direct-acting antivirals to avoid producing resistant strains of virus that weren't destroyed. You will see a lot of combo treatments. We will generally not mention drugs in Phase I development, nor those that require injections.

WILL WE STILL NEED IFN?

Interferon (IFN) has been used for the treatment of Hep C for more than 20 years. SVR (sustained viral response or "cure") rates back then were low, but were improved when ribavirin (RBV) was added, and improved still more when the IFN was pegylated (pegIFN), allowing for just one injection per week. Those improvements helped over 50% of patients to attain SVR. Unfortunately, that treatment (pegIFN/RBV) took up to 1 year or even 18 months of treatment, and had many side effects--arguably worse than the disease itself, according to some reports. The pharmaceutical companies continued to search for something more effective, with fewer side effects, no injections and shorter treatment times. As a result, we now have several effective oral direct-acting antivirals (DAAs), which include many that are effective without pegIFN/RBV. Some are now available. PegIFN/RBV may eventually be needed only 1) to reduce treatment time or the number of DAAs used, 2) in patients with difficult-to-treat genotypes, 3) in those who fail treatment with DAA therapies, or 4) in those who have difficult viral mutations. (*www.ncbi.nlm.nih.gov/pubmed/24548815*)

HOW DO I FIND A CLINICAL TRIAL FOR ME?

Your doctor may also suggest that you join a clinical trial for new treatments, or you may want to bring up this option with your doctor. Clinical trials are carefully designed research studies that test promising new HCV treatments. Patients who take part in research may be the first to benefit from improved treatment methods. These patients also can make an important contribution to medical care because the results of the studies may help many people. Patients participate in clinical trials only if they choose to and are free to leave at any time. There can be some risk involved, of course. For information about phases of clinical trials, see **Appendix G**. For information about clinical trials, go to *www.clinicaltrials.gov*

As you read about the following clinical trials, please consider the following:

HOW DO I UNDERSTAND AND COMPARE TRIAL RESULTS?

You might think it's easy. You look at the SVR12 rate (now considered a "cure"), and 100% is better than 75%, right? Not so fast! It is very difficult to compare clinical trial results and choose a treatment based on the information from studies such as those presented at even the top medical conferences such as EASL. Why? The studies don't usually compare the various drugs to those produced by other pharmaceutical companies (head-to-head studies).

The trials producing the best results might be published and those with poorer results might not. (This has not been found in Hep C trials, thanks to clinical trials registries like ClinicalTrials.gov).

The studies may use different duration of treatment and types of patients, different combinations of drugs and doses, differences regarding baseline viral load, presence of viral mutations, genotype, IL28b allele, state of the liver, age, gender, previous treatment, exercise, body mass index, use of alcohol and other substances. Some may treat a few patients, while others may treat thousands. One may treat patients in one clinic. Others may be multi-national. Be aware of these things when you are reading about trial results.

Most trials publicly report the people who dropped out. Some don't. Some trials use few people, while others use many.

You should also take into account the side effects and how serious they were.

(www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001526)

IV.1.0 HCV DIRECT-ACTING ANTIVIRALS (DAAs)
In order to replicate, HCV requires the proper functioning of various enzymes. These enzymes are the targets of some of the next generation of anti-HCV drugs. DAAs include NS3/4A protease inhibitors and polymerase inhibitors, which can be non-nucleoside NS5B, nucleoside NS5B, and NS5A inhibitors.

IV.1.1 PROTEASE INHIBITORS
Once HCV enters a liver cell, its genes guide the production of proteins that will become the inner core and surface coat of new viral units. First of all, the HCV makes an immature protein--a kind of unfinished sheet of material, which the Hep C protease cuts into the finished proteins, which then become the virus's outer cloak. Scientists have developed protease inhibitors, which stick to protease and stop its scissor-like function. This type of drugs has been used in the treatment of HIV for years.
(www.veritasmedicine.com).

APPROVED:
Merck's **boceprevir** (Victrelis) and Vertex's **telaprevir** (Incivek)—were approved in the US and Canada. They are called the first generation DAAs (direct-acting antivirals)--the first protease inhibitors to form part of standard treatment. Vertex stopped selling Telaprevir as of October 2014 and Incivek is withdrawing, as well.

Olysio/Galexos (simeprevir) and paritaprevir are second generation protease inhibitors, also now approved.

The protease inhibitors below have reached Phase II, either alone or with IFN/RBV. The combo trials can be found in the section **Direct-Acting Antiviral Combos.**

IV.1.1a ABT-493
Enanta and AbbVie were developing the protease inhibitors ABT-450 and ABT-493 together, but Enanta backed out of the agreement. ABT-450 has been approved as part of the successful Holkira™ Pak (Canada) or the Viekira™ Pak triple regimen.

"ABT-493 is designed to enable once-daily dosing without ritonavir and it is expected to be co-formulated with ABT-530." ABT-530 is an NS5A inhibitor.
(www.drugdevelopment-technology.com/news/newsabbvie-begins-phase-iib-clinical-trial-of-hcv-drug-candidate-abt-493-4369639)

"We believe that the development and commercialization of our HCV protease assets, ABT-450 and ABT-493, are in good hands with the expertise and resources of a global biopharmaceutical company such as AbbVie," said an Enanta representative.
(www.streetinsider.com/Corporate+News/Enanta+Pharma+%28ENTA%29+Will+Not+Exercise+co-Development+Option+on+ABT-493/9924703.html
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IV.1.1b Emricasan (PF-03491390 formerly IDN-6556)
Idun Pharmaceuticals designed small molecule caspase protease inhibitors to inhibit cell death (apoptosis) in tissues and organs. It was developed to slow the progression of fibrosis. Based on phase II trials, the drug had been given orphan drug status in the US for use in transplant patients. Idun was acquired by Pfizer in 2005. A trial treating 204 HCV patients showed that AST/ALT levels returned to pre-treatment levels when the drug was stopped. Increased doses did not help. The most common side effects were fatigue and headaches. The drug was put on a clinical hold. Conatus Pharmaceuticals (formed by the former executive management team if Idun Pharmaceuticals) saw potential in the drug and bought it from Pfizer. The clinical hold has been lifted and trials are underway, with Phase III being planned. The drug has proven its ability to reduce fibrosis.
(www.hivandhepatitis.com/2004icr/39easl/documents/0503/050304_hcv_a.html)
(http://chronicfatiguesyndrome.researchtoday.net/archive/6/4/1621.htm 29 April 2010 in Aliment Pharmacol Ther, 31(9): 969-78).
(http://seekingalpha.com/article/1713862-does-conatus-pharmaceuticals-have-a-winner-with-emricasan)
(https://propthink.com/intercept-isnt-way-play-rare-liver-diseases/)

IV.1.1c Grazoprevir (MK-5172)
Merck announced at the AASLD 2011 that their next-generation NS3/4 protease inhibitor MK-5172 lowered the viral load to undetectable with 7 days of monotherapy, in 75% of GT1 patients and in 38% of GT3 patients. 87% of GT1 patients treated with the highest dose (800 mg) of MK-5172 had their viral

load lowered to undetectable. The antiviral activity continued for some days beyond treatment, with no viral rebound seen during treatment, no discontinuations due to side effects, and no serious lab test results affecting patient safety. The study is ongoing. At 1 month follow-up viral loads were still below their starting point in some patients. *(www.merck.com/newsroom/news-release-archive/prescription-medicine-news/2011_1105.html and NATAP)* Phase II studies combining Grazoprevir with pegIFN/RBV in 266 treatment-naïve GT1 patients produced 261 SVRs. All non-responders were GT1a patients. *(http://cid.oxfordjournals.org/content/59/12/1657)* See Grazoprevir combos: C-WORTHY

IV.1.1d Sovaprevir (ACH-1625)

On March 30, 2011, Achillion Pharmaceuticals proudly announced results of its Phase IIa clinical trial showing RVR (Rapid Virologic Response) rates of 75-81% with a once-daily dose of its protease inhibitor ACH-1625, combined with pegIFN/RBV. The trial is treating 64 patients with either 200 mg, 400 mg or 800 mg of the drug plus pegIFN/RBV for 4 weeks, and then pegIFN/RBV for 44 weeks more. Most of the patients are GT1a (genotype 1a), but 1 out of 4 are GT1b. 75% were IL28b genotype CT/TT, those who have less chance of responding to IFN. There was no breakthrough in any of the patients who completed 4 weeks of ACH-1625 treatment.

"These data reflect a positive outcome with high RVR, irrespective of IL28B status, which places ACH-1625 among the most potent protease inhibitors in development," stated the Vice President and Chief Medical Officer of Achillion. *(www.natap.org/2011/EASL/EASL_02.htm)*

The FDA put Sovaprevir on hold, but lifted the hold in June of 2014, so testing can resume. Some of the healthy, volunteer Phase I trial participants had shown elevated liver enzymes when the drug was combined with BMS' Reyataz (ataznavir) boosted with AbbVie's ritonavir. Since then, Achillion has worked with the FDA closely, and Phase II 12-week trials in 550 patients have been going well. (*www.firstwordpharma.com/node/1216224)*

See Combos: Sovaprevir/ACH-3102/ACH-3422 and Sovaprevir/ACH-3102/RBV

IV.1.1e Vaniprevir (MK-7009)

Merck's Vaniprevir is an NS3/4A HCV protease inhibitor. The Phase IIb study of Vaniprevir combined it with standard treatment, and treated 91 GT1, treatment-naïve, non-cirrhotic subjects for 4 weeks. Then they were treated with standard treatment alone for another 44 weeks. Their response rate was better than standard treatment alone. Most of the patients had an RVR (week 4). The higher doses of Vaniprevir resulted in SVR rates of 78-84%, compared to 63% with standard treatment alone. The side included mild to moderate vomiting but no patient dropped out because of that.
(www.clinicaloptions.com/Hepatitis/Conference%20Coverage/AASLD%202010/Tracks/HCV%20Treatment/Capsules/82.aspx)

A Phase III trial has been completed. The subjects were 294 Japanese, treatment-naïve patients, and treatment combined Vaniprevir with pegIFN/RBV for 12 or 24 weeks (pegIFN/RBV for 48 weeks in some arms) SVR24 rates were 84% (Sept 2014)
(https://clinicaltrials.gov/ct2/show/NCT01370642?term=NCT01370642&rank=1&sect=X70156#outcome1)

IV.1.1f Vedroprevir (GS-9451) is a protease inhibitor produced by Gilead. Its 3-day monotherapy trial well-tolerated and effective in both GT1a and GT1b. *(www.natap.org/2012/APASL/APASL_24.htm)* Vedroprevir is being studied in Phase II combo trials with other Gilead products, such as their **Vedroprevir/Sovaldi** and the **Vedroprevir/Sovaldi/Ledipasvir** trials.

IV.1.1g Other Protease Inhibitors (approved in other countries, in early development, on hold, discontinued, etc.)

Below, you will see some promising protease inhibitors that are in early stages of research, have been discontinued, put on hold, have been sent to other countries, or are still fulfilling FDA requirements. Many drugs have been discontinued, even though they looked promising, because other similar drugs have better results. (A desperate patient *might* be able to convince a specialist to request one of these through a compassionate or special access program, if the drug wasn't stopped due to safety issues. Personal note: A couple of members of HepCBC both owe their SVRs to a trial drug with no side-effects that was put on hold in the US, and both were 5-time non-responders!)

- **Sunpreva (Asunaprevir or BMS 650032) – Awaiting approval**
  Sunpreva, when combined with BMS's drug Daklinza (daclatasvir), has shown great success in clinical trials, but the company has decided to withdraw its application for approval of the Sunpreva in the US, and use Daklinza with other already-approved drugs. The Daklinza-Sunpreva combo is already approved in Japan. (Daklinza still awaits Canadian and US FDA approval, but must undergo further trials combined with other DAAs).

(http://news.bms.com/press-release/rd-news/bristol-myers-squibb-statement-about-asunaprevir-us)
Sunpreva and Daklinza are forming part of a non-IFN all DAA **combo trial** with beclabuvir.

- **Narlaprevir (SCH 900518) - Approved in Russia and CIS**
  Merck's Narlaprevir (NVR) is an NS3 protease inhibitor. A Phase II trial showed SVR up to 85% in GT1 patients with NVR/r (NVR + RTV) once a day + pegIFN/RBV for 12 weeks, followed by pegIFN/RBV alone for 12 weeks. A lead-in treatment with pegIFN/RBV alone did not improve SVR rates. Average SVR rate in African Americans was 66.7% and in GT1a was 75%.
  (www.multiwebcast.com/aasld/2011/thelivermeeting/17133/doctor.john.m.vierling.once.daily.narlaprevir.(nvr.sch.900518).and.ritonavir.html)
  In 2012, Merck granted the pharmaceutical company R-Pharm the right to develop and sell narlaprevir in Russia and the CIS (Commonwealth of Independent States.) It is expected to be available for sale there in 2017. *(http:///r-pharm.com/en/news/article-129/)*

- **GS-9857 – NO NEWS**
  GS-9857 is a pan-genotypic protease inhibitor developed by Gilead. Phase I clinical trials began recruiting patients as of June 2014. An estimated 92 patients with GT 1, 2, 3 or 4 will be treated with up to 300mg or 600mg of GS-9857 tablets or a placebo, twice daily for three days, under fasted conditions. Patients will be monitored for 48 weeks.
  (https://clinicaltrials.gov/ct2/show/NCT02185794)

- **ACH-2684 - NO NEWS**
  ACH-2684 is a discovery of Achillion. It has completed Phase I trials in HCV+ patients, and was found to be safe. The 3-day Phase Ib trial showed promise even in cirrhotic subjects and produced a drop of up to 3.73 $\log_{10}$ in viral loads, remaining effective against mutations. Achillion has announced plans to begin an 8-week Phase II trial combining the drug with the NS5A inhibitor ACH-3102.
  (*www.avarx.com/)*

- **Danoprevir (previously ITMN-191 or (RO5190591) - NO NEWS**
  Roche's Danoprevir is an NS3/4A serine protease inhibitor. Danoprevir or a placebo was tested in combination with pegIFN alpha-2a and RBV for 14 days. HCV RNA was undetectable in most of ITMN-191 treated patients in all dosing arms at day 15. No viral rebound was seen during treatment. *(EASL Conference 2009)* InterMune was collaborating with Roche to develop the drug, and in October 2010, Roche bought full rights to danoprevir.
  The **Danoprevir/Ritonavir + PegIFN/RBV Combo**: This trial was designed for GT1 non-responders to previous pegIFN/RBV plus Danoprevir. Breakthrough was 50% for the GT1a patients by week eight. *(www.clinicaloptions.com/Hepatitis/Conference%20Coverage/Vienna%202010/Tracks/HCV/HCV/Pages/Page%207.aspx and http://en.wikipedia.org/wiki/Ritonavir)*
  It was part of a Phase II combo trial with **mericitabine and ribavirin** in 2012. (SEE **ANNAPURNA**)

- **AVL-192 - NO NEWS**
  AVL-192 was produced by Avila Therapeutics, Inc. believed that AVL-192 was possibly their best-in-class candidate because it retains its potency even long after it is removed, it works in all the genotypes, and it might be used as monotherapy. Celgene acquired Avila Therapeutics in 2012, but unfortunately that company is busy developing Avila's non-HCV drugs, and there is no news about AVL-192. See: *www.fiercebiotech.com/story/celgene-snaps-avila-therapeutics-925m-buyout/2012-01-26)* and *www.avilatx.com*

- **Faldaprevir (BI 201335)** - **WITHDRAWN**
  Faldaprevir is an NS3/4A protease inhibitor produced by Boehringer Ingelheim Pharmaceuticals that was being studied in Phase III trials. *(www.natap.org/2011/HCV/043011_03.htm 27 April 2011)*–In June 2014 Boehringer Ingelheim decided to withdraw from the field of HCV and halted development of faldaprevir, taking into account the new all-oral treatment options such as those produced by Gilead, AbbVie, Janssen, and BMS.
  (http://hepatitiscnewdrugs.blogspot.ca/2014/06/boehringer-ingelheim-exits-hepatitis-c.html)

- **GS-9256 – DISCONTINUED**
  GS-0256 is a protease inhibitor developed by Gilead. It was investigated in a study about drug resistant mutations (DRM). It was hypothesized that each infected person has pre-existing DRMs. Software was developed to analyze the results, and found that no DRMs were found in the patients before treatment, but on day 2, 19/27 patients had DRMs, as did 21/21 on day 4. The placebo arm had no DRMs. The drug lowered the viral load up to 3.8 $\log_{10}$. The drug has been discontinued.
  (www.ncbi.nlm.nih.gov/pubmed/22837328)
  (http://en.wikipedia.org/wiki/Gilead_Sciences#Terminated_from_product_pipeline)

IV.1.2 NS5A INHIBITORS

Scientists have developed NS5A inhibitors to destroy one of the parts of the virus - a non-enzymatic protein that the virus needs to replicate. Some forms of NS5A protein help produce the virus. Others work together with host proteins. Some may be involved with interferon resistance. We don't yet know what it does, exactly. So finding something that would stop it from working is very difficult, and took a lot of hard work and quite a bit of luck. Bristol-Myers Squibb (BMS) developed the first one, now known as Daklinza (BMS-790052 or daclatasvir) which is now approved in Japan. They have become an important part of combos, helping ensure that the virus doesn't survive and mutate. (http://hepatitiscnewdrugresearch.com/what-are-ns5a-inhibitors.html)

APPROVED: The following NS5A inhibitors are now approved. They are among the first generation DAAs (direct-acting antivirals).

- **Daklinza** (BMS-790052) was the very first NS5A inhibitor to be developed. It has been approved in Japan and is much sought after as an ingredient in combo trials.
- **Ledipasvi**r, already approved, has proven to a very successful 2nd generation NS5A inhibitor, already part of the product **Harvoni**.
- **Ombitasvir** (ABT-267) is part of the approved **Holkira Pak.**

The NS5A inhibitors below have reached Phase II, either alone or with IFN/RBV. The combo trials can be found in the section below, **Direct-Acting Antiviral Combos.**

IV.1.2a ABT-530

AbbVie's ABT-530 is a next generation NS5A inhibitor that compared favorably to others in development as of March 2014. In clinical trials, it was seen to work effectively against GT 1-6, and works well against strains resistant to protease and polymerase inhibitors *in vitro.* *(www.natap.org/2014/CROI/croi_11.htm)*

A Phase II clinical trial with GT1 patients, with or without cirrhosis, treated them with ABT-530 as monotherapy for 3 days. A parallel trial with ABT-493 (protease inhibitor) was done during the same time period, also as monotherapy.

Both drugs were easily tolerated. Mild side effects included headache most frequently. There were no discontinuations, nor any lab abnormalities. Each drug produced a viral load drop of 3.5-4 $\log_{10}$.
After the 3 days of monotherapy with either of ABT-493 or ABT-530, patients continued with ABT-450r (paritaprevir--a protease inhibitor—boosted with ritonavir) + ombitasvir + dasabuvir + RBV for 12 weeks. (*www.natap.org/2014/AASLD/AASLD_52.htm)*

ABT-493 and ABT-530 appear on AbbVie's pipeline as the company's combo in development (2015).
See more: **ABT-493/ABT-530**

IV.1.2b ACH-3102

Discovered by Achillion in 2011, ACH-3102, a 2nd generation NS5A inhibitor, was given Fast Track designation by the US FDA. Proven to be safe in three phase II studies with 8 to 12 weeks of treatment, it has demonstrated good antiviral activity in GT1a patients, and has been shown to be effective in all genotypes in pre-clinical trials. It has a half-life that makes once-a-day dosing possible.
Click to see info about the **ACH-3102 + Sovaldi,** the **Sovaprevir/ACH-3102/RBV** and the **Sovaprevir/ACH-3102/ACH-3422** combo trials**.**

IV.1.2c EDP-239

EDP-239 is an NS5A inhibitor being developed by Enanta that has shown to be effective against all HCV genotypes. Enanta is working together with Novartis to explore the results of their varous DAAs, such as Alisporivir, in combination with each other. See more about **EDP-239 + Alisporivir**

IV.1.2d Elbasvir (MK-8742)

In Elbasvir's Phase I monotherapy clinical trial numbered NCT01532973, Merck enrolled GT1 patients in part 1, GT3 patients in part 2, and only GT1a patients in part 3. The study planned to enrol 48 male participants beginning in 2012.

Elbasvir. Merck's NS5A inhibitor is included in Phase II combo trial called C-Worthy, together with the protease inhibitor grazoprevir. As of March 2014, elbasvir and grazoprevir are being tested in HCV patients with kidney disease, in a trial numbered NCT02092350. The **C-Swift** Trial combines Grazoprevir/Elbasvir/Sovaldi. The **C-Crest** Trial combines Grazoprevir/Elbasvir/MK-3682.

IV.1.2e GS-5816

Gilead's GS-5816, is an NS5A inhibitor. Researchers discovered that some of the types of NS5A don't respond to the first generation drugs during monotherapy. This drug targets HCV GT 1-6 patients and

was expected to be more effective against all types of NS5A, and combines well with other DAAs in lab tests. (*www.natap.org/2013/EASL/EASL_34.htm*) In a 3-day monotherapy trial in 87 patients with genotypes 1-4, the drug was given once daily in several doses. Average viral load reductions were over 3 log10 for all doses and all genotypes.
The combo trial of GS-5816 and sofosbuvir (Sovaldi) did well. Click on the link to see more:
GS-5816 + sofosbuvir

IV.1.2f GSK2336805
Janssen announced the addition of Glaxo's NS5A inhibitor GSK2336805, already in Phase II development, to its arsenal of Hep C drugs in October 2013. The company plans to do more testing of the drug in DAA combos, especially with simeprevir and their TMC647055, a non-nuc polymerase.

IV.1.2g JNJ56914845
Janssen's JNJ56914845 is an NS5A inhibitor. Phase I and II clinical studies showed that JNJ56914845 once a day is well tolerated and lowers HCV RNA substantially in treatment-naïve HCV+ patients, either given alone in a single dose, or for 4 weeks with pegIFN/RBV.

An IFN-free Phase IIa trial of JNJ56914845, TMC647055 and Olysio was announced in December 2014:
Olysio/TMC647055/NJ56914845

IV.1.2h MK-8408
MK-8408 is a Merck NS5A inhibitor, now being investigated in Phase II combo trials. Earlier trials showed the drug to be effective against GT 1-6, and it is hoped to provide more protection against resistant strains than earlier NS5A inhibitors, and combine well with other DAAs.
(www.natap.org/2014/AASLD/AASLD_40.htm)

IV.1.2i PPI-668
On January 9, 2012, Presidio announced the end-of-treatment Phase Ia results for PPI-668 (aka ASC16), its 2nd generation HCV NS5A inhibitor, which studied 32 healthy volunteers in New Zealand. All doses were well-tolerated up to 5 days and showed that the drug can be given once a-day. The company has discovered some polymerase inhibitors that could be combined with PPI-668.
(www.hivandhepatitis.com/hepatitis-c/hepatitis-c-topics/hcv-treatment/3428-achillion-presidio-and-inhibitex-announced-hcv-drug-pipeline-developments)

On November 10, 2014, Ascletis and Presidio announced their partnership agreement for Presidio's PPI-668, also known as ASC16. Ascletis will develop and sell PPI-668 in Greater China. Presidio will keep all rights in the rest of the world. *(http://ascletis.com.cn/N11102014.html)*

Also on November 10, 2014, Pharco and Presidio announced that Pharco will pay for developing and marketing PPI-668 in Egypt and possibly the MENA (Middle East/North Africa) region. Pharco's goal is "to provide highly effective, safe pharmaceutical products to patients at an affordable price."
(*www.businesswire.com/news/home/20141110005178/en/Pharco-Pharmaceuticals-Licenses-Clinical-Stage-Hepatitis-Virus#.VMNJp0fF-VM*)

- PPI-668 was part of a notable Phase II clinical IFN/-free trial, combined with Boehringer Ingelheim's protease inhibitor faldaprevir, and the polymerase inhibitor deleobuvir, + RBV, obtaining SVRs up to 100%. Unfortunately, faldaprevir may have been discontinued. **Faldaprevir/PPI-668/Deleobuvir +/- RBV**

IV.1.2j Samatasvir
Idenix conducted a Phase I study of IDX719, now known as samatasvir, an NS5A inhibitor, effective against multiple genotypes. The first part of the trial tested the drug in healthy volunteers, and the second part was a 3-day trial in treatment-naïve genotype 1 patients.
(www.hivandhepatitis.com/hepatitis-c/hepatitis-c-topics/hcv-treatment/3428-achillion-presidio-and-inhibitex-announced-hcv-drug-pipeline-developments)
A Phase II Combo called **HELIX-1** is testing Samatasvir and Simeprevir.

IV.1.2k Other NS5A Inhibitors (approved in other countries, in early development, on hold, discontinued, etc.)

- **Daklinza (daclatasvir)** is expected to be approved in the US and Canada soon. It has been approved in Japan and Europe.
- **AZD-7295 (previously A-689) - NO NEWS**

This drug is from Arrow's second series of NS5A inhibitors, especially designed for GT1b. It began preclinical development in 2007. *(www.arrowt.co.uk/product-hcv.asp)* Arrow was acquired by AstraZeneca in 2007. The best results for a clinical trial in both treatment-experienced and -naïve GT1 and GT3 patients with no cirrhosis were in the highest doses in GT1b subjects, showing drops of 1.2 to 2.1 $logs_{10}$ at Day 6. A Phase II trial combining AZD7295 with pegIFN/RBV in GT1b patients began in 2008. AstraZeneca dropped Arrow's hepatitis C program in 2010. There seems to be no news about the drug since then, and it doesn't appear on AstraZeneca's pipeline.
www.ncbi.nlm.nih.gov/pmc/articles/PMC3251753/

- **PPI-461 - NO NEWS**
  PPI-461, Presidio's first NS5A inhibitor, was shown to be effective against all HCV genotypes. The Phase Ib 3-day clinical trial in treatment-naïve genotype 1 patients showed tolerable side effects and no related drop-outs or dose reductions. The 100 mg arm produced an average 3.7 log_{10} drop. One patient had an unusually poor response, but started the trial with a very resistant virus.
  (www.natap.org/2011/EASL/EASL_03.htm) The company seems to prefer their later NS5A inhibitor, PPI-668. The drug hasn't continued to Phase II trials yet.
- **ACH-2928 - DISCONTINUED**
  ACH-2928 was Achillion's first NS5A inhibitor. It is no longer being developed. *(http://i-metrix.edgar-online.com/ipo.aspx?colleft=613ecf6a-b2a7-4b42-a0c8-809161372aec&colright=76baaeb6-2549-44f5-8e1d-cd700701e704&cikid=121986&tabindex=2&coname=achillion%20pharmaceuticals%20inc&fnid=71139&ipo=0)*

IV.1.3 POLYMERASE INHIBITORS
The HCV NS5B protein is a viral–dependent RNA polymerase. It looks like a flat donut and contains 3 areas which interact, called fingers, palm and thumbs. These areas form a circle around the active site, creating a hole. This hole, or cleft, is a target for drug development. The NS5B Coding region is very similar in all the genotypes, and is unique to HCV. *(McHutchison, J. MD, Hepatology, November 2002)*
There are different kinds of polymerase inhibitors, basically: nucleoside, nucleotide, non-nucleoside. Nucleoside inhibitors bind to the polymerase's active site. Non-nucleoside inhibitors bind to allosteric sites of the enzyme. The advantage of polymerase inhibitors over other DAAs is that they are usually effective against all genotypes.

Several companies have developed or are developing polymerase inhibitors. They stop the virus from replicating in one of two ways. Nucleoside analogues stop the elongation of the RNA strands, and non-nucleoside inhibitors block the polymerase itself. Ribavirin is a nucleoside analogue, but its mechanism is not well understood yet. (*http://findarticles.com/p/articles/mi_m0EXV/is_2_10/ai_n13648061/pg_2*)
Besides the products below, there are many other polymerase inhibitors in pre-clinical trials. These are exciting times!

IV.1.4 NON-NUCLEOSIDE POLYMERASE INHIBITORS

APPROVED:
Exviera (Dasabuvir or ABT-333), a non-nuc polymerase inhibitor, is part of AbbVie's Holkira Pak.

The non-nucleoside polymerase inhibitors below have reached Phase II, either alone or with IFN/RBV. Information about the combo trials can be found in the section **Direct-Acting Antiviral Combos,** or by clicking on the links.

IV.1.4a Beclabuvir (BMS-791325)
Beclabuvir is an NS5B non-nucleoside polymerase inhibitor produced by Bristol-Myers-Squibb. It has passed through Phase I safety trials. There have been several clinical trials combining Beclabuvir with other DAAs. See more: **Sunpreva/Beclabuvir** and **Sunpreva/Daklinza/Beclabuvir**

IV.1.4b Deleobuvir (BI 207127) is a non-nucleoside NS5B polymerase inhibitor.
In December 2013, Boehringer Ingelheim had decided to end development of deleobuvir since "recent findings from phase III trials did not suggest sufficient efficacy."
(http://en.wikipedia.org/wiki/Deleobuvir) But perhaps it wasn't so. EASL 2014 presented encouraging results from its triple combo of **FALDAPREVIR/PPI668/DELEOBUVIR**.
Results*: www.natap.org/2014/EASL/EASL_36.htm*

IV.1.4c GS-9669 is a non-nucleoside polymerase inhibitor, produced by Gilead. It has been investigated in Phase II clinical trials for genotype 1 treatment. Its history is fascinating, but a bit complicated to understand without a scientific background. Its discovery was unexpected. Here's an

interesting abstract:
www.ncbi.nlm.nih.gov/pubmed/24144213 It has been used in trials alone (up to Phase Ib in 2011), and in some combos such as these:

- **Sovaldi/Ledipasvir with GS-9669 or Vedroprevir**

IV.1.4d PPI-383 is a non-nucleoside polymerase inhibitor produced by Presidio, and now in development by Ascletis. It is effective against all genotypes. It was well tolerated in preclinical studies. It can be dosed once or twice daily, and is expected to work well in combos with any types of DAAs. (*www.natap.org/2012/EASL/EASL_59.htm)*
A Phase Ia/Ib clinical trials began in the UK in August 2013 and was still recruiting participants in August 2014, both healthy and HCV+. *(https://clinicaltrials.gov/ct2/show/NCT01928147)*

IV.1.4e Setrobuvir (RG7790 previously ANA598)
Anadys Pharmaceuticals developed Setrobuvir (ANA598), a non-nucleoside polymerase inhibitor designed to treat GT1a and 1b patients. The product was fast-tracked by the US FDA in December 2008. Anadys conducted a Phase IIb study combining it with pegIFN/RBV (Pegasys/Copegus) in non-responders and treatment-naïve patients. On June 2, 2011, the product was granted a US patent. *(http://processandproduction.pharmaceutical-business-review.com/news/us-patent-for-anadys-pharma-covering-setrobuvir-020611)* Anadys Pharmaceuticals was acquired by Roche in 2011. *(www.roche.com/media/media_releases/med-cor-2011-10-17.htm Oct 17, 2011)*

Setrobuvir appears on Roche's pipeline with an expected filing date of 2016. Roche has been combining Mericitabine, a nucleoside polymerase inhibitor, with other drugs such as danoprevir and telaprevir (protease inhibitors) and setrobuvir in phase II trials, to see which of those combinations it will market in 2016. (*http://lsconnect.thomsonreuters.com/sovaldi-innovative-unnafordable/)* Results from one such trial were presented at the AASLD 2013 Meeting. (See ANNAPRUNA study)

IV.1.4f TMC647055
Tibotec, later known as Janssen, discovered TMC647055, a non-nucleoside polymerase inhibitor. The company's lead compounds identified in pre-clinical trials showed nanomolar potency in HCV replicon cells, limited toxicity and promising results. In a Phase Ib trial with HCV genotype 1-infected patients, the product was found to be safe and well-tolerated and demonstrated potent antiviral activity, and later, worked well with TMC435. TMC647055 was tested in the **Olysio/TMC647055/samatasvir** combo trial, and in the **Olysio/TMC647055/JNJ56914845** combo trial.
(www.ncbi.nlm.nih.gov/pubmed/24144360)

IV.1.4g Other Non-Nucleotide Polymerase Inhibitors (new, discontinued, on hold, etc.)

- **Tegobuvir (GS-9190) - DISCONTINUED**
  Gilead's Tegobuvir (GS-9190) is a non-nucleoside polymerase inhibitor. Gilead has indicated that it has discontinued studies of tegobuvir.
  (www.hivandhepatitis.com/hcv-treatment/experimental-hcv-drugs/4520-gilead-4-drug-hepatitis-c-regimen-shows-modest-efficacy-in-phase-2-trial)
- **Filibuvir (FBV, formerly PF-00868554) - DISCONTINUED**
  Filibuvir is an NS5B non-nucleoside polymerase inhibitor. In spite of somewhat promising clinical trials, Pfizer dropped the drug in March 2013, which was not so effective as similar drugs by Gilead and AbbVie. *(www.pmlive.com/pharma_news/pfizer_drops_hepatitis_c_candidate_filibuvir_466696)*
- **IDX375** - **DISCONTINUED**. (*http://hepatitiscnewdrugs.blogspot.ca/2013/01/new-therapeutic-strategies-in-hcv.html*)
- **MK-3281** - **DISCONTINUED**
  (www.natap.org/2009/EASL/EASL_28.htm) The trial has been terminated.
  (http://clinicaltrials.gov/ct2/results?term=MK-3281)

IV.1.5 NUCLEOS(T)IDE POLYMERASE INHIBITORS

APPROVED: Gilead's **Sovaldi** (sofosbuvir), is a nucleotide polymerase inhibitor.
Even though Sovaldi is approved as part of **Harvoni**, it is still being used in experimental trials with other drugs.
WARNING: Do not take Amiodarone with Sovaldi or Harvoni.
Click on the links to see more:

- **GS-5816/Sovaldi**
- **Ledipasvir/Sovaldi/RBV**

- **Ledipasvir/Sovaldi + GS-9669 or Vedroprevir Combo**
- **Vedroprevir/Ledipasvir/Sovaldi +/- RBV**
- **Grazoprevir/Elbasvir/Sovaldi**

The nucleos(t)ide polymerase inhibitors below have reached Phase II, either alone or with IFN/RBV. The combo trials can be found in the section **Direct-Acting Antiviral Combos,** or by clicking on the links.

IV.1.5a ACH-3422
Achillion presented results of a pre-clinical and Phase I trials of its uridine-analog nucleotide polymerase inhibitor ACH-3422, showing it to be even more effective that sofosbuvir for genotype 3 patients. It is expected to combine favourably with ACH-3102.
(www.firstwordpharma.com/node/1216224#axzz3OTFgPcHz)
Phase II combo studies with ACH-3102, a 2nd generation NS5A inhibitor, were being planned, according to the presentation at the AASLD in November 2014.
(*www.achillion.com/ACH3422*) *(www.natap.org/2014/AASLD/AASLD_17.htm)*

IV.1.5b ALS-2200 (VX-135)
In June 2011, Vertex acquired 3 HCV polymerase inhibitors from ViroChem Pharma in March of 2009, including worldwide rights to the nucleotide polymerase inhibitors ALS-2200 and ALS-2158.

ALS-2200 has been affected by a USA FDA partial hold, restricting the Phase II trial to doses of 100mg, due to an increase in liver enzymes in patients participating in the European trial. Vertex discontinued all research of hepatitis C, but Alios BioPharma took over Vertex's VX-135 (ALS-2200), its last remaining Hep C drug. Janssen (Johnson & Johnson) acquired Alios BioPharma as of November 2014. The drug still appears on *clinicaltrials.gov*, in a Phase II trial combined with Daklinza, scheduled to collect final data in July 2015. See **DAKLINZA/VX-135** *Combo.*
(www.hepmag.com/articles/vertex_ends_hepatitis_c_investment_2831_25553.shtml)
(http://hepatitiscnewdrugs.blogspot.ca/2014/05/vertex-ends-hepatitis-c-investment-as.html)
(www.pharmaceutical-technology.com/news/newsjohnson-johnson-alios-biopharma-4432833)

IV.1.5c IDX21437
In 2014, Merck bought out Idenix, including its lead Hep C product, a nucleotide polymerase inhibitor called IDX21437, still in early development. Merck hopes to combine it with Grazoprevir (MK-5172, a protease inhibitor) and Elbasvir (MK-8742), an NS5A inhibitor.
See: **Grazoprevir/Elbasvir/IDX21437**
(www.reuters.com/article/2014/06/09/merck-co-idenix-pharma-idUSL4N0OQ2Y320140609)

IV.1.5d Mericitabine (RO5024048, formerly RG7128)
Pharmasset and Roche presented the results of their "PROPEL" clinical trial which studied 408 mostly GT1 patients, some with cirrhosis. The patients were treated for 8 or 12 weeks with mericitabine and pegIFN/RBV, then with pegIFN/RBV alone, for 24 or 48 weeks. Mericitabine (MCB), a nucleoside polymerase inhibitor, with pegIFN/RBV was proven safe and more effective than PegIFN/RBV alone. It is being used in several DAA combo trials.
(*www.clinicaloptions.com/Hepatitis/Conference%20Coverage/AASLD%202010/Tracks/HCV%20Treatment/Capsules/81.aspx*
See the **ANNAPURNA** study - STV/DNVr/MCB+RBV.
In February 2015, results were given for the Matterhorn clinical trial, combining mericitabine with danoprevir boosted with ritonavir (DNVr), with or without PegIFN/RBV in prior partial responders, for 24 weeks. The IFN-free arm produced an SVR24 of 45.5%, triple therapy (without IFN), 80.5% and the quadruple (with pegIFN/RBV) had results of 83.8%. Some of the patients were randomized to an aditional 24 weeks of PegIFN/RBV. 18 patients had serious side effects.
(www.healio.com/hepatology/hepatitis-c/news/online/%7Bd6e38688-40a0-4162-9196-97b6ed522d68%7D/quadruple-therapy-yields-high-svr-rates-in-patients-with-hcv)

IV.1.5e MK-3682 (formerly IDX21437)
MK-3682 is an NS5B polymerase inhibitor. Phase I/IIa trial results for MK-3682 were presented (Abstract #1974) at The Liver Meeting 2014. 24 GT1 and 20 GT2/3 received a placebo or 50, 150 or 300 mg of MK-3682 once a day for 7 days. The lower dose groups were discontinued. In the 300 mg arms, the best results were a reduction of viral load of 4.6 and 4.1 $\log_{10}$ IU/mL in a total of 7 GT2 and GT3

patients, respectively. In the 8 GT1a and GT1b subjects, the reductions were 4.8 and 3.9 log_{10} IU/mL, respectively. No serious side-effects were reported. (*www.mercknewsroom.com/news-release/research-and-development-news/interim-data-proof-concept-study-mercks-investigational-h)*

MK-3682 is being tested in Phase 2 trials with Grazoprevir and Elbasvir in the **C-Crest Trial**.
MK-3682 is also being combined Grazoprevir and the NS5A inhibitor, MK-8408, in the same trial. See **Grazoprevir/MK-3682/MK-8408**

IV.1.5f Other Nucleoside and Nucleotide Polymerase Inhibitors (new, discontinued, on hold, etc.)

- **GS-9851 (Formerly PSI-7851) NO NEWS**
  Gilead's drug GS-9851, acquired when the company bought Pharmasset, reported data from its Phase Ia trial of GS-9851, a **nucleotide** polymerase inhibitor, which showed the drug to be safe in humans, and a Phase Ib trial in patients with genotype 1. GS-9851 is approximately 15 to 20 times more powerful than the polymerase inhibitor R7128. GS-9851 has been shown to be effective against all of the most common HCV genotypes in laboratory trials. This study will assess the safety, tolerability and antiviral activity in HCV-infected individuals treated with GS-9851 over 3 days, in ascending doses. Another trial tested G0938 alone and with sofosbuvir, with successful results. (Journal of Viral Hepatitis 10/2013; 20(10):699-707) No further testing info is available yet.
- **AL-335** is a uridine base nucleotide analog still in pre-clinical trials **- NEW**
- **AL-516** is a guanosine nucleotide analog belonging now to Janssen about to enter Phase 1 trials - **NEW**
- **BMS-094 (formerly BMS-986094 and INX-189) - SUSPENDED**
  Inhibitex presented an update on their nucleotide polymerase inhibitor INX-189 at the AASLD 2011 conference, showing viral load drops of up to 4.25 log_{10}. On January 7, 2012, Bristol-Myers acquired Inhibitex. Their latest clinical trial, BMS-094 with daclatasvir, was suspended in 2012. One of the subjects developed heart failure while taking the highest dose.
  (www.natap.org/2012/HCV/080312_01.htm)
- **Balapiravir (R1626) - SUSPENDED**
  A Phase IIa clinical trial of Roche's nucleoside polymerase inhibitor balapiravir (R1626) proved to be toxic (neutropenia and lymphopenia). The researchers have halted development of Belapiravir for now. *(www.natap.org/2010/EASL/EASL_57.htm)*
- **IDX19370 - NO NEWS**
  Merck acquired Idenix. There is no news about nucleotide polymerase inhibitors IDX19368 (cardiac events) and IDX19370. Neither appears on the Merck pipeline with those names.
  (www.hivandhepatitis.com/hepatitis-c/hepatitis-c-topics/hcv-treatment/3428-achillion-presidio-and-inhibitex-announced-hcv-drug-pipeline-developments)
- **MK-0608 - DISCONTINUED**
  A nucleoside analogue polymerase inhibitor, Merck's MK-0608 clinical trial was terminated, and the product has been discontinued.
  (http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2009.03927.x/full)
- **TMC649128 - DISCONTINUED**
  Medivir, together with Tibotec, developed TMC649128, a nucleoside NS5B polymerase inhibitor, dropped due to insufficient antiviral activity.
- **MK-0608** is a nucleoside polymerase inhibitor, **DISCONTINUED** due to toxicity.
  (http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2009.03927.x/full)
- **PSI-938 - DISCONTINUED**
  Pharmasset's nucleotide polymerase inhibitor PSI-938 caused elevated enzymes at higher doses. *(www.natap.org/2011/HCV/121711_01.htm)* Pharmasset has been acquired by Gilead.
- **GS-6620** - **DISCONTINUED**
  GS-6620 *hasn't gone beyond Phase I, and development has been terminated.*
  (http://en.wikipedia.org/wiki/Gilead_Sciences)
- **ALS-2158 - DISCONTINUED**
  In September 2012 Vertex discontinued development of ALS-2158, nucleotide polymerase inhibitor, because of lack antiviral activity.
- **GS-0938 - DISCONTINUED**
  A combo trial with Gilead's GS-0938/sofosbuvir/RBV was stopped due to elevated liver enzymes in some patients**.**

IV.1.5g Other Polymerase Inhibitors

Clemizole
Clemizole, is an already-approved drug, used as an antihistamine. It can be used off-label, for other illnesses. It is produced by Eiger BioPharmaceuticals, is an inhibitor of the virus' NS4B-RNA binding, which has become a target for new drugs, since it is needed for the virus to replicate. Clemizole is being investigated in all genotypes, in several clinical trials, as a substance to boost standard of care medications, making them more effective and decreasing resistance, since it targets the interaction between NS4B and the HCV-RNA. Adding clemizole to protease inhibitors may allow them to be used at lower doses, while keeping the desired antiviral effect and avoiding the side-effects caused by the protease inhibitors such as rash and anemia. "Clemizole has the potential to be an ideal component of future anti-HCV cocktails," said the company's founder, Dr. Jeffrey Glenn, M.D., Ph.D.
(www.therapeuticsdaily.com/news/article.cfm?contentValue=715070&contentType=newsarchive&channelID=26 Jul. 01, 2010

IV.1.6 OTHER DIRECT-ACTING ANTIVIRALS

IV.1.6a Helicase Inhibitors
The hepatitis C virus NS3 is not only a protease, but also a helicase--an enzyme that binds to double-stranded HCV RNA and unwinds it so the resulting strands can be used to produce more RNA or translate it into proteins. If these strands couldn't unwind, HCV could not reproduce. The helicase is Y-shaped, with 3 linked areas separated by clefts, which are possible targets for drugs. Many antiviral drugs target the protease, but not many helicase inhibitors that work as antivirals are reported. Some scientists are using a procedure called a G-quadruplex-based assay, which detects luminescence in the presence of HCV helicase activity. Part of the problem is how to develop good techniques to identify effectuve helicase inhibitors. To our knowledge, no helicase inhibitor has entered clinical trials yet.
http://pubs.rsc.org/en/Content/ArticleLanding/2015/SC/c4sc03319a#!divAbstract
Pakistani scientists, in an attempt to treat GT3a patients, have found that there are 6 important antiviral molecules that should inhibit GT3a: quercetin, beta-carotene, resveratrol, catechins, lycopene and lutein. *(www.ncbi.nlm.nih.gov/pubmed/25188400)*

- **Cocrystal helicase inhibitor**
  The company Cocrystal is studying helicase inhibitors and believe theirs will be a first-in-class drug, to be combined with an RNA polymerase inhibitor to improve its effectiveness and prevent resistance. Having reported their findings, the company merged with RFS Pharma, in order to broaden their pipelines. Hopefully they will continue the research.
  http://cocrystalpharma.com/news/news.php?date=141115
- **Ebselen**
  A study of ebselen (2-phenyl-1,2-benzisoselenazol-3-one), previously proven to be an HCV antiviral, inhibits helicase activity by 50%. It has no effect on the protease. At concentrations higher than 10 μM, helicase inhibition was irreversible. Ebselen analogues replace selenium with sulfur and were just as effective as ebselen. Ebselen analogues were more effective as antivirals and less toxic to liver cells than ebselen. *www.ncbi.nlm.nih.gov/pubmed/25126694*
- **Cholesterol sulfate**
  This study identified cholesterol sulfate as a helicase inhibitor by using extracts from marine organisms (possibly the marine sponge *Amphimedon* sp., called C-29EA, spoken of in other articles). Researchers found that the binding activity was partially inhibited, and probably won't bind to RNA. It may induce changes in the virus by way of interaction with certain parts of the NS3 part of the virus. *http://informahealthcare.com/doi/abs/10.3109/14756366.2013.766607*
- **Psammaplin A (PsA)** has the ability to inhibit HCV helicase catalyzed RNA unwinding (IC50 = 17 μM) in addition to ATPase and RNA binding activity. PsA inhibited the subgenomic viral replication derived from genotype 1b and genotype 2a, with EC50 6.1 and 6.3 μM, respectively.
  www.ncbi.nlm.nih.gov/pmc/articles/PMC3825274/
- **Tropolone**
  Researchers Peter Borowski and colleagues have studied an agent called Tropolone (2-hydroxy-2,4,6-heptatriene-1-one) as an HCV NS3 helicase inhibitor. The results were not expected, showing that the agent and its derivatives don't "unwind" the virus, nor do they block the NTP-binding site. They occupy an allosteric regulatory site.
  (*http://lib.bioinfo.pl/pmid:17542155 Antivir Chem Chemother. 2007;18 (2):103-9 17542155)*
  Keep an eye on the tropolone derivatives, BTN10, BTN11,97–100 and trixsalen.

IV.1.6b IRES Inhibitors
The internal ribosome entry site (IRES) is a part of the hepatitis C virus that is found in different genotypes. It is an essential part of the replication process, so scientists believe that, by finding an IRES inhibitor, they could decrease production of the virus. Several companies are working with possible IRES inhibitors. It has recently been discovered that interferons work because they are IRES inhibitors. *(Liver Int, 2005; 25(3):580-594)* Both RNA- or DNA- mechanisms might be used to develop future compounds. Watch for DNAzymes...
(www.medscape.com/viewarticle/716161_4) (www.ncbi.nlm.nih.gov/pubmed/25079672)

Lately, researchers seem to be concentrating on the IRES subdomain IIa, which is a sort of RNA conformation switch. See more here: *www.ncbi.nlm.nih.gov/pubmed/24138284*
SomaGenics, together with Roche and Tekmira, is studying shhRNAs in a chimeric mouse model, to see if it can inhibit HCV IRES activity. *(http://jvi.asm.org/content/88/9/4647.abstract)*

MERCK is using artificial ribozymes to target HCV IRES *in vitro* and *in vivo* (*Curr Opin Mol Ther. 2001 Jun;3(3):278-87).* Merck has partnered with PTC Therapeutics to research and develop these therapies. *(www.schering-plough.com/schering_plough/news/release.jsp?releaseID=833484 Mar 2006)*

VGX-410 and **VGX-410C**
VGX Pharmaceuticals' IRES inhibitors VGX-410 and VGX-410C have been **DISCONTINUED** due to toxicity and lack of efficacy. The company is now concentrating on HIV.

IV.1.6c RNAi-Based Antisense Therapies
RNAi (RNA interference) is a mechanism used by the body's cells to control the expression of genes and the replication of viruses with the help of small interfering RNA molecules. RNAi is the newest nucleic-acid based therapy being studied for HCV infection. All regions of the virus are susceptible to RNAi. There are 2 types of RNA viruses - those with a "sense" strand of RNA, like HCV, and those with an "antisense" strand (with the opposite coded genetic information). Antisense therapy involves using "therapeutic" strands of RNA which make it difficult if not impossible for the viral RNA to perform its function. Antisense targets parts of the HCV genetic code that probably don't mutate over time, and attacks the microRNA required for HCV to multiply. *(http://cpmcnet.columbia.edu/dept/gi/hepC.html)*
"Antisense drugs are short, chemically-modified RNA-like and DNA-like molecules that scientists design to complement a small, specific segment of messenger RNA, or mRNA."
(http://phx.corporate-ir.net/phoenix.zhtml?c=94554&p=irol-newsArticle&ID=755950&highlight=hepatitis%20C).
MicroRNAs are tiny RNA molecules that control gene expression. Just one can control a whole network of genes. Diseases such as HCV can alter their function, and researchers think that by using ani-miRs, they can change whole biological pathways, providing a new, important class of drugs. *(www.regulusrx.com)*

- **Miravirsen** is an antisense oligonucleotide that inhibits microRNA-122 ("miR-122"). Santaris Pharma announced Phase IIa data for Miravirsen (formerly SPC3649**)** monotherapy which showed a 2-3 $\log_{10}$ drop in HCV with only 4 weeks of treatment. The virus was undetectable in 4 of the 9 patients treated with the highest dose. The viral drop has been maintained for over 4 weeks after ending treatment. The drug was given as 5 subcutaneous injections, one per week. It was well tolerated by the patients. (*www.marketwatch.com/story/santaris-pharma-as-phase-2a-data-of-miravirsen-shows-dose-dependent-prolonged-viral-reduction-of-2-3-logs-hcv-rna-after-four-week-treatment-in-hepatitis-c-patients-2011-11-05*)

  Santaris also sponsored a Phase II trial which began in June 2013. It combined Miravirsen with telaprevir and RBV. The study treated 20 GT1 patients. The trial was scheduled to end in January 2015. No results have been posted yet.
  (*https://clinicaltrials.gov/ct2/show/NCT01872936?term=Miravirsen&rank=2*)

- **RG-101** is Regulus Therapeutics' microRNA inhibitor. The company was proud to announce the results of its clinical trial which enrolled 14 treatment-naïve and 2 treatment-experienced (relapsers) patients previously treated with IFN. The patients were treated with a single subcutaneous injection (4 mg/kg) of RG-101 as monotherapy. Two received a placebo. The drug targets microRNA-122 ("miR-122"). In the 14 who received RG-101, the viral load decreased by an average of 4.8 $\log_{10}$ at day 29. Nine of them had undetectable HCV RNA at day 57, and will be tested during the next 6 months in hopes of finding some SVRs. Unfortunately it looks like the drug will have to be part of a combo.

  A previous trial used a dose of 2mg/kg of RG-101, and at day 85, 4 out of the 14 patients treated had undetectable virus. 2 of them relapsed after day 57. The company is happy to see such results with a single dose, and is planning Phase II trials.
  (http://ir.regulusrx.com/releasedetail.cfm?ReleaseID=895314)

  More about miR-122: www.dddmag.com/news/2015/02/building-understanding-hepatitis-c-virus-replication

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IV.1.6d Entry Inhibitors

- **ITX-5061:** The company iTherx has produced ITX-5061, an HCV Entry Inhibitor, as monotherapy for viral load reductions, safety and tolerability. This drug is designed to be part of a "cocktail" of HCV inhibitors that prevent entry of HCV into the host cell. The drug has shown to be effective in previous studies by inhibiting both genotype 1 and genotype 2 HCV viruses. *(hcvadvocate.org February 9, 2009 and www.itherx.com/hepatitis.html)*

  A Phase I pilot study began in 2011 and ended in May 2013. The company recruited 24 HCV+ subjects for a Phase I study in liver transplant patients, who were treated pre-transplant and daily for 1 week post-transplant. The product has also been shown to be a powerful antiviral in preclinical trials, and has a good safety profile. The researchers believe that this product can prevent re-infection of the new liver—something that transplant patients experience universally. (*www.clinicaltrials.gov/ct2/show/NCT01292824?term=ITX-5061&rank=2*)

- **SP-30:** Samaritan Pharmaceuticals' HCV antiviral has been deemed safe and well-suited to be used either alone or in combination treatments, possibly as an oral drug. The product surrounds the cell to prevent the virus to enter, allowing the immune system to find and eliminate it. Its targets are in the host cell, so it might not develop resistance. It may work in AIDs patients, as well. A Phase I trial was in the planning stage. *(www.samaritanpharma.com/aids_hiv_program_sp-30.asp)*

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IV.1.6e Cyclosporine/Cyclophilin Inhibitors

"The most clinically advanced therapies directed toward host factors include the cyclosporin A analogs that are thought to disrupt the interaction between CYPA and HCV NS5A protein." [Future Virology. 2014;9(11):947-965]

- **Alisporivir** (**DEB025**) is a non-immunosuppressive cyclophilin inhibitor originally developed by Debiopharm, in collaboration with Novartis was formed in January 2010. On January 12, 2015, Debiopharm announced that it had retained full rights to the drug. The product has been shown to be effective against all genotypes. It has already been tested in over 2,000 patients, showing promising results even in those difficult to treat. A study whose results were presented at EASL 2011 treated G1 (genotype 1) treatment-naïve patients, with the product alone or combined with SOC (standard of care, or PegIFN+RBV), for 48 weeks. The main side effect was an increase in bilirubin, and was reversible. SVR24 rates were 76% in the arm including SOC, vs 55% for SOC alone. There are some ongoing Phase I and II IFN-free studies, some with ribavirin, and some with a protease inhibitor. No study results have been posted yet (Feb 2015). *(www.marketwatch.com/story/debiopharm-grouptm-regains-full-rights-to-alisporivir-program-2015-01-12)*
  Alisporivir is being studied together with Enanta's NS5A inhibitor EDP-239. See **EDP-239 + Alisporivir**
- **NIM811** is a mitochondrial permeability inhibitor, produced by Novartis. It is a cyclosporin analag. A dose-finding Phase II trial for NIM811 + PegIFN/RBV enrolled 51 GT1 previous non-responders took place between September 2009 and April 2011. The drug or a placebo was given twice daily for 4 weeks. (Identifier NCT00983060) Results have not been posted. NIM811 was already deemed as safe in earlier studies. *(https://clinicaltrials.gov/ct2/show/NCT00983060?term=NIM811&rank=1)*
- **Sangamides** are a type of cyclophilin inhibitor. They come from amide derivates of a natural cyclophilin-binding product called sanglifehrin A. The developers believe that sangamides have improved potential over other products such as Alisporivir for treating HCV. *http://pubs.rsc.org/en/content/articlelanding/2012/md/c1md00227a#!divAbstract* The discovery and development was done by Shanghai's ShangPharma.
- **SCY-635** (Scynexis) Probably the most famous of the cyclophilin inhibitors is Cyclosporine A, used for decades for anti-rejection of transplanted organs. Scynexis' SCY-635 is the first candidate in a new class of non-immunosuppressive cyclophilin inhibitors. SCY-635 lets the immune system detect the virus, and stops it from replicating, preventing contact between cyclophilin A and NS5A in GT1, 2 and 3. Mutations don't seem to stop it from being effective.

  Results from the Phase Ib monotherapy trial in 56 genotype 1 patients were presented at the EASL 2009 Conference. The study lasted 15 days, and) was well tolerated. The highest dose showed important antiviral activity, with an average viral load drop of 2.2 $\log_{10}$ on the last day of treatment. The maximum drop occurred on the 15th day, suggesting that longer treatment may be more effective. *(www.scynexis.com, http://au.sys-con.com, http://www.hcvadvocate.org May 5, 2009)*

  Scynexis presented data at the AASLD 2011 in San Francisco. SCY-635 monotherapy showed increased concentrations of interferons like IFN alpha and lambda-1 in GT1a patients. Two other studies were also presented. One showed a correlation of SCY-635 levels and the presence of type 1

and type 3 interferons in vitro, and that SCY-635 is as effective as IFNα-2b in clearing the virus and preventing rebound in vitro. The other studied drug interactions between SCY-635 and telaprevir and showed that SCY-635 was less likely to produce adverse drug interactions compared in vitro to other cyclophilin inhibitors. *(www.scynexis.com/scy-635-restores-the-bodys-innate-immune-response-to-hcv/ Nov 7, 2011)*

A Phase IIa trial combined SCY-635 with PegIFN/RBV in GT1 difficult-to-treat patients. Results were presented at the AASLD in 2012. In November 2014, Scynexis entered into an agreement with Waterstone, which will have the right to commercialize it, paying royalties to Scynexis. *(http://globenewswire.com/news-release/2014/11/03/679083/10105692/en/SCYNEXIS-Inc-Enters-Into-Worldwide-Agreement-With-Waterstone-Pharmaceutical-for-the-Development-and-Commercialization-of-SCY-635-for-Viral-Diseases.html?print=1)*

IV.1.6f Viroporin Inhibitors

The hepatitis C virus, along with other viruses, has a tiny protein, part of its replication system, called viorporin p7, defined as a "virus encoded ion channel", but its mechanism was not well understood, since no antibodies for it had been found…until a couple of years ago, when scientists generated an epitope-tagged p7 that would function in the replication of the virus, effectively cloning the virus, in a form allowing them to track it and figure out how it works. (Amantadine and rimantadine are p7 inhibitors). Read more here:
http://jvi.asm.org/content/87/3/1664.full and *www.ncbi.nlm.nih.gov/pmc/articles/PMC3851685/*

- **BIT225**
  Biotron produces BIT225, a viroporin inhibitor. The company is developing it for treatment of HCV and HIV, especially in those co-infected. Trials in HCV GT1 patients resulted in all patients taking BIT225 + PegIFN/RBV tested negative for the virus at 48 weeks, compared to 75% receiving PegIFN/RBV alone. *(www.biotron.com.au/)*

IV.1.7 DOUBLE DAA COMBOS

At this point in time, our Direct Acting Antivirals (DAAs) are usually combined in trials with pegIFN and RBV, but a serious search is being conducted for all-oral treatments without interferon and its side-effects. Here are some of interferon-free combo trials that have been taking place:

Drug Pipeline: Quick Reference Chart

(This chart is reprinted and adapted with thanks for permission from www.hcvadvocate.org February 5, 2015)

PHASE II DAA Combos (IFN-Free)

Drug Name / Category	Drug Name / Category	Company
ABT-493 Protease Inhibitor	ABT-530 NS5A Inhibitor	AbbVie
ABT-493 Protease Inhibitor ABT-530 NS5A Inhibitor	Paritaprevir (ABT-450)/ritonavir Protease Inhibitor Dasabuvir (ABT-333) Polymerase Inhibitor Ombitasvir (ABT-267) NS5A Inhibitor	AbbVie / Enanta
ACH-3102 NS5A Inhibitor	Sovaldi (Sofosbuvir) Polymerase Inhibitor	Achillion / Gilead
ACH-3102 NS5A Inhibitor	Sovaprevir (ACH-1625) Protease Inhibitor Sovaldi (Sofosbuvir) Polymerase Inhibitor	Achillion / Gilead
ACH-3102	Sovaprevir (ACH-1625)	Achillion

NS5A Inhibitor	Protease Inhibitor ACH-3422 Polymerase Inhibitor	
ACH-3102 NS5A Inhibitor	ACH-3422 Polymerase Inhibitor	Achillion
ALS-2200 (VX-135) Polymerase Inhibitor	Daklinza (Daclatasvir) NS5A Inhibitor	J&J / BMS
Daklinza (Daclatasvir) NS5A Inhibitor	Olysio (Simeprevir) Protease Inhibitor	BMS / Janssen
Grazoprevir (MK-5172) Protease Inhibitor	MK-3682 Polymerase Inhibitor Elbasvir (MK-8742) NS5A Inhibitor or MK-8408 NS5A Inhibitor	Merck
Ledipasvir Protease Inhibitor	Sovaldi (Sofosbuvir) Polymerase Inhibitor Vedroprevir Protease Inhibitor ± RBV	Gilead
Ledipasvir Protease Inhibitor Sovaldi (Sofosbuvir) Polymerase Inhibitor	GS-9857 Protease Inhibitor GS-5816 NS5A Inhibitor ± RBV	Gilead
Olysio (Simeprevir) Protease Inhibitor	IDX719 (Samatasvir) NS5A Inhibitor TMC647055 Polymerase Inhibitor /Ritonavir	Janssen / Merck
Olysio (Simeprevir) Protease Inhibitor	Daklinza (Daclatasvir) NS5A Inhibitor Sovaldi (Sofobusvir) Polymerase Inhibitor	Janssen/Medivir BMS Gilead
Sovaprevir (ACH-1625) Protease Inhibitor	ACH-3102 NS5A Inhibitor	Achillion

PHASE III – DAA COMBOS (IFN-FREE)

Drug Name / Category	Drug Name / Category	Company

Daklinza (Daclatasvir) NS5A Inhibitor	Sovaldi (Sofosbuvir) Polymerase Inhibitor	BMS / Gilead
Daklinza (Daclatasvir) NS5A Inhibitor	Sunpreva (Asunaprevir) Protease Inhibitor Beclabuvir (BMS-791325) Polymerase Inhibitor	BMS
Grazoprevir (MK-5172) Protease Inhibitor	Elbasvir (MK-8742) NS5A Inhibitor	Merck
GS-5816 NS5A Inhibitor Ribavirin	Sovaldi (Sofosbuvir) Polymerase Inhibitor	Gilead

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IV.1.7a Protease/Polymerase Combos

- **Danoprevir/ritonavir/Mericitabine "INFORM-SVR"**

Danoprevir (protease, boosted) + Mericitabine (polymerase) with or without RBV
A Phase IIb IFN-free combo trial called INFORM-SVR treated 64 HCV+ people twice daily with the boosted protease inhibitor danoprevir/r and the polymerase inhibitor mericitabine, with (Arm A) or without (Arm B) ribavirin, once daily, for 12 or 24 weeks. Because the both arms had poor results in the first 12 weeks, RBV was added to arm B, and treatment was extended in both arms to another 12 weeks. Patients with GT1b responded better than those with GT1a (71% vs 26%). Strangely, those with non-CC IL28b alleles had more SVR12 responses than those with type CC (44% vs 32%). The researchers concluded that, although the combo was safe, the SVR rates…25% in GT1a, 63.6% in GT1b…were poor.
(www.ncbi.nlm.nih.gov/pubmed/24814388 Jan 2015)

- **ITMN-191+ R7128 "INFORM-1"**

ITMN-191 (protease) + R7128 (polymerase)
Probably the most exciting news at the EASL conference back in 2009 was the report from a study combining two oral HCV drugs—a milestone in HCV drug development. The Phase I INFORM-1 study enrolled 57 treatment-naïve patients in Australia and New Zealand, combining the protease inhibitor ITMN-191 (aka R7227, now Danoprevir) with the polymerase inhibitor R7128. More arms were added for non-responders and null responders, for studying twice-a-day dosing, and for higher doses of ITMN-191. The trial did not include interferon. Results showed the combination is safe and effective, even without IFN, in treatment-naive HCV patients.

Patients receiving the combination of R7227 and R7128 for 14 days—without pegIFN or RBV—had an average drop in viral levels of 4.8 to 5.2 $\log_{10}$, with the highest doses. Adding R7128 to R7227 resulted in 63% of patients dropping to undetectable. 25% in the highest dosage groups tested undetectable at 14 days. *(EASL Conference 2009)*

IV.1.7b Protease/NS5A Combos

- **ABT-493/ABT-530**

ABT-493 (protease) and ABT-530 (NS5A)
This combination of drugs seems to be AbbVie's favourite since the approval of the Holkira Pak combo. None of their previous drugs appear on their pipeline. There are 3 clinical trials listed for this combo at *www.clinicaltrials.org* , which are recruiting at this time (2015).

NCT02243280, a Phase II trial, is for non-cirrhotic GT1 patients, and was to begin in August 2014 with an estimated 280 subjects. The planned completion date is June 2015. Treatment is with either a high dose or a low dose, daily for up to 16 weeks.

NCT02243293, also a Phase II trial, began enrollment in September 2014 of about 80 non-cirrhotic GT2 and GT3 patients, who will be treated with or without RBV. Treatment is for 12 weeks. The estimated completion date is February 2016.

NCT02296905 is a small Phase I trial which is treating 24 subjects: 6 with mild liver damage, 6 with moderate but stable damage, 6 with severe but stable damage, and 6 with normal liver functions. The study began in October 2014 and is scheduled to be completed in September 2015. Healthy volunteers will be treated, as well, for comparison. The patients will be given only 2 or 3 doses of either or both drugs.

- **Grazoprevir/Elbasvir + RBV Combo**

Grazoprevir (protease) + elbasvir (NS5A)
Based on the results of a Phase II **"C-Worthy"** trial, by mid-2015 Merck plans to request approval to the US FDA of its combination of grazoprevir/elbasvir, a drug designed to be taken once a day for treating hepatitis C. Grazoprevir is an NS3/4A second-generation protease inhibitor and elbasvir is an NS5A inhibitor. 253 patients with or without cirrhosis were enrolled and treated with or without RBV for 12 or 18 weeks. SVR12 rates ranged from 90-97%.
www.hcplive.com/artides/Merck-to-Seek-Approval-of-New-Hepatitis-C-Drug-by-Midyear#sthash.9PIM27OE.dpuf

- **Grazoprevir/Elbasvir Combo for Kidney Patients**

Grazoprevir (protease) + elbasvir (NS5A)
In a Phase II/III trial numbered **NCT02092350**, designed to treat Hep C patients with kidney disease, Merck recruited approximately 220 GT1 patients with/without cirrhosis as of March 2014. The trial is expected to end in August of 2015.

- **Olysio/Daklinza Combo** *or* **TMC435/Daklinza**

Olysio (simeprevir) or TMC435—protease inhibitors + Daklinza (daclatasvir-- NS5A)
Bristol Myers-Squibb and Tibotec worked together to investigate combining the NS5A inhibitor Daklinza (daclatasvir or BMS-790052) with the NS3 protease inhibitor, TMC435 in a Phase II trial expected to start in the first part of 2012. Researchers will be looking for SVR at 12 and 24 weeks post treatment in GT1 patients. There will be 3 once-a-day treatment arms: daclatasvir/TMC435/pegIFN/RBV; 2) daclatasvir/TMC435/RBV; or 3) only daclatasvir/TMC435. Their goal is to find an all-oral treatment for hepatitis C.
(www.businesswire.com/news/home/20111202005035/en/Bristol-Myers-Squibb-Enters-Clinical-Collaboration-Agreement-Tibotec Dec. 02, 2011

- **Olysio/Daklinza + RBV**

Olysio (simeprevir) + Daklinza (daclatasvir--NS5A) with/without ribavirin
This combo achieved SVR12 rates of 75-85% in treatment-naïve patients, and 65-95% in prior null-responders, all GT1b patients. GT1a previous null-responder patients had the highest rate of breakthrough. The treatment-naïve patients scored 67% SVR12. The combo was mostly well tolerated, with or without RBV. Most of the side effects occurred in the RBV arm. More studies are planned.
(www.natap.org/2014/CROI/croi_09.htm)

- **Paritaprevir/ritonavir/Ombitasvir/ (PTV/r/OBV)**

Paritaprevir (protease) boosted with ritonavir + ombitasvir (NS5A)
On January 30, 2015, Abbvie announced results of a Phase III 12-week trial, called the GIFT-1 study, with GT1b Japanese patients, either treatment-naïve or previous non-responders to interferon treatment. The trial -- ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) --produced a 95% SVR12. The patients, all with a high viral load, were divided into 2 groups. The first group contained a placebo arm, and those patients had no cirrhosis. The patients in the second group had compensated cirrhosis, and none received a placebo. *(www.prnewswire.com/news-releases/abbvie-announces-top-line-results-from-phase-3-study-of-all-oral-treatment-for-hepatitis-c-in-japan-300028651.html)*

- **Sovaprevir + ACH-3102 + RBV**

Sovaprevir (ACH-1625--protease) + ACH-3102 (NS5A) + RBV
ACH-3102 is a 2nd generation NS5A inhibitor that has been noticed for being the only such drug to achieve SVR without another DAA or IFN in GT1b patients. The combination of Sovaprevir and ACH-3102 and ribavirin was not ideal in GT1a patients. Several of them suffered viral breakthrough or relapse after 2 weeks of treatment. That combo produced an SVR12 for 100% of the GT1b patients. There were no serious side effects. *(www.natap.org/2014/APASL/APASL_27.htm)*

- **Sunpreva/Daklinza Combo** (HALLMARK-DUAL)

Sunpreva (asunaprevir-- protease)+ Daklinza (daclatasvir-- NS5A)
(Note: Daklinza has been approved for sale in parts of Europe and Japan).

Bristol-Myers Squibb's clinical trial called HALLMARK-DUAL enrolled over 5500 subjects: GT1 cirrhotic or non-cirrhotic – treatment-naïve or non-responders to pegIFN/RBV or ineligible/intolerant. The patients were treated with daclatasvir once a day, and asunaprevir, twice a day. The combo was deemed safe and well-tolerated. SVR12 rates were 90% among treatment-naïve patients, 82% among non-responders, and ineligible/intolerant patients, 82% in those under 65, 87% in those over 65, 88% in males, 78% in females, 84% in whites, 88% in blacks, 83% in Asians. The response was better with a viral load under

800,000. The best response in II28b was surprisingly in the TT group (90%), followed by CC (85%) and CT (81%)
(http://news.bms.com/press-release/rd-news/bristol-myers-squibb-presents-phase-iii-data-demonstrating-investigational-all)

- **Vedroprevir/Ledipasvir Combo**

Vedroprevir (protease) + ledipasvier (NS5A)
Researchers recruited 14 GT1 patients who relapsed after a 24-week sofosbuvir/RBV trial, and published the results in the November 4, 2014 issue of *Annals of Internal Medicine*. In this Phase IIa trial, the patients were treated for 12 weeks. The SVR rate was 100%, including 7 patients with cirrhosis. There were no serious side effets. This is the first study to re-treat non-responders to sofosbuvir.
www.medscape.com/viewarticle/834309

- **Simeprevir/Samatasvir Combo**

Simeprevir (protease) and Samatasvir (NS5A)
Phase 2 HELIX-1 study of simeprevir and Idenix's once-daily pan-genotypic NS5A inhibitor samatasvir (IDX719) is studying the combo in treatment-naïve genotype 1b and genotype 4 hepatitis C patients.
(www.investor.jnj.com/releasedetail.cfm?ReleaseID=795554)

IV.1.7c NS5A/Polymerase Combos

WARNING**:** Do not take Amiodarone with Sovaldi.

- **ACH-3102/Sovaldi Combo**

ACH-3102 (NS5A) + Sovaldi (polymerase)
A pilot Phase II study studied the ACH-3102 (Achillion's 2nd generation NS5A inhibitor, combined with Gilead's Sovaldi (a nucleotide polymerase inhibitor) in treatment-naïve, GT1 HCV patients, treating them for 6 or 8 weeks, laying the foundation for the use of the company's own polymerase inhibitor, ACH-3422. (*www.achillion.com/ACH3102)* A Phase III study with that combination produced an SVR in all of its GT1 patients. The results were presented at the AASLD 2014.
(www.hivandhepatitis.com/hcv-treatment/experimental-hcv-drugs/4989-aasld-2014-ach-3102-plus-sofosbuvir-cures-all-hepatitis-c-patients-in-phase-2-study)
The Phase II study results of 6 weeks of treatment in 12 treatment-naïve GT1 patients achieved 100% SVR12, including patients with high viral loads. A triple therapy combining **sovaprevir, ACH-3102, and ACH-3422** for 4-6 weeks is being planned, as is their SPARTA Phase II combining **ACH-3102 and ACH-3422** *(http://ir.achillion.com/releasedetail.cfm?ReleaseID=895306)*

- **Daklinza/Sovaldi Combo**

Daklinza (daclatasvir--NS5A) and Sovaldi (sofosubuvir--polymerase)
Bristol-Myers Squibb and Gilead presented results of Phase III trials at the AASLD 2014 conference.

ALLY-1 tested 113 cirrhotic or post-transplant GT 1-6 patients with DCV/SOF/RBV (daclatasvir/Sovaldi/ribavirin for 12 weeks (NCT02032875)
ALLY-2 tested 203 HCV/HIV co-infected GT 1-6 patients with DCV/SOF for 8 or 12 wks (NCT02032888)
ALLY-3 tested 152 treatment-naïve or –experienced GT3 patients with DCV/SOF for 12 weeks. Results showed SVR12 rates of 90% in treatment-naïve patients, 86% in treatment-experienced patients, and 96% in non-cirrhotic patients. (NCT02032901). Gilead has turned down a BMS offer of a joint Phase III trial. *(www.fool.com/investing/general/2014/10/08/bristol-myers-tells-gilead-sciences-you-win.aspx)*

- **Daklinza/ALS-2200 Combo**

Daklinza (daclatasvir--NS5A) + ALS-2200 (VX-135--polymerase)
ALS-2200 used to be Vertex's VX-135. Vertex had partnered with BMS to do a clinical trial. Unfortunately VX-135 was put on hold. In the meantime, Vertex sold the drug to Alios, and it becamse ALS-2200. The Phase II combo trial (NCT01842451) with Daklinza still appears on *www.clinicaltrials.gov* as "Active. Not recruiting." They were enrolling 20 treatment-naïve patients. The drugs were to be taken for 12 weeks, with 2 arms: a low-dose and a high-dose of ALS-2200. Results are expected for June 2015. *(http://hcvdrugs.com/detailed_ref.html)*
(https://clinicaltrials.gov/ct2/show/NCT01842451?term=VX-135&rank=3)

- **GS-5816/Sovaldi Combo**

GS-5816 (NS5A) and Sovaldi (nucleotide polymerase)
The combination of Sovaldi and GS-5816 was tested for 12 weeks in 77 treatment-naïve patients with GTs 1-6. The higher dose of GS-5816 showed better results. SVR12 results with the higher dose were 100% in all genotypes except for one GT3 patient relapsed and one GT4 was lost to follow-up. Gilead plans to use this combo, if approved, in developing countries at a reduced cost. It has already been approved in India. The combo is being in India, where it will be distributed in a single tablet…the first all-oral single tablet treatment for HCV. The drug is effective in all genotypes, thus avoiding the cost of

genotype testing. *www.gilead.com/news/press-releases/2015/1/gilead-expands-hepatitis-c-generic-licensing-agreements-to-include-investigational-pangenotypic-agent*

- **Ledipasvir/Sovaldi + RBV**

Ledipasvir (NS5A) + Sofosbuvir (nucleotide polymerase) + RBV
In a combo Phase II of 101 participants with ledipasvir, sofosbuvir and RBV in 2013-2014, in a large trial in New Zealand starting in 2010, with GTs 1, 2 and 3 with those same drugs, and results are available

- **Ledipasvir/Sovaldi/RBV**

Ledipasvir (NS5A) + Sofosbuvir (nucleotide polymerase) + Ribavirin
The trials with ledipasvir, sofosbuvir + RBV produced SVR rates between 90-100%.
(https://clinicaltrials.gov/ct2/show/results/NCT01260350?term=GS-9669&rank=3)
(www.hivandhepatitis.com/hepatitis-c/hepatitis-c-topics/hcv-treatment/4102-sofosbuvirledipasvir-coformulation-shows-good-early-response-with-or-without-ribavirin)

IV.1.7d Other Double Combos (Not yet approved, discontinued, etc.)

- **ACH-3102/ACH-3422 NEW**

ACH-3102 (NS5A) + ACH-3422 (polymerase)
Achillion presented three posters at AASLD. The in vitro results demonstrated that ACH-3422 works especially well for genotype 3 HCV as compared to sofosbuvir. In another poster presentation, Achillion showed that ACH-3422 works well in lab tests, when combined with ACH-3102 or sovaprevir, Achillion's protease inhibitor.
Achillion has reported that ACH-3102, cured 100% when combined Sovaldi for 6 weeks in a Phase II trial, but its Sovaldi "substitute" ACH-3422, produced a lower log reduction in viral load in Phase I studies.
http://hepatitiscnewdrugresearch.com/2014-hepatitis-c---breaking-conference-reports.html#sthash.OVjlVuwm.dpuf
http://hcvadvocate.blogspot.ca/2014/12/why-achillion-pharmaceuticals-shares.html

- **EDP-239 + ALISPORIVIR NO NEWS**

EDP-239 (NS5A) + Alisporivir (DEB025) (Cyclophyllin)
A Phase I began in October 2014 and was completed in November 2014. The clinical trial (NCT02173574) was conducted in 42 healthy subjects by the US FDA in Germany. Results have not yet been posted.
(https://clinicaltrials.gov/ct2/show/NCT02173574?term=EDP-239+%2B+Alisporivir&rank=1)

- **Incivek (VX-950) + Balapiravir (R1626) BALAPIRAVIR DISCONTINUED**

Incivek (protease) + Balapiravir (R1626--polymerase)
A study presented at EASL conference in April of 2007 combined the protease inhibitor VX-950 (telaprevir/Incivek-approved in 2011) and the polymerase inhibitor now known as Balapiravir (R1626)
(www.natap.org/2007/EASL/EASL_35.htm)

IV.1.8 TRIPLE DAA COMBOS

Already approved:
Holkira (Viekira in the US), a triple DAA combo, has already been approved.
Paritaprevir/Ombitasvir/Dasabuvir/RBV
Holkira combines Paritaprevir (protease), ombitasvir (NS5A), dasabuvir (polymerase), and RBV
AbbVie's combo produced an SVR12 of up to 97.5% in treatment-naïve patients, and 93.3% in prior non-responders. Some of these successful individual drugs may be part of further trials.

- **Danoprevir/Setrobuvir/ RBV with or without Mericitabine ("ANNAPURNA")**

Danoprevir (protease), Setrobuvir (non-nuc polymerase), Mericitabine (nucleoside polymerase)
The ANNAPURNA study combined Setrobuvir, boosted Danoprevir and RBV with or without Mericitabine (ANNAPURNA study: STV/DNVr/MCB+RBV), with SVR12 rates of 96% in GT1a 70% in GT1b patients. *(www.natap.org/2013/AASLD/AASLD_75.htm)* The Phase II study has was completed in November 2013, but no results have been posted yet. *(https://clinicaltrials.gov/ct2/show/NCT01628094)*

- **Faldaprevir/PPI-668/Deleobuvir +/- RBV**

Faldaprevir (protease) + PPI668 (NS5A) + Deleobuvir (non-nuc polymerase)
Rusults from a Phase IIa trial were presented at the EASL conference in London. SVR12 was achieved in 92% of the GT1a patients, when combined with RBV. 36 patients were enrolled, and divided into 3 troups. The first two groups took the combo without RBV, with either a high or low dose of faldaprevir.

The third group used high dose faldaprevir, but no RBV. 92% of the first two groups had SVR12s. The third group had problems. One patient was encarcerated, and another relapsed at week 8 due to non-compliance. Two more were added, and 8 achieved SVR12. One had stopped therapy after 8 weeks, but achieved an SVR8. *(www.hepmag.com/articles/faldaprevir_deleobuvir_2501_25493.shtml)*

- **Grazoprevir/Elbasvir/Sovaldi ("C-Swift Trial")**

Grazoprevir (MK-5172, Protease) + Elbasvir (MK-8742, NS5A) + Sovaldi (nucleotide polymerase)
Merck's trial results were not as hoped for this combo. Data presented in November 2014 showed an impressive 94.7% cure rate in cirrhotic, treatment-naïve subjects at 8 weeks, but the goal was to cure them in 4 weeks, and the 38.7% wasn't good enough. At 6 weeks, the SVR climbed to 80% in those with cirrhosis, and 86.7% in those without. All patients had GT1 virus. The question is if the results can compete with other DAAs. (The Grazoprevir/Elbasvir is now called MK-5172A)
(*www.fiercebiotech.com/story/mercks-hepatitis-c-cocktail-drug-fails-4-week-challenge/2014-11-10)*

- **Grazoprevir/Elbasvir/MK-3682 ("C-Crest Trial")**

Grazoprevir (MK-5172, Protease) + Elbasvir (MK-8742, NS5A) + MK-3682 (formerly IDX21437 a nucleotide polymerase)
This is a Phase II trial investigating shorter treatment times. There is another combination of drugs involved, as well: Grazoprevir/MK-3682 and MK-8408, a newer drug (See below for the combo).
(www.mercknewsroom.com/news-release/research-and-development-news/interim-data-proof-concept-study-mercks-investigational-h)

- **Grazoprevir/MK-3682/MK-8408 ("C-Crest Trial")**

Grazoprevir (protease) + MK-3682 (polymerase) and MK-8408 (NS5A) are being investigated in part of the C-Crest Phase II trial (See above) in non-cirrhotic patients. Part A of the trial will treat patients with 8 weeks of therapy, and if the results are successful, Part B will investigate shorter treatment times.

- **Ledipasvir/Sovaldi + GS-9669 or Vedroprevir**

Ledipasvir (NS5A) + Sovaldi (non-nuc polymerase) and either of two experimental drugs: GS-9669 (non-nuc polymerase) OR Vedroprevir (GS-9451 [protease]).

A Phase IIa trial treated 60 treatment-naïve GT1 patients in 3 arms. Group A (20 patients) took 6 weeks of ledipasvir and Sovaldi (SOF-LDV), plus GS-9669. Group B (20 patients) took 6 weeks of SOF-LDV, plus vedroprevir. Group C (20 volunteers) joined later. They took only SOF-LDV for 12 weeks. Group A results showed 19 patients with SVR12 (1 relapsed). Group B results had the same results (1 patient couldn't be located). Group C showed all patients cured with only the 2 drugs. None of the patients had significant side effects. Most of the patients were black and had GT1a and a high baseline viral load (harder-to-cure patients). See more at this link: *www.hcplive.com/articles/Six-week-Oral-Drug-Trial-Produces-High-Hepatitis-C-Cure-Rates#sthash.OwHaFGJm.dpuf*

- **Olysio/TMC647055/Samatasvir**

Olysio (protease) + TMC647055 (polymerase) + samatasvir (NS5A)
A combo trial with these drugs began in May 2013, treating approximately 143 patients. Results are expected in May 2015. Three groups are planned. TMC647055 will be used in one of the three groups, Group C, for GT 1a and 1b patients. The patients are receiving Olysio (simeprevir), TMC647055 + RTV (ritonavir—a booster), samatasvir (IDX719), and ribavirin.
(https://clinicaltrials.gov/ct2/show/NCT01852604?term=TMC647055&rank=6)

- **Olysio/JNJ56914845/TMC647055**

Olysio (protease), JNJ56914845 (NS5A) and TMC647055 (polymerase)
A Phase IIa all-oral combo trial was announced in December 2013 by Medivir AB for GT1 patients to evaluate 12-weeks of this therapy. *(www.biospace.com/News/medivir-ab-release-an-all-oral-phase-2a-study/318542)*

- **Sovaprevir/ACH-3102/ACH-3422**

Sovaprevir (ACH-1625-–protease) + ACH-3102 (NS5A) + ACH-3422 (polymerase)
This trial will test all three of Achillion's Hep C drugs for treatments of 4 and 6 weeks, hoping to beat Harvoni's 8 week treatment. (In the future, they hope to combine Sovaldi with ACH-3102 and sovaprevir). *(www.techtimes.com/articles/31938/20150210/achillion-posts-postive-results-in-hep-c-treatment-trial.htm)* The 6-week combo of ACH-3012 with Sovaldi resulted in an impressive SVR12 of 100% in treatment-naïve subjects. *(www.natap.org/2014/HCV/021315_05.htm)*

- **Sunpreva/Daklinza/Beclabuvir ("DCV TRIO")**

Sunpreva (Asunaprevir--protease)+ Daklinza (Daclatasvir--NS5A) +Beclabuvir (non-nuc polymerase)

  - **UNITY-1 Phase III**

    A Phase II of this combo for 12 weeks reported an SVR12 up to 92% in GT1 treatment-naïve non-cirrhotic patients, The SVR12 for GT4 patients was 100%. The combo is designed to be taken twice a day.

The Phase III trial (NCT01979939) treated non-cirrhotic GT1 Patients: 312 were treatment-naïve and 103 were treatment-expienced. 229 were GT1a and 73 were GT1b. Most had non-CC IL28b alleles. The overall SVR12 results were 91%. 8 pts stopped due to no response. 3 had adverse events, but all achieved SVR12 anyway.1 got pregnant and stopped at week 6, but she also achieved SVR12.The GT1b patients had SVR12 rates of 98% (naïve)-100% (experienced) SVR12. Only two GT1b pts didn't achieve SVR12. One had GT1b, and had a virologic failure. One had GT non-1a/1b after a later analysis. There was one death due to a heroin overdose.

- **UNITY-2 Phase III**

GT1a or 1b compensated cirrhotics were divided into two arms: treatment-naive and treatment-experienced. Results showed an SVR12 of 93% with TRIO alone, and 98% with TRIO + RBV, in treatment-naïve patients. In the treatment-experienced arm, 87% obtained an SVR12 with TRIO alone, while 93% achieved SVR12 with TRIO + RBV. Development of resistant strains didn't seem to affect results. The treatment was generally safe and well-tolerated. (Info from a BMS Power Point presentation)

A Phase IV trial has been planned to recruit about 35 patients GT1 patients.to start treatment in March 2015 and end in February 2016.
(*https://clinicaltrials.gov/ct2/show/NCT02292966?term=Beclabuvir+%2B+HCV&rank=1*)

- **Vedroprevir/Ledipasvir/Sovaldi +RBV**

Vedroprevir (GS-9451--protease)/Ledipasvir (NS5A)/Sovaldi (polymerase) + RBV
A Phase II combo trial enrolling 50 GT1 treatment-experienced patients with cirrhosis is sponsored by Gilead Sciences as of July 2014. It is expected to end in July 2015. In an earlier trial ("Synergy Trial") of this combo without RBV, in treatment-naïve subjects, who were treated for only 6 weeks, Over half of the participants had GT1a. Over 75% had genes that suggested they wouldn't respond to IFN. (IL28b?) *Between 25-40% patients had severe liver damage. All of the patients achieved SVR12. (www.catie.ca/en/treatmentupdate/treatmentupdate-202/hepatitis-c-virus/sofosbuvir-ledipasvir-just-six-weeks-therapy) (https://clinicaltrials.gov/show/NCT02226549)*

- **Vedroprevir/Ledipasvir/Tegobuvir/RBV**

Vedroprevir (GS-9451-protease + Ledipasvir (NS5A) + Tegobuvir (polymerase) + RBV
Tegobuvir** has been **DISCONTINUED
This combo reported SVR rates of 63-81% in treatment-naïve patients without cirrhosis, treated for 12 (48%) or 24 weeks (63%). The results did not compare well to the trials of Sovaldi/ledipasvir.
http://webcache.googleusercontent.com/search?q=cache:7B00kquvBdAJ:www.hcvadvocate.org/news/newsLetter/2014/advocate0314.html+&cd=9&hl=en&ct=clnk&gl=ca
(www.hivandhepatitis.com/hepatitis-c/hepatitis-c-topics/hcv-treatment/4078-easl-2013-hep-c-quad-regimens-quashed-but-some-components-go-forward

IV.1.8a More Elaborate DAA Combos

ABT-450r/ ABT-493/ABT-267/ABT-530/ ABT-333/RBV
Paritaprevir boosted with ritonavir (ABT-450r) and ABT-493 (protease) + ombitasvir (ABT-267) and ABT-530 (NS5A) + dasabuvir (ABT-333--non-nuc polymerase)
The drugs ombitasvir, paritaprevir and dasabuvir are already approved as part of the Holkira/Viekira Pak, so the "newcomers" are the additional protease inhibitor ABT-493, and the extra NS5A inhibitor, ABT-530. These two drugs are being tested with the others in a trial that can be found at *https://clinicaltrials.gov/ct2/show/NCT01995071?term=ABT-493+and+ABT-530&rank=2*

Niney-six 96 treatment-naïve, GT1 subjects were to be enrolled. The trial began in November 2013 and is planning to finish in June 2015. The trial has 12 arms, all with ABT-450r/ ABT-267/ABT-333/RBV, plus either of the experiemental drugs: ABT-493 in 6 arms, and ABT-530 in the other 6 arms, which are given as monotherapy for the first 3 days (6 different doses), followed by either 12 or 24 weeks of the other drugs.

IV.2.0 OTHER THERAPIES

IV.2.1 Alinia (Annita, Nitazoxanide)
Romark's nitazoxanide, called Alinia, is a thiazolide. It inhibits synthesis of structural proteins of the virus. Alinia is already under development in the US for treating some gastrointestinal problems (parasites, Crohn's, etc.) *(/PRNewswire/ Jan 10, 2006, Romark to Develop Alinia® (nitazoxanide) as New Treatment for Chronic Hepatitis C)* Studies have shown it to be an effective inhibitor of HCV and it doesn't cause resistant mutations. It works synergistically with IFN and DDA's (Direct-Acting Antivirals) without adding toxicity. It may be able to replace ribavirin in GT4 patients. It has been studied in HCV/HIV co-infected patients.

The drug has undergone many clinical trials for several diseases and disorders. On April 15, 2010, Romark announced results from its STEALTH C-3 Phase II clinical trial of Alinia (nitazoxanide) in treatment-naive GT1 patients, and presented tThe results at the 2010 EASL Conference. 44% of patients treated with Alinia/Pegasys/Copegus achieved SVR12 vs. 32% of those taking only Pegasys/Copegus. Strangely, the higher the baseline viral load, the higher the SVR12 rates. Phase III trials were to begin later in 2010, with pegIFN with or without RBV. Other trials are already using the controlled-release tablets in GT1 and 4 patients. Important recent studies have included one arm that combined Alinia with pegIFN/RBV in GT1 non-responders. Data for this trial was released on April 17, 2011. *(www.prnewswire.com/news-releases/romark-announces-data-from-clinical-trial-of-nitazoxanide-in-treatm www.prnewswire.com/news-releases/intercell-and-romark-join-forces-in-combining-therapies-against-hepatitis-c-105416213.htm)*

In 2015, clinicaltrials.gov had 13 studies recorded for Alinia and hepatitis C. Only one is recruiting subjects--a 3-arm trial in Egypt for treatment of Hep C. One of the trials for hepatitis C (NCT01197157) was completed in Egypt in April 2014. No results have been posted yet. Another is testing the drug combined with PegIFN/RBV in GT4/HIV+ patients. It should be completed in February 2015.
(https://clinicaltrials.gov/ct2/results?term=nitazoxanide+AND+hepatitis+C&Search=Search)

IV.2.2 Amantadine
There have been several Amantadine trials, mostly disappointing. We continue to include it here to remind ourselves of the hope this drug gave us at one time, pre-pegIFN/RBV.

Two studies in 2006 produced conflicting results: In the February 2006 *Journal of Hepatology*, a trial in 200 treatment-naive chronic genotype 1 patients taking standard treatment plus amantadine showed no improvement in viral load reduction or in quality of life over standard treatment alone. However, in another 200-person study by Marianne Maynard, *et al*, published on the *Journal of Hepatology* website, non-responders who received standard treatment plus amantadine were more likely to achieve SVR than those taking standard treatment alone. The response rates were 24% and 16%, respectively. *(www.hcvadvocate.org/news/newsRev/2006/HJR-3.3.html#3)* Clinical trials of amantadine for hepatitis C infection have been **CANCELLED***. (http://hcvadvocate.org/hepatitis/hepC/HCVDrugs.html#Cancelled Nov 2007)*

IV.2.3 CB5300
Canopus BioPharma's CB5300, a flavivirus inhibitor, has already been FDA-approved and found to be generally safe, A Phase II trial in humans took place in the US and Australia.
(http://markets.chron.com/chron?GUID=3653679&Page=MediaViewer&Ticker=CBIA Oct 31, 2007)

In 2015, Canopus names CB5300 as one of its lead Hep C compounds on its website, also naming CB2029, CB2030, and CB2009. It looks like the entry on the website was made in 2010, and reports a Phase IIb trial with CB5300, saying recruitment had begun at the Brooke Army Medical Center in Texas.
(www.canopusbiopharma.com/research-and-development/antivirals/hepatitis-c)

IV.2.4 Celgosivir (MX-3253)
MX-3253 (celgosivir), an oral alpha-glucosidase I inhibitor by Micrologix is a derivative of the Australian Black Bean chestnut tree. It was studied extensively and has been declared ineffective.
(https://books.google.ca/books?isbn=0199844291 p. 149)

IV.2.5 CF102 (Cl-IB-MECA)
A Phase I clinical trial of Can-Fite's CF102 found the drug to be safe in 25 healthy adults. The Phase I/II trial began in July 2009, and planned to enroll 32 genotype 1 subjects, treating them with oral CF102 twice a day for 16 weeks. The trial is expected to be completed in July 2011. A separate study is taking place for the product as a liver cancer treatment. This drug binds to the adenosine 3 receptor (A3R), which is found on cancer and inflammatory cells, promoting apoptosis (programmed cell death).
(http://clinicaltrials.gov/ct2/show/NCT00790673) The company's pipeline mentions CF102 as a liver cancer drug. *(www.canfite.com/?KPageId=20)*

IV.2.6 CTS-1027
Conatus Pharmaceuticals' CTS-1027, an oral, small molecule, matrix metalloproteinase (MMP) inhibitor, reduced liver damage, reduced ALTs and improved survival and liver histology in a Phase I trial.
(www.medicalnewstoday.com/articles/87771.php 06 Nov 2007 and http://clinicaltrials.gov/ct2/show/NCT00570336?spons=%22FGK+Clinical+Research+GmbH%22&spons_ex=Y&rank=3) The Phase II trial of CTS-1027 has been **TERMINATED** due to worrisome side effects and abnormal lab results in some patients. *(www.biospace.com/news_story.aspx?StoryID=237817&full=1)*

IV.2.7 Fluvastatin

Fluvastin is a drug that is already approved for lowering cholesterol by inhibiting a liver enzyme, HMG Co-A reductase. The drug is expected to prevent serious fibrosis. This study treated 209 treatment-naïve G1b patients with fluvastatin or placebo plus SOC for 48 weeks. Fluvastatin was given for a total of 72 weeks, no matter the patient's lipid levels. The results showed that SVR was 74.39% in the fluvastatin combo, vs. 58.44% from SOC. And fluvastatin is affordable! *(EASL 2011)*

IV.2.8 HCV Monoclonal Antibodies (mAb's)

- **Bavituximab** (formerly Tarvacin), developed by UT Southwestern Medical Center, and produced by Peregrine is the first of anti-phosphatidylserine (anti-PS) monoclonal antibodies that bind to atypical cells such as tumours, and to normal parts of a cell that become exposed when infected with a virus, and to the surface of enveloped viruses. These antibodies may stimulate the immune system to destroy both the virus particles and the infected cells.
  (http://money.cnn.com/news/newsfeeds/articles/prnewswire/LATU12707082007-1.htm Aug 07, 2007)

  Data from a Phase Ib study was presented at the 2007 AASLD Meeting. Twenty-four patients were divided into 6 dosing groups. Eleven were non-responders, 8 were relapsers and 5 were treatment-naïve; 15 were GT1, 8 were GT3 and 1 was GT2. They were given 90 minutes of the drug IV twice a week for 2 weeks, at different doses, then followed for 12 weeks. Infusions up to 6 mg/kg were safe and well-tolerated. No serious adverse events or early discontinuations were reported. Two weeks of dosing showed antiviral effect in some patients. *(J Levin www.natap.org)*

  Peregrine enrolled 66 GT1 treatment-naïve patients for a Phase II trial of Bavituximab. The drug has been shown to be safe in 3 previous Phase I HCV studies. The drug is also being tested in patients with pancreatic and lung cancer. Participants were treated for up to 12 weeks with Bavituximab or PegIFN/RBV. Bavituximab was better tolerated. The higher dose was more effective. *The company is seeking partners with drugs that will combine well with Bavituximab.*
  (www.marketwatch.com/story/peregrine-completes-patient-enrollment-in-randomized-phase-ii-hcv-trial-for-bavituximab-2011-09-26) (www.proactiveinvestors.com/companies/news/22915/peregrine-reports-initial-results-from-phase-2-hep-c-drug-study-22915.html)

- **Civacir** - Human antibodies to HCV, produced using XTL's Trimera mouse system (a mouse genetically altered to carry human tissues for *in vivo* [in a living organism] experiments) were used to develop a product called Civacir, Nabi's polyclonal antibody to hepatitis C, developed from antibodies taken from screened HCV+ donors and purified. These antibodies neutralize the hepatitis C virus. The product is being developed to prevent re-infection in transplant patients. Civacir was granted fast track status by the US FDA in 2006. Nabi has partnered with Kedrion, a biopharmaceutical company in Italy, to sell Civacir in Europe as well as in the US.

  In January 2007, a Phase II clinical trial began, treating 20 patients with Civacir vs. 10 patients treated with IFN/RBV. Results were expected in the second half of 2008.
  (www.nabi.com/pipeline/pipeline.php?id=4)

  Nabi Biopharmaceuticals initiated another Phase II clinical trial for Civacir—a proof-of-concept trial. The developers plan to use it to prevent the recurrence of HCV in liver transplants, or to prevent infection in transplant patients who received a liver infected with HCV. The product is being developed with Kedrion. It is hoped that post-transplant patients can be treated with Civacir sooner after transplant surgery than with other drugs. *(www.prnewswire.com/news-releases/nabi-biopharmaceuticals-announces-initiation-of-civacirr-phase-ii-proof-of--concept-clinical-trial-53513912.html Jan. 16, 2011)*

  Preliminary data was presented at the AASLD conference in November 2014, showing very good results for Civacir's ongoing Phase III trial, which is treating HCV+ pre-transplant patients with antiviral meds before transplant. Half of the patients are just being observed. The other half is being treated according to their weight. 30% of transplant patients usually need a second transplant within 5 years. At the time of the conference, none of the higher-dose group has relapsed, opposed to 35% of the non-treated patients.
  (www.biotestpharma.com/index.php?src=news&srctype=detail&category=Biotest%20Pharmaceuticals%20Corporation%20News&refno=24&submenu=News)

- **CT-1011** CureTech and Teva will collaborate on a Phase I/II trial of the monoclonal antibody CT-1011 around the end of 2009. The trial will enroll 20 patients. CureTech is also studying the drug in a Phase II trial for liver and bowel cancer.
  (*www.israel21c.org/index.php?option=com_content&view=article&id=7123:curetech-to-begin-*

hepatitis-vaccine-trial&catid=62:briefs&Itemid=141 August 18, 2009)
It seems that CureTech only has clinical trials for lymphoma, now, (*www.curetechbio.com/* 2015), and Teva is specializing in asthma.

- **MBL-HCV1** Researchers at MassBiologics, part of the University of Massachusetts Medical School, began a Phase I clinical trial on July 28, 2009, testing their hepatitis C neutralizing vaccine, MBL-HCV1, a human monoclonal antibody that neutralizes HCV. The trial administered MBL-HCV1 to 30 healthy subjects. It is hoped that the drug will be used as a therapy before and during transplant surgery, to prevent infection of the new liver. It may be used combined with other new drugs to treat newly-diagnosed Hep C patients, as well. *(www.huliq.com/11/84595/new-antibody-targets-hepatitis-c-virus)*

  The disease progresses more rapidly in the new liver, developing cirrhosis in 5 years in 20% of the recipients. Betweeen August 2010 and June 2011, the company enrolled 16 patients in a Phase II trial part 1, of MBL-HCV1 with one dose, then 16 more with double that dose (100 mg/kg). In this study, patients would receive the drug or a placebo 1 to 4 hours before surgery, right before the new liver is transplanted, 8 hours after surgery, once daily for the first week after the transplant surgery, and once more 14 days after surgery. Not all of the patients finished the trial. See more at *www.ncbi.nlm.nih.gov/pmc/articles/PMC3618536/* The drug was safe and tolerable, but the patients were not protected from infection of the new liver. The researchers believe that the combination of a monoclonal antibody with other DAAs could work effectively, and reduce liver damage before and after transplant. Studies are being planned.

IV.2.9 Interferon Alpha Gene Therapy
Interferon Alpha Gene Therapy is a treatment for hepatitis C that delivers genes for IFN alpha-2b specifically to liver cells, to make the treatment more effective.

In a laboratory trial HCV completely disappeared, suggesting that IFN-alpha produced by gene transfer effectively inhibits HCV replication in liver cells. This study supports the development of IFN-alpha gene therapy for HCV-associated liver diseases (*www.ncbi.nlm.nih.gov/pubmed/12878183).*

In an Egyptian study in rats, IFN-alpha gene transfer was studied to see if it would protect them from damage from known toxins, and was found to be effective in preventing liver fibrosis and cancer. "IFN-alpha gene therapy may be justified in clinical trials for high-risk candidates with hepatic carcinogenesis." *(www.egeinfonet.i8.com/pub/2005/1.html)*

Medgenics developed 4the InfraDure Biopump, designed to be implanted in the body to provide constant levels of interferon for 3 to 9 months. The company set up Phase I/II clinical trials in Israel for HCV+ patients who relapsed on previous therapy. The trials were to start on January 30, 2013, but were **TERMINATED** in March of 2014, and withdrawn before enrolling patients.
(http://adisinsight.springer.com/drugs/800037476)
(https://clinicaltrials.gov/ct2/show/NCT01430000?term=NCT01430000&rank=1)

IV.2.10 Interleukins
Early laboratory trials showed that some interleukins might be able to suppress the hepatitis C virus, although more recent studies have shown they are not very effective. Even so, scientists continue trying to develop interleukin compounds against hepatitis C.

- **NEUMEGA** A study of 5 microg/kg of rhIL-11(Neumega) injected daily for 12 weeks showed improved biopsy results in 11 of the 20 subjects enrolled. The treatment seemed to cause a decrease in ALT levels from an average of 113 IU/L to 65 IU/L at week 12; however, viral load was not affected. Platelets increased, too. The study results suggest that rhIL-11 may be good for patients with liver inflammation and advanced liver disease from chronic HCV.
- *(www.ncbi.nlm.nih.gov/pubmed/15571583)*

  Pfizer's Neumega, also known as Interleukin eleven (IL-11) is FDA-approved. It is used for cancer patients and for treating thrombocytopenia.

- **CYT107** Cytheris began the Phase I/IIa (ECLIPSE 2) clinical trial of its CYT107 recombinant interleukin in May 2007, for GT1 non-responders who were not responding to PegIFN/RBV. CYT107 was injected once a week, four times, along with standard treatment. The study, which took place in Europe, was scheduled to end in March 2012.
  (https://clinicaltrials.gov/ct2/show/NCT01025596?term=CYT107+%2B+%22hepatitis+C%22&rank=1)

  Interim results of the Eclipse II were presented at the AASLD meeting in San Francisco (Nov. 4-8, 2011), showing that the highest dose produced a result of non-detectable in previous non-responders to PegIFN/RBV. *(http://hepatitiscnewdrugs.blogspot.ca/search?q=cyt107)*

IV.2.11 JKB-122

Jenken Biosciences' JKB-122, an antifibrotic, underwent Phase II clinical trials in around 150 HCV+ non-responders, over 3 months, alone or combined with PegIFN/RBV. The trial was to start at the beginning of 2007, and was to take 1 to 2 years to complete. In previous trials with alcoholic patients, it reduced inflammation and normalized liver enzymes. *(www.jenkenbio.com/news_061214.shtml)*

A Phase II trial is recruiting 148 HCV+ patients as of May 2014, and is scheduled to end in August 2016. The drug will be taken as monotherapy for 12 weeks. (https://clinicaltrials.gov/ct2/show/NCT02293941)

IV.2.12 NOV-205

The development of NOV-205 has been **SUSPENDED** and the IND (Individual New Drug) application was withdrawn in 2011.
(www.sec.gov/Archives/edgar/data/1279704/000114420414041708/v381571_s-1a.htm)

IV.2.13 Oglufanide

Physicians at Southern Health have started a Phase IIa clinical trial with Implicit Bioscience's drug, oglufanide disodium, a regulator of the body's immune response, is being given to patients with chronic Hep C. It was originally used to treat severe infectious disease in Russia, and was studied in cancer clinical trials in the US. It was acquired by Implicit Bioscience in 2005. The Phase IIa trial of intranasal oglufanide disodium will complement the ongoing Phase Ib study of subcutaneously administered drug in Brisbane's Princess Alexandra Hospital. (www.medicalnewstoday.com/articles/80603.php Aug 25, 2007) *(www.medicalnewstoday.com/articles/72827.php 31 May 2007 and www.cytheris.com)*

Implicit is studying purple sea urchin eggs, which have a jelly coating containing a type of carbohydrate. So does green sea urchin sperm. The jelly acts as a barrier to stop cross-breeding. Mammal "eggs" have complex carbohydrate molecules instead, the researchers believe. They are trying to use the carbohydrates, delivered through the nose, to produce an immune response of the body.
*(*Oglufanide disodium as regulator as a regulator of immune responses of body intranasally intranasal administration to patients with chronic hepatitis C virus infection. *www.tsfseap.org/the-jelly-coating-contains-a-general-type-of-carbohydrate-in-the-purple-sea-urchin.html Dec 19, 2014)*

IV.2.14 Rosiglitazone

Previous short trials of glitazones had controversial biopsy results. Researchers hoped for better results with longer treatment, and re-enrolled 53 patients who had completed the FLIRT trial, which was 1 year of Rosiglitazone (RSG) or placebo. They were enrolled in two more years of treatment, all with RSG. 40 finished and were biopsied for a 3rd time. In the placebo/RSG group, steatosis (fatty liver) decreased by an average of 15% and in the RSG/RSG group, there was a 20% reduction of steatosis only in the first year. Fibrosis did not change. Researchers concluded that RSG has a good effect on steatosis during the first year, but no benefit after that, other than maintaining a good effect on insulin and liver enzyme levels. *(EASL 2009)* The drug has been tested for patients with diabetes, and elevations of liver enzymes have been observed. The US FDA has suggested that it NOT BE USED in patients with liver disease. *(www.ncbi.nlm.nih.gov/pmc/articles/PMC3371462/)*

IV.2.15 Taribavirin (Viramidine)

Viramidine (VRD) is a pro-drug of ribavirin produced by Valeant Pharmaceuticals. A prodrug is a drug that is concentrated in a certain organ such as the liver rather than distributed throughout the entire blood system. The body has to change it to an active form before the full effect can be seen. Studies seem to indicate that viramidine is safer, but less effective than ribavirin. Since Viramidine directly targets the liver, it is supposed that it won't cause anemia so easily.
(www.hivandhepatitis.com/hep_c/news/2006/032406_a.html)

The Phase III ViSER 2 study enrolled 972 treatment-naïve patients, who were treated with peg-IFN alpha-2b and either a fixed-dose or weight-based RBV. SVR rates were 37.7% with VRD and 52.3% with RBV, but incidence of anemia was about four times lower with VRD than with RBV.
(www.ncbi.nlm.nih.gov/pubmed/19585653 2009 and *www.medscape.com/viewarticle/760953_4*)

IV.2.16 Toll-like Receptor Agonists (TLR agonists)

The use of specific agonists directed toward RIG-I and TLR3 or other toll-like receptors (TLRs) was suspected to induce IFN and ISG expression and pro-inflammatory chemokines and cytokines. A study by Bedrad and colleagues discovered a class of isoflavone compounds that act like agonists of the RIG-I signaling pathway, thus activating the IRF-3 transcription factor and downstream antiviral gene

expression. TLR7 agonists such as isatoribine, PF-4878691 and AA773, have been shown to decrease HCV RNA levels, and modulate immune biomarkers while dsRNA activation of TLR3 has a strong anti-HCV effect in lab cell culture models of HCV replication. (*www.medscape.com/viewarticle/836774_7*)

- **ANA773**
  Anadys Pharmaceuticals has been acquired by Roche, who seemed to have plans for continuing the development of the drug, but it doesn't appear in the hepatitis C part of their pipeline.
  (www.roche.com/media/media_releases/med-cor-2011-10-17.htm Oct 17, 2011)

  Anadys' ANA773 is an oral drug that induces interferons and acts through the toll-like receptor 7 (TLR7) pathway. On August 11, 2009, the company announced data for the final group of patients that took part in the Phase I clinical trial, a 10-day study of the drug as monotherapy, conducted in the Netherlands. Subjects who took 2000 mg of ANA773 every 2 days for 10 days had an average of 1.3 $\log_{10}$ drop in viral load, while those receiving placebo had an average decline of 0.3 $\log_{10}$ drop.

  More recently Anadys presented data from a Phase I cancer study of ANA773 at the 2011 American Society of Clinical Oncology (ASCO) Annual Meeting on June 4, 2011. The product was shown to be safe at a dose that produced the desired effects on the immune system, with a partial response in a cancer patient.
  (http://hepatitiscnewdrugs.blogspot.com/2011/05/anadys-highlights-ana773-data-to-be.html May 25, 2011)

- **IMO-2125 and IMO-2055**
  Idera has begun a Phase I trial with IMO-2125, a Toll-like Receptor (TLR) 9 agonist designed to make the body produce its own interferon and other immune responses against HCV. When tested in primates, IMO-2125 proved effective at producing cytokines that inhibit replication of HCV. This trial is planned for 40 non-responders, in 4 arms of different doses. Eight of them will receive a placebo. The trial consists of one injection weekly for 4 weeks.
  (*www.iderapharma.com/file/News%202007_09_17.pdf Oct 4, 2007*)

  In a press release dated Dec.2, 2014, Idera says it has two TLR agonists: IMO-2055 and IMO-2125. Clinical trials of IMO-2055 showed the drug to be well tolerated in about 80 HCV+ patients. Idera is currently conducting further preclinical research to evaluate the potential of IMO-2055 and IMO-2125 to enhance the anti-tumor activity of checkpoint inhibitors in cancer immunotherapy.
  (http://ir.iderapharma.com/phoenix.zhtml?c=208904&p=irol-newsArticle_print&ID=1994362)

- **MitoQ**
  Antipodean Pharmaceuticals' MitoQ is a super antioxidant that binds with coenzyme Q10 and prevents aptosis (programmed cell death). Oxidation in liver cells can be very dangerous to those with liver disease so some clinical trials have been done.

  A Phase II trial began in March 2007, and ended in November 2007. The trial studied 30 HCV+ patients, ALTs were measured before treatment with MitoQ. Patients received either MitoQ 40 mg/day, MitoQ 80 mg/day, or a placebo for 28 days, producing a decrease in ALTs of 28% with the higher dose. There were no safety problems.
  (www.earthtimes.org/articles/show/antipodean-pharmaceuticals-announces-results-of,365835.shtml)
  (https://clinicaltrials.gov/ct2/show/NCT00433108?term=MitoQ+AND+hepatitis+C&rank=1)

  A 90-day Phase II trial beginning in November 2010 compared 2 tablets daily of MitoQ to a placebo in participants with elevated liver enzymes. The trial was terminated. No results were posted.
  https://clinicaltrials.gov/ct2/show/NCT01167088?term=MitoQ+AND+hepatitis+C&rank=2

  Antipodean's website seems to have expired in 2012, but research goes on. A study was published in December 2014. There is an abstract on PubMed about MitoQ tested in mice. It showed that, even though the drug deterred obesity blamed on liver damage, and improved liver function, it did not increase energy intake. (*www.ncbi.nlm.nih.gov/pubmed/25301169)*

- **SD-101**
  Dynavax Technologies has developed SD-101, an oligonucleotide called a TLR-9 agonist, which is made to boost the body's immune response to HCV by affecting the T-cell and natural killer cells by way of the toll-like receptor 9 (TLR-9) and encouraging our bodies to make more interferon-alpha.

  In a Phase 1b trial, 34 treatment-naïve genotype 1 patients were injected once a week with doses of SD-101 ranging from 0.1 mg. to 5.0 mg. or placebo. There were few side effects. SD-101 produced a drop in viral load after only one dose of SD-101 given as mono-therapy. The fast drop of HCV RNA indicated that more trials should be done. *(www.kenes.com/easl2010/posters/Abstract188.htm)*

IV.2.17 UDCA (ursodeoxycholic acid)

There is no proven therapy for fatty liver. This trial gave 30 mg per kg of weight each day of UDCA

(ursodeoxycholic acid) or placebo to 126 patients with non-alcoholic steatosis, (NASH or fatty liver) and ALT levels over 50 IU/L to see if it was safe. The treatment lasted 12 months. The goal was a lower ALT, indicating less inflammation. ALT decreased an average of 55% with UDCA, and 35% with placebo. Average AST and GST decreased 59% with UDCA, and increased with placebo. The UDCA group reported more diarrhea, pain in the abdomen, and gastrointestinal problems than the non-UDCA group, but also reported improvement in strength and less right upper quadrant pain. *(EASL Conference 2009)*
UDCA won't get rid of HCV, but it may prevent inflammation and fibrosis, while patients are waiting for effective therapy. The drug is approved, and is called Actigall, Ursosan, Urso, etc., and can relieve itching in some patients. *(http://en.wikipedia.org/wiki/Ursodeoxycholic_acid)*

IV.2.18 Zadaxin (Thymosin)
Researchers believe that Zadaxin, SciClone's thymosin alpha-1, a synthetic polypeptide, works by boosting the ability of the body's immune system to produce T-cells. It is approved for treatment of chronic hepatitis B, in over 30 countries, but not in the US or Europe. (*www.sciclone.com/product-portfolio/zadaxin/)*

Results from a Phase III trial for non-responders, who completed 48 weeks of triple therapy combining Pegasys with Zadaxin, showed an SVR in 6 out of the 30 patients (20%) at week 72. 26 of the patients were infected with genotype 1, and their SVR rate was 23% (6 out of 26 patients).

It has been proven safe in patients from 13 months old to 101 years old, as well as with patients who are immunocompromised. *(www.sciclone.com/product-portfolio/zadaxin/)*

IV.3.0 VACCINES
Wouldn't it be wonderful if, just like polio or smallpox, no one had to worry about catching Hep C ever again? Vaccines do that. Unfortunately, there is no vaccine against Hep C, but researchers keep trying… and it looks like they may be getting very close!

"Treatment will form part of the control of the disease; however, successful treatment of an infection has never led to eradication. The search for an effective prophylactic vaccine should continue, and advances in molecular vaccinology will enable progress in the coming years."
(LANCET Seminar, Hepatitis C, Webster, Dr Daniel P, et al. 13 February 2015)

What type of vaccine would work best for the Hep C virus? Ideally, it would be a vaccine that would prevent initial infection (prophylactic vaccine), AND it would prevent the infection from becoming chronic, curing the disease in those already infected (therapeutic vaccine). The problem is that the virus has many strains and mutates easily. Other problems include developing a vaccine that gives people lasting protection, and finding good models to use for testing.

The search for a vaccine suffered a big setback back in 2007. It was hoped that a "therapeutic" vaccine, that could also cure those already infected, could be found, but therapeutic antibody treatments weren't working. Then researchers found out why: Usually a virus replicates inside a cell, and large numbers of the virus burst out and start over again. Some viruses don't have to leave the cell. They can infect it by travelling directly from cell to cell. HCV uses both methods. It can travel directly to the next cell, avoiding the body's neutralizing antibodies and medical treatments. That may be why HCV antibodies don't control the virus.
(http://news.bbc.co.uk/2/hi/health/7075569.stm and www.natap.org Nov 2, 2007)

This important information showed scientists where to find new targets for antiviral therapy. An HCV vaccine is now looking more possible. Even more promising is that researchers are generously sharing their information and building upon each other's work. Part of this collaboration has come from the researchers deciding to unite and pool their knowledge to rid the world of Ebola--and the technologies they have developed should work with HCV, too. Below, you will see several types of possible vaccines. Some are prophylactic, and some are therapeutic, like DAAs. The vaccines seem to target and inhibit many reproductive parts of the virus, not just one, and are effective against many genotypes. More interesting is that the researchers are combining the kinds of vaccines, first building up the patient's immune system—priming it, so to speak—and then aiming at the virus itself, using one or even more of the following vaccine types. Some of these new vaccines aren't even numbered yet! It's hard to organize them into categories, since many now combine one or more of these techniques:

TYPES OF POSSIBLE VACCINES:

Passive Immunization: One would think that having HCV antibodies would cure the disease and protect a person against re-infection, but it doesn't work that way with the hepatitis C virus. Attempts at using this method on chimpanzees seem to have failed, however, a study from 2013 tested this method on some chimeric ("humanized") mice, and researchers found they produced antibodies against HCV envelope proteins which inhibited genotypes 1a, 1b and 2a. Those antibodies protected the mice against infection and "might be used in the development of a prophylactic vaccine."
(www.ncbi.nlm.nih.gov/pubmed/23673355?dopt=Abstract&holding=npg)

Envelope Glycoprotein Vaccines: This type of vaccine causes the body to make antibodies to parts of the virus' outer coating, called E1 and E2. This vaccine seems to be showing promise in chimpanzees. The structure of E2 envelope glycoprotein, possibly the protein that HCV uses to invade liver cells, was clarified by researchers from The Scripps Research Institute (TSRI) in November 2013. This discovery may make it easier to design a vaccine which will be effective against several virus strains. *(http://en.wikipedia.org/wiki/Hepatitis_C_vaccine)*

***Epitope Based Vaccines*:** An epitope is the part of a protein that is recognized by the immune system—by antibodies, B cells or C cells. This type of computer-generated vaccine is designed to make the body produce a strong immune response (CD4+ and CD8+) using T-cell epitopes. It is hoped that this technology won't allow mutations to escape, and that it will cover several genotypes, not just one. The disadvantages are that the technology requires large computer databases, and an effective vaccine would probably have to include some protein from actual HCV.
(www.brown.edu/Courses/Bio_160/Projects2000/HepatitisC/hcvvaccines.html)
In spite of this, great progress has been made: Scientists have collected a set of 245 HCV-specific CD8 T-cell epitopes, of which they chose 17 promising ones…and shared their work! Eventually, after many series of procedures, they were able to select 6 epitopes that they predicted to produce the best T-cell response in any patient, in spite of his/her genetic makeup. This information is available for public use. *(www.hindawi.com/journals/jir/2013/601943/)*

Naked DNA Vaccines: "Naked" DNA means DNA that isn't associated with a virus, so it can't infect the patient with anything**.** Therapeutic DNA is introduced into a virus to deliver it to the body. The "C" gene of the hepatitis C virus is often used in these experiments, because it is similar in all the genotypes. Side effects of a vaccine of this type may be a problem, and safety may be an issue, although some researchers say there are no viral parts to cause unwanted immune responses, infections, or permanent changes in the cell's genetic makeup.
(www.brown.edu/Courses/Bio_160/Projects2000/HepatitisC/hcvvaccines.html)
Techniques are being developed to overcome the problems with DNA vaccines:

- **Alphaviral Particle** (promising results in mice).
- **Polytopic Vaccines** (comprised of one E2 protein and two E1 and core proteins).
- **Bacillus Calmete Gurein** (BCG) used as a vector with HCV epitope delivery.
- **NS Genes-based DNA Vaccines** (Non-structural genes like the NS5a or the NS2 are good candidates).
- **Glycoprotein-based DNA vaccines** (E1 and E2 are good targets, inducing a polyclonal humoral response desirable in an HCV vaccine). Human clinical trials have begun. (e.g., ChronVac-C, CIGB-230, Novartis-Okairos-Chiron's Vaccine and Adelaide University's DNA Vaccine)

***Viral Vector Vaccines*:** These vaccines, like naked DNA vaccines, are designed to place foreign DNA into a cell to stimulate the immune system. Viral vector vaccines have an advantage because they allow specific host cells to be targeted, so that the vector will not enter the genetic material of the cell. Few vaccines like this have been tried, so little is known about how effective they are.
(www.brown.edu/Courses/Bio_160/Projects2000/HepatitisC/hcvvaccines.html)

Recombinant viruses can be used to deliver DNA efficiently. Experiments in animals have induced protective immunity to many viruses, and some are being tested for HCV vaccines. A favorite virus is the defective adenovirus (a virus that causes colds) because its natural "habitat" is the liver. However, the tragedy of a death in a gene therapy trial using adenovirus has severely dampened the enthusiasm for the use of this viral vector in humans.
(www.medscape.com/viewarticle/410848_6)

There is an adenovirus vector called BID (BH3–interacting domain death agonist), designed to cause cells infected with HCV NS3/NS4A protease to commit suicide (aptosis), stopping the progression of the disease. Studies done with chimeric mice at the Ontario Cancer Institute, and reported in the May 2003 issue of *Nature Biotechnology*, showed the treatment to be effective, and nontoxic to healthy neighboring cells. "A targeted therapeutic approach using modified BID may be useful as a prophylactic against accidental virus exposure, in the early stages of hepatitis, during limited infection of the liver, or for ex vivo therapy of hepatocytes. It may also reduce virus loads in chronically infected patients, and in conjunction with interferon and ribavirin therapy, might eradicate HCV from the infected host," say the researchers *(Reuters Health 05/01/03).*

Peptide Vaccines: Researchers think this kind of HCV vaccine can work because helper T-cells (some of our immune system's "soldiers") recognize antigens (invaders) that they should attack, because of peptide fragments bound to molecules on the surface of the cells that carry the antigen (in this case, the HCV polyprotein). Peptides containing epitopes from the core regions of the virus have induced strong immune responses in mice. A peptide called HVR1 contains a neutralizing epitope, so it is a good target for a vaccine. This strategy has seemed to work in trials with chimpanzees. Unfortunately, this peptide is subject to mutations. *(www.medscape.com/viewarticle/410848_7)*

Recombinant Protein Subunit Vaccines: The first attempt to develop an HCV vaccine was by generating a recombinant protein subunit vaccine. Chiron used recombinant HCV E1 and E2 proteins in early vaccination studies. Results of these experiments showed that the vaccine did not protect any of

the chimpanzees when challenged with the virus, but self-limited infection occurred more frequently than in non-vaccinated animals. The results show that even though no sterilizing immunity was achieved, chronic infection might be prevented.

IV.3.1 CIGB-230, a DNA-vaccine candidate, is constructed from plasmid pIDKE2 that express HCV structural antigens and HCV core protein. The product is the result of a combined effort of the Center for Genetic Engineering and Biotechnology and of Heber Biotech.

CIGB-230 has been used in clinical trials. The Phase I trial produced antibodies, and 46% of the immunized patients cleared the virus. One-third of them produced cellular immunity against HCV, as well. In the Phase II trial, which lasted 48 weeks, the product was combined with IFN and products like RBV. Only the patients who received the CIGB-230 had satisfactory responses. Response depended on the number of doses and the timing in relation to the IFN therapy. Increases of neutralizing antibodies and of IFN-γ were linked to SVR. This combination is already in use in some countries.
(www.academia.edu/4095708/Recent_advances_in_Development_of_DNA_Vaccines_against_Hepatitis_C_virus)
(www.ncbi.nlm.nih.gov/pubmed/24415868 Jan 7 2014)

IV.3.2 GSK VACCINES
GlaxoSmithKline has acquired the vaccines from Chiron, Novartis and Okairos. First Chiron sold its vaccines to Novartis in 2006, and then Novartis sold its vaccines to GlaxoSmithKline in 2014.

- **GSK/Chiron Prophylactic Vaccine**
  Chiron began developing two possible HCV vaccines, including a recombinant vaccine and a second-generation DNA vaccine, to induce an immune response. They were to be used in combination with pegIFN/RBV. (*www.chironvaccines.com/company/vaccines_hepatitis_c_vaccine.php).*

  Chiron provided HCV antigens, and CSL provided its Iscomatrix technology, ISCOM, an immune stimulating complex, intended to improve the immune response induced by vaccines. ISCOM is made from the bark of the *Quillaia saponaria molina* tree, mixed with lipids. *(www.csl.com.au/)* GSK has developed other adjuvant systems similar to ISCOMs, such as AS01 and AS02, for example.

  A Phase II trial at Saint Louis University treated 200 patients, using a different adjuvant (a drug to help the body respond better to vaccines). The research was sponsored by the National Institutes of Health and Chiron Corp. *www.medicalnewstoday.com/articles/42781.php)*

- **GSK/Okairos-Novartis T-cell Vaccine**
  This still-developing vaccine is the result of the efforts of many collaborators. At this time, the vaccination is expected to include two vaccines.

  The "prime" vaccine uses ChAd3, an adenovirus developed by Okairos (now part of GSK) and Oxford researchers, and a modified Ankara vector (MVA). These researchers have improved on vaccines that use only an adenoviral vector, by using a simian adenoviral vector called ChAd3. This ChAd3-induced T-cell, boosted with MVA, called "the prime-boost vaccination strategy", was used in the study, managed by Oxford University and colleagues from Okairos and Stanford University. It was carried out at two sites in the US, using 15 healthy IV drug users. The vaccine was given in two steps. The vaccine showed good results in this first-ever study in humans, inducing immunity against HCV, much like what occurs in spontaneous clearance of the virus in 25% of those infected.

  The first vaccine is followed 8 weeks later by a second vaccine, a type of modified Ankara vector (MVA) that is effective against the NS3, NS4, NS5A, and NS5B proteins of GT1b of the virus, which strengthens the immune system so it can get rid of the virus.

  The volunteers' responses, similar to those produced by people who spontaneously clear the virus, were sustained over 6 months. The researchers are waiting for results of the efficacy studies. A Phase II trial is underway, with efficacy results expected in 2015-2016.
  (www.ox.ac.uk/news/2014-11-05-new-vaccine-generates-strong-immune-response-against-hepatitis-c)

More Phase I trials are underway in both healthy and HCV+ subjects at Oxford, together with the Jenner Institute and the Peter Medawar Building for Pathogen Research, and is supported by the Medical Research Council of the UK and the NIHR Biomedical Research Center of Oxford.
(www.expmedndm.ox.ac.uk/tgu/principal-investigators/researcher/ellie-eleanor-barnes)

IV.3.3 CERC T-CELL VACCINE
Michael Houghton is the Chair at the La Ka Shing Institute of Virology at the U of Alberta, where he and John Law are working on the CERC program (Canada Excellence Research Chairs). He was also on the team that discovered HCV in 1989. He has developed a vaccine shown to be effective in all known HCV genotypes. His work, done mostly when he was with Novartis, has taken over 10 years. He was funded

by the National Institutes of Health. He used a vaccine on humans at his lab at the U of A, using a single strain of the virus. He and his team at the U of A are awaiting results of the Okairos T-cell vaccine studies. "We are developing a 2nd-generation HCV vaccine that elicits broad cross-neutralising antibodies and broad cross-reactive T cell responses."
(http://uofa.ualberta.ca/news-and-events/newsarticles/2012/02/vaccinediscoveredforhepch)
(www.ammi.ca/media/53295/thurs_april_4_-_m._houghton.pdf)

IV.3.4 E1E2-MF59 VACCINE
(HCV E1E2 protein + MF59 as an adjuvant)
In order to develop a vaccine to induce T 30 cell and antibody responses, the researchers constructed "adenoviral vectors expressing full-length and truncated 31 E1E2 envelope glycoproteins from HCV genotype 1b" *(http://jvi.asm.org/content/early/2014/02/27/JVI.03574-13.full.pdf)*

Researchers (including Michael Houghton--see U. of A. section above) analyzed immune responses during re-treatment of 78 GT1a/1b previously-treated patients in a Phase Ib study. They were randomly assigned to vaccine, pegylated interferon and ribavirin (PR) for 48 weeks, or the PR + vaccine combination (PR+V). The patients received a total of eight IM injections, one every 4 weeks, for a total of 8 injections. 4 PR+V patients achieved SVR, as did 2 PR patients. The vaccine, combined with PR was safe and created "E1E2 neutralizing antibodies and specific CD4 + T-cell proliferation." The subjects who went through this Phase I trial had a better viral load response to Phase II. It is hoped that combining this vaccine with the new DAAs will protect against re-infection.
(www.ncbi.nlm.nih.gov/pubmed/24750327) (www.ncbi.nlm.nih.gov/pubmed/24750327)

IV.3.5 TG4040 VACCINE
Transgene's TG4040 is a recombinant poxvirus therapeutic vaccine that uses the MVA virus as a vector to carry encoded HCV proteins NS3, NS4 and NS5B. The MVA vector is already used with the smallpox vaccine.

Results from their 153-patient Phase II trial (HCVac study) in treatment-naïve GT1 subjects, were presented at the AASLD 2011 conference. The vaccine was well-tolerated, and when combined with pegIFN/RBV, produced SVR12 rates of 64% vs 30% early viral suppression with pegIFN/RBV alone. The drug was given in subcutaneous injections. Data showed that TG4040 combined with PegIFN/RBV resulted in improved SVR24 rate, additional immunogenicity, and specific T-cell and humoral responses, compared to PegIFN/RBV. This data was presented at EASL 2013. There were 3 cases of severe hematological side effects. All 3 patients recovered.
(www.transgene.fr.(*www.hivandhepatitis.com/hepatitis-c/hepatitis-c-topics/hcv-treatment/3400-aasld-recombinant-hepatitis-c-vaccine-tg404-shows-promise-in-phase-2-trial*
and www.euronext.com/en/content/transgene-present-new-data-tg1050-and-tg4040-treat-chronic-hepatitis-b-and-c-easl-2013)

Inovio Pharmaceuticals, Transgene and ChronTech Pharma have planned a trial to test a vaccination strategy called a repeat "boost" approach: an initial prime vaccine, then a boost of the same vaccine. This was to be tested in a Phase I trial, using different "prime and boost" vaccines and examining the different immune responses. The Phase I trial would use ChronTech's DNA vaccine with Inovio's electroportation device as the prime, and then TG4040 as the boost.
(www.proactiveinvestors.com/companies/news/13916/inovio-to-test-prime-and-boost-vaccine-strategy-with-chrontech-and-transgene-13916.html)

IV.3.6 AdCh3NSmut1 and MVA-NSMut Prophylactic HCV vaccine
This vaccine is being tested in 450 IV drug users who are HCV-negative. The trial began in March 2012 and will be completed in January 2016. There are two arms, and each has a stage I and II. 34 members of Arm A will receive an injection of AdCh3NSmut1 on day 0, and then 56 days later, if there was an immune response, 191 additional members will receive the second injection: MVA-NSMu. Arm B patients will receive a placebo, first 34 patients and then 191 more, as in Arm A. This trial is sponsored by National Institute of Allergy and Infectious Diseases (NIAID). Trial locations are U of C San Francisco (Tenderloin Clinical Research Center) and Johns Hopkins (Wood Clinic).
(https://clinicaltrials.gov/ct2/show/NCT01436357)

IV.3.7 TT-034 VACCINE
TT-034 is a ddRNAi-based therapeutic vaccine candidate. It targets HCV RNA at three separate sites, acting as if it were "triple therapy", giving the virus no chance to mutate. Once inside the liver cells, it makes its way to the nucleus and produces three separate RNAs that last as long as the cell's lifetime.

TT-034 should be able to both treat HCV infection and prevent reinfection, hopefully for years. Extensive pre-clinical trials have shown no adverse effects.

On January 5, 2015, Benitec Biopharma announced that their third patient was given a dose of TT-034 as part of their Phase I/IIa clinical trial, taking place at the Duke Clinical Research Unit at the University of California, San Diego. The first two patients have been declared clear of any treatment-related side effects by the Data Safety Monitoring Board (DSMB). This third patient received a higher dose than the first two. TT-034 is hoped to be a "one-shot" cure, but this latest dose is still below what is thought to be needed for that. The patient will be watched for 6 weeks, and will be examined for side-effects. If there are none, then the first two patients will be allowed to receive an additional dose, hopefully at the same time. There are several patients ready to take advantage of a positive outcome.
(http://hepatitiscnewdrugs.blogspot.ca/2015/01/benitec-advances-hepatitis-c-clinical.html)

On March 11, 2015, Benitec reported that their 4th patient had been dosed and the 5th patient is prepared. These patients will still not receive what is expected to be a full dose.
(*www.proactiveinvestors.com.au/companies/news/61197/benitec-biopharma-continues-clinical-trial-for-hepatitis-c-treatment-61197.html)*

IV.3.8 Autologous Dendritic Cell Vaccine
The University of Navarra, Spain, conducted a Phase I/II clinical trial numbered NCT02309086 in five HCV+ GT1b non-responders to IFN/RBV therapy. The treatment began in May 2011 and data collection was completed May 2013. The patients received 3 subcutaneous injections of different doses of autologous dendritic cells transduced with Ad-encoding NS3. No results have been posted.
(https://clinicaltrials.gov/ct2/show/NCT02309086)

IV.3.9 Vaxeal/CMC Hepatitis C Vaccine
A chart published in 2014 on their website indicates that Vaxeal has teamed up with China Medical City (CMC) in the development of a Hep C vaccine, showing their plans for a Phase I/II clinical trial in 2015. The company has kindly verified this.
(www.vaxeal.net/wp-content/uploads/2014/03/Executive-Snapshot-March-2014-Generic-Distribution.pdf)

IV.3.10 ChronVac
ChronVac is a therapeutic vaccine (given to people already infected with HCV, to reinforce their immune response). ChronVac-C® is also a "genetic vaccine", which means that, rather than just filling syringes with the vaccine, the vaccine's genetic code (DNA) is used, producing a vaccine to activate an immune response. *(www.alacrastore.com/storecontent/markintel/LIFE_SCIENCE_ANALYTICS-50217368)*

Data from a Phase I/IIa clinical trial of ChronVac-C was presented at the EASL Conference in 2009. *(www.natap.org/2009/EASL/EASL_32.htm)*
A small, encouraging study of PegIFN/RBV + ChronVac-C reported results in 2011. Surprisingly, 5 of the 6 patients had an SVR24, compared to the usual 40-45% for GT1 with standard therapy alone, or 60-70%, adding a protease inhibitor.
(http://hcvadvocate.blogspot.com/2011/03/unusually-high-cure-rate-recorded-after.html)

Results were announced April 2, 2014 for a small trial. The vaccine was combined with IFN/RBV in 17 patients, and results were compared to 12 patients taking only IFN/RBV. The ChronVac-C vaccine was given in 2 doses one month apart, administered with Medpulser. Side effects were lower in the vaccine group. 71% in the vaccinated group achieved SVR12, compared to 58% in the non-vaccinated group, which wasn't considered to be a significant improvement.
(http://chrontech.se/english/news/press_releases?releaseid=758513)
In July 2013, ChronTech sold its hepatitis technologies to Avac Pharma, but bought them back in September 2014. Hopefully we will hear news from them soon.
(http://chrontech.se/english/news/press_releases?releaseid=792590)
(http://chrontech.se/english/news/reports?releaseid=940772)

IV.3.11 INO-8000/VGX-6150
In October 2013, Innovio, together with VGX International (Korea) announced a Phase I trial in Korea, to begin in 2014. Innovio is also a long-time partner of ChronTech. The drug will be tested in 18 HCV+ patients who are previous standard-treatment non-responders. INO-8000/VGX-6150 is designed with Innovio's SynCon process, for genotypes 1a and 1b. It targets the NS3 (protease), NS4A, NS4B, and NS5A proteins.
(http://ir.inovio.com/news/news-releases/news-releases-details/2013/Inovio-Pharmaceuticals-Therapeutic-Vaccine-for-Hepatitis-C-Enters-Phase-I-Clinical-Trial/default.aspx)

The clinical trial is sponsored by GeneOne Life Science, Inc., and is scheduled to end in August 2015. The trial will use 3 doses of the vaccine, in the form of IM injections, 4 weeks apart.
(http://en.wikipedia.org/wiki/Hepatitis_C_vaccine) (https://clinicaltrials.gov/ct2/show/NCT02027116)

IV.3.12 KURUME PEPTIDE VACCINE
Researchers from Kurume University, Japan, conducted a Phase I trial of a personalized peptide vaccine (PPV) in 12 genotype 1b non-responder patients. The patients' T-cells and plasma IgG were tested, and 4 peptides were chosen as possible candidates. Only the peptides causing a reaction were given twice a week at different doses. There were no severe side effects. There was a good immune reaction to at least one of the peptide candidates after the 7th dose. ALT was reduced in 5 patients, and viral load was reduced in 3 patients after the 14th dose.
(Vaccine, *2007;25(42):7429-35 www.newsrx.com/article.php?articleID=788039&f=wu22 NOV 19, 2007*)

Between December 2000 and May 2013, a clinical trial was conducted to test the safety and immune responses of PPV for 42 Hep C patients with advanced liver cancer (HCC). Up to four HLA-matched peptides were chosen according to prior responses to 32 different peptides, including one HCV-derived peptide and 31 peptides from 15 different tumor-associated antigens (TAAs). The patients were given a subcutaneous injection once a week for 8 weeks. Other than some skin reaction at the injection site, no other serious side effects were apparent. Peptide-specific cytotoxic T cell (CTL) responses before vaccination were seen only 3 of 42 patients, but were apparent in 23 of 36 patients tested after vaccination. (CTLs kill cancer cells) Peptide-specific IgG responses were also higher in 19 of 36 patients. The researchers recommend more PPV studies for HCV-positive advanced HCC, based on these promising results. *(www.hindawi.com/journals/jir/aa/473909/)*

IV.3.13 OTHER VACCINES – NEW, DISCONTINUED, NO NEWS, ETC
Much valuable research done on possible Hep C vaccines has been handed over to other companies and/or incorporated into new strategies. This may have happened to those below.

- **Adelaide University's DNA vaccine NEW**
  Adelaide University researchers have developed a therapeutic, DNA vaccine for HCV and HIV patients, which would also be a preventative vaccine. Most vaccines target the muscles, but this one injects DNA into the skin, where there is a better proportion of dendritic cells (a type of white blood cells). This vaccine stimulates the body's immune system. They plan to test in human trials in about 40 HCV+ people in 2015, with hopes that it will be available for use in 5 years.
  http://www.abc.net.au/pm/content/2014/s3971278.htm

- **VIDO Vaccine NEW**
  Researchers at the University of Saskatchewan's InterVac International Vaccine Centre, located next door to VIDO (Vaccine and Infectious Disease Organization) hope they have found a vaccine for hepatitis C that will also help those already infected (therapeutic vaccine). To make the vaccine, researchers took dendritic cells (key immune cells) from mice, exposed them to one of the most common proteins occurring in all HCV genotypes, and treated the cells with an immune stimulator. They hope that by returning the activated cells, they can "teach" the original cells to activate an immune response. Researchers used another virus in the mice to simulate HCV. VIDO's Hep C project will develop a DNA-based regime, using the HCV non-structural protein-3 (NS3) as a target for the dendritic cell-based vaccines. In encouraging lab trials, mice were injected with inactivated HCV particles. Their serum was then injected into samples of HCV+ human liver cells, suppressing the virus. *Funding has been renewed for these studies through 2015.*
  (www.vido.org/research/vaccine_dev/hepatitis.php www.vido.org/Introducing_intervac/index.php and The StarPhoenix, Jan 11, 2006)
  (http://webapps.cihr-irsc.gc.ca/funding/detail_e?pResearchId=5067514&p_version=CRIS&p_language=E&p_session_id=)

- **Intercell's vaccine (IC41) NO NEWS**
  IC41 was developed in partnership with Novartis. A Phase II trial enrolled 50 naïve genotype 1 patients who received 8 injections of the drug bi-weekly for 14 weeks. In the second week after the last injection, a 0.2 $\log_{10}$ viral load drop was observed. The drop increased with each application. In patients with a high viral load, there was an average drop of 0.4 $\log_{10}$.
  (www.biopharma-reporter.com 21/08/2007)

  Intercell and Romark worked together on a European Phase II clinical trial combining Intercell's IC41 with Romark's Alinia (nitazoxanide). In a previous trial in 50 treatment-naïve genotype 1 patients with high viral loads, the results showed SVR24 of over 75%.

(www.intercell.com/main/forbeginners/news/news-full/article/intercell-and-romark-join-forces-in-combining-therapies-against-hepatitis-c/ Oct 21, 2010) GSK has bought Novartis' vaccines.

•Chimigen NO NEWS
The Chimigen HCV vaccine candidate is a dendritic cell-targeted vaccine produced by ViRexx (Edmonton, AB)
(www.genengnews.com/news/bnitem.aspx?name=1124489XSL_NEWSML_TO_NEWSML_WEB.xml 12/12/2005)

Trial results showed that the vaccine produced HCV antigen-specific T-cells. The vaccine uses an insect cell expression system, giving it special immunological characteristics.
(http://cnrp.ccnmatthews.com/client/virexx/release.jsp?actionFor=581279)

In May 0f 2007, ViRexx announced that it would collaborate with the National Research Council Canada's National Institute for Nanotechnology (NINT) and Defence Research and Development Canada, Suffield (DRDC Suffield). Researchers at NINT planned preclinical studies of the Chimigen HCV prophylactic and therapeutic vaccine candidate. *(www.bioalberta.com/news_details.asp?ID=69)* Chimigen was sold to Akshaya Bio. Sadly, there is no news since 2013 on their website, nor on Paladin Labs' site (Paladin acquired ViRexx in 2008).

•Toray Vaccine NO NEWS
Toray worked with the National Institute of Infectious Diseases (NIID) and other institutions to develop a vaccine for hepatitis C. One of the vaccine candidates prevented 66% of genotype 1a infections, the most common genotype in Japan, and 85% of genotype 2a infections. The company found a way to incubate the virus in large quantities, to concentrate and refine them. NIID discovered a cell that is able to incubate the virus.
(www.hepatitis-central.com/mt/archives/2007/09/future_hcv_medi.html 28 August 2007 and www.eiu.com/index.asp?layout=ib3PrintArticle&article_id=1794748164&printer=printer&rf=0 Aug 11, 2009)

•PEV2A/PEV2B (Prophylactic, therapeutic) **NO NEWS**
Pevion Biotech combined the PeviPRO (induces T cell response) and PeviTER (induces CTL response) platforms. This Phase I HCV vaccine trial of Pevion's HCV vaccine, tested 4 Virosome-formulated peptides in 30 healthy volunteers, who were given escalating doses of the vaccine or a placebo. The trial #NCT00445419 ran from December 2006 to June 2008, in Switzlerland. No results were posted. (*https://clinicaltrials.gov/ct2/show/NCT00445419*) The company's website *www.pevion.com* is no longer functional, and there has been no news.

•Tarmogen (GI-5005) TERMINATED
Globe Immune's GI-5005 is a recombinant Saccharomyces Cerevisiae expressing an HCV NS3-Core Fusion Protein, designed to cause HCV-specific T-cell responses. The Phase II trial enrolled 140 genotype 1 patients. 74% were treatment-naïve. Patients received pegIFN/RBV with or without GI-5005. GI-5005 was injected subcutaneously once a week for five weeks, then once every 2 weeks, for a total of 12 weeks, followed by pegIFN/RBV plus monthly injections of GI-5005 for 48 weeks. The Phase II trial of GI-5005 was terminated due to side effects and abnormal lab tests in some of the subjects and an investigation is underway.
(www.biospace.com/news_story.aspx?StoryID=237817&full=1 10/26/2011)

PART V: PERSONAL CHOICES

V.1.0 NUTRITION

V.1.1 WHAT DO I DO ABOUT NUTRITION?
Many dieticians and medical experts working with hepatitis C feel that except for alcohol, diet has little direct effect on the activity of the virus and the outcome of long-term infection. There is no specific dietary approach that can be recommended which can guarantee to alter the outcome of any particular liver disease. This isn't to say that modifying your diet has no effect. Nutrition and the liver are interrelated in many ways. Everything we eat, breathe and absorb through our skin must be refined and detoxified by the liver, special attention to nutrition and diet can help keep the liver healthy.

85-90% of the blood that leaves the stomach and intestines caries important nutrients to the liver where they are converted into substances the body can use.

Bitter foods are useful as they stimulate the digestive process and assist the liver. Eating salads containing bitter leaves such as dandelion or chicory 10-15 minutes before meals is a long-standing European recipe to aid the liver.
In Taiwan, a diet high in vegetables was associated with a lowered risk of liver cancer in people with

hepatitis C.

Vegetable juices have a particular nature that helps lessen the bloated and stagnant feelings often associated with liver conditions.
Vegetable juices act to flush out the body and relieve some of the symptoms that people with liver disease experience, such as heaviness and lethargy. The juice of carrots, beets, cucumber, spinach, celery, wheat grass and parsley are all used in liver cleansing fasts, and are generally thought to be good for livers.

Drinking 2-3 liters of water each day is universally recommended for good health, but also protects against lymphatic congestion, which would put further strain on the liver.
As for diets in particular, *The Alternative Medicine Guide* says:
Jonathan Wright, M.D. recommends a diet low in protein to minimize stress on the liver—a whole foods diet that follows a hypoglycemic regime, of small meals throughout the day, avoiding stressor foods such as refined sugars, alcohol, and caffeine. Consume plenty of filtered water. Drinking fresh lemon juice water every morning and evening followed by vegetable juice is one of the most therapeutic regimes for the liver. Do this consistently for two to four weeks and then several mornings a week for several months and whenever liver symptoms reoccur. Have lots of vegetables each day. Ideal is at least one salad and one meal of steamed or lightly sautéed vegetables per day. Grains that are easily digestible, such as millet, buckwheat, and quinoa are very good.

According to the *Encyclopedia of Natural Medicine*:
A natural diet, low in natural and synthetic saturated fats, simple carbohydrates (sugar, white flour, fruit juice, honey, etc.), oxidized fatty acids (fried oils) and animal fat, and high in fiber is recommended.
And this from the *Canadian Journal of Health and Nutrition:* "Natural substances to help your liver detoxify are as close as your kitchen cupboard. Eating foods rich in lecithin (soybean), essential fatty acids (salmon, flax oil) and green leafy vegetables rich in fiber and antioxidants like vitamins C and E, are all gourmet cuisine for your liver. Lowering your intake of saturated fats, refined carbohydrates and animal protein and avoiding excessive amounts of alcohol are other recommendations that are good both for your liver and overall body health. Dandelion root and artichoke are both excellent spring time dietary condiments that are very helpful in improving liver bile flow. In addition to these food choices, supplements like L-methionine are an excellent choice for a congested liver. This sulfur-containing amino acid not only improves bile flow but also helps protect liver glutathione. Glutathione peroxidase is one of the body's major detoxification enzymes and is in part defended by methionine during a toxic challenge to the liver..." The article goes on to describe the function of Milk Thistle.

It concludes that the most potent substances for protecting the liver are Milk Thistle, Dandelion and L-methionine. L-methionine is classed as a "supplement," and Milk Thistle and Dandelion as "botanical medicines." - "Protecting and Enhancing Liver Function," by Ronald G. Reichert, ND, *Alive: Canadian Journal of Health and Nutrition* (#161, March 1996): pp. 14-16.

THE MEDITERRANEAN DIET
The benefits of the Mediterranean Diet are more than just losing weight, according to a study done at St. Vincent's Hospital in Melbourne. They studied 12 patients without diabetes with non-alcoholic fatty liver disease (NAFLD), and showed that the diet improved their liver health even with no weight loss. The participants had a big improvement in insulin sensitivity, thus lowering their risk for Type 2 diabetes, possibly indicating that the diet improves metabolism. Even 6 weeks on the diet could lower liver fat by 39%, compared with "a current recommended healthy diet". Until now, there have been few studies for NAFLD, which causes fat to be stored in the liver, and the only suggestion has been for patients to lose weight. NAFLD can be discovered by testing liver enzymes, by ultrasound, or by doing a biopsy.
(www.aasld.org/LM2011/PRESS/Pages/pressfive.aspx Nov 7, 2011. More info:
http://en.wikipedia.org/wiki/Mediterranean_diet)

V.1.2 ARE THERE FOODS TO AVOID?

PEANUTS: Some foods, especially peanuts, contain aflatoxins, a mould which increases the chance of liver cancer.
RAW SHELLFISH: *Vibro vulnificus*, a bacteria, can be contracted by eating raw oysters, etc. Shellfish, if uncooked, can be very dangerous for people with liver disease. Either avoid or be careful that the shellfish you eat is well-cooked.
SATURATED FATS: It's generally best to keep fats at a minimum.
Many people complain of increased pain in the liver area after eating high fat meals. With saturated fats, the liver must work harder than normal to neutralize their harmful effects.
GRAPEFRUIT: Generally, grapefruit is great for you. Naringenin, an ingredient in grapefruit, can cut levels of bad cholesterol, and seems to stop the Hep C virus from "hitching a ride" between blood cells, cutting transmission between cells by 80%.

(www.timesonline.co.uk/tol/life_and_style/health/article3902438.ece May 10, 2008)
It has been discovered that grapefruit juice blocks some enzymes in the small intestine that destroy many medications, preventing the body to absorb them. When the enzymes aren't blocked, the patient gets more of the medication than planned, and sometimes this can be dangerous. If you are taking one of the DAAs boosted with ritonavir, for example, you could be affected by grapefruit. You can see more here: *http://en.wikipedia.org/wiki/Grapefruit%E2%80%93drug_interactions*

V.1.3 NUTRITION AND CIRRHOSIS

Many chronic liver diseases are associated with malnutrition. One of the most common of these is cirrhosis. Cirrhosis refers to the replacement of damaged liver cells by fibrous scar tissue which disrupts the liver's important functions. Cirrhosis occurs as a result of excessive alcohol intake (most common), common viral hepatitis, obstruction of the bile ducts, and exposure to certain drugs or toxic substances. People with cirrhosis often experience loss of appetite, nausea, vomiting and weight loss, giving them an emaciated appearance.

Diet alone does not contribute to the development of this liver disease. People who are well nourished, for example, but drink large amounts of alcohol, are also susceptible to alcoholic disease.

Adults with cirrhosis require a balanced diet rich in protein, providing 2,000 to 3,000 calories a day to allow the liver cells to regenerate. However, too much protein will result in an increased amount of ammonia in the blood; too little protein can reduce healing of the liver. Doctors must carefully prescribe the correct amount of protein for a person with cirrhosis. In addition, the physician can use two medications (lactulose and neomycin) to control blood ammonia levels. Persons with cirrhosis often experience an uncomfortable buildup of fluid in the abdomen (ascites) or a swelling of the feet, legs, or back (edema). Both conditions are a result of portal hypertension (increased pressure in the veins entering the liver). Since sodium (salt) encourages the body to retain water, patients with fluid retention can cut their sodium intake by avoiding such foods as canned soups and vegetables, cold cuts, dairy products, and condiments like mayonnaise and ketchup. In fact, most prepared foods contain liberal amounts of sodium, while fresh foods contain almost no sodium at all.

The best-tasting salt substitute is lemon juice. In general, reducing meat protein, which is the most toxic protein to the brain, and substituting vegetable protein is advised when cirrhosis is present.

V.1.4 CAFFEINE AND OTHER STIMULANTS

In the book *Healthy Healing* by Linda Rector-Paige, N.D., PhD, she says: "...Some of the health problems of caffeine are...well known—headaches and migraines, irritability, stomach and digestive problems, anxiety, and high blood pressure. As an addictive stimulant, it works as a drug, causing jumpiness and nerves, heart disease, heart palpitations. Caffeine in excessive amounts can produce oxalic acid in the system, causing a host of problems waiting to become diseases. It can lodge in the liver, restricting proper function, and constrict arterial blood flow.
It leaches out B vitamins from the body...It depletes some essential minerals, including calcium and potassium...however the carcinogenic effects often blamed on caffeine are now thought to be caused by the roasting process used in making coffee, tea and chocolate.
Since decaffeinated coffee has been implicated in some forms of organ cancer, conclusions are being drawn that caffeine is not the culprit—the roasted hydro-carbons are..."
Unfiltered coffee raises serum cholesterol and liver enzymes. One study in the British Medical Journal shows that cafetiere (brewed, unfiltered) coffee raises serum LDL cholesterol levels and serum concentrations of alanine aminotransferase (ALT). Cafetiere coffee is made by pouring boiling water over ground coffee in a container with a sieve plunger. Dr. Rob Urgert and others at Wageningen Agricultural University in the Netherlands observed that unfiltered coffee raised alanine aminotransferase 80% above baseline levels relative to filtered coffee. Once the subjects stopped drinking cafetiere coffee, the liver enzyme and LDL cholesterol concentrations returned to baseline levels. The Dutch investigators write that "Daily consumption of five to six cups of strong cafetiere coffee affects the integrity of liver cells..." and they attribute the increases in cholesterol and alanine aminotransferase concentrations to the diterpenes cafestol and kahweol that are abundant in cafetiere. - (*BMJ* 1996;313:00-00)
A study done by the Tohoku University Graduate School of Medicine in Sendai, Japan found that coffee consumption reduced the risk of liver cancer. Another study by the National Cancer Center in Tokyo says that five or more cups of coffee a day cut the chance of liver cancer in half. It was noted that these studies were not performed on HCV patients. It is not known if they will receive the same benefits from coffee. *(J Cancer* 2005 Aug 10;116(1):150-4, *J Hepatol* 2005 apr;42(4):528-34)
www.sciencedirect.com/science/article/pii/S0016508511002733)

The HALT-C study found that drinking coffee—but not tea—was somehow linked to a greater chance of successful treatment with pegIFN/RBV. It may be because coffee seems to protect the liver and detain the progression of the disease, but why would it affect treatment? The study used low-dose pegIFN as maintenance therapy for 885 non-responders with fibrosis or to see if it could slow the progression to

cirrhosis. The patients filled out questionnaires, which included coffee consumption. Those who drank at least 3 cups a day had twice as much of a drop in their viral load compared to those who didn't drink coffee, and 60% of them were able to fend off anemia and take full doses of ribavirin. Decaffeinated coffee produced the same results, but neither black nor green tea was beneficial.
(www.sciencedirect.com/science/article/pii/S0016508511002733)

V.1.5 SALT

Those who are prone to episodes of ascites should try to maintain a very low sodium diet (less than 3 gr/day).

V.1.6 WATER

Thanks to Alan Franciscus for this important reminder

We've all been told that it is essential for proper health maintenance to drink at least 8 glasses of water (8 oz. each glass) every day. This is especially true for those of us with hepatitis C and, if you are on treatment with interferon and ribavirin, it is even more important to drink plenty of water. In fact, you should try to drink as much water as possible even if you are not thirsty. This will help with the many potentially nasty side effects that may be experienced while on treatment.

The exception to this rule is the person who has ascites (accumulation of fluid in the abdominal cavity), in which case a medical professional will instruct you on the correct diet and fluid intake.

Drinking at least 8 glasses of water can be a problem, but it is not as hard as it appears. Many people fill containers with filtered water so they can track the exact amount of water they drink daily. Frequently, I buy bottled water to take with me when I am on the go. I refill these bottles with filtered water every morning to keep track of the amount I consume daily.

Remember, you are going to have to urinate much more frequently and want to make sure you are near a restroom. If you know that you will not have easy access to a bathroom, you may want to stop drinking an hour or so before an outing.

Even with these obstacles, you will find that the health benefits of drinking large amounts of water greatly outweigh the inconvenience and the frequent runs to the restroom.

Some of the health benefits of drinking adequate amounts of water include:

- Weight loss – suppresses appetite and metabolizes stored fat.
- Digestion – improves the digestive process and can relieve or prevent constipation
- Dry Skin – moisturizes the skin
- Body wastes and toxins – rids the body of wastes and toxins
- Body temperature – regulates body temperature to keep you cool in hot temperatures
- Nutrients – contains many essential nutrients
- Joints – lubricates and cushions joints
- Cancer – helps with preventing some cancers, such as colon and liver cancer

Remember to consume water instead of coffee or colas that contains caffeine. Beverages that contain caffeine deplete body fluids. In order to replace these lost fluids, you must drink two glasses (16 oz.) of water for every glass (8 oz.) of a beverage that contains caffeine. Additionally, make sure you check the content of the water. You should stay away from any water that contains sodium. (On the other hand, studies have shown that coffee may ward off liver cancer and seems to improve chances of responding to Hep C treatment).

So take that plunge. Drink WATER!

V.2.0 ALTERNATIVE OPTIONS

There have been few research trials to check the effectiveness of natural therapies, but many people report positive benefits. If you decide to use natural therapies, it's vital that you see a practitioner who is properly qualified, knowledgeable and well-experienced. It's also advisable to continue seeing your regular doctor or specialist. If a natural therapist suggests that you stop seeing your medical specialist or doctor, or stop a course of pharmaceutical medicine, **consider changing your natural therapist**. Ask searching questions of whichever practitioner you go to:

- Is the treatment dangerous if you get the prescription wrong?
- How have natural therapies helped people with hepatitis C?
- What are the side effects?
- Are you a member of a recognized natural therapy organization?
- How much experience have you had of working with people with hepatitis C?
- How have you measured the health outcomes of the therapy?

- How do you plan to help **me**?

Most typical health insurance will not cover alternative medical procedures, but that's beginning to change. Many alternative procedures are now covered under medical insurance in the states of Washington and Oregon, and it looks like it's a trend which is beginning to spread. Alternative Health Insurance Services of Thousand Oaks, California covers both allopathic and complementary/alternative treatments. Patients may choose any provider, M.D. or N.D., or D.O. or D.C.

Subscribers must meet a deductible of up to $1000, and the plan pays 80% of the first $5,000 eligible medical expenses in a year, then 100 percent thereafter, with a $2 million maximum. The plan includes prescription drug cards, with a $5 copayment, as well as "named partner" coverage for homosexual or non-married couples and their families. Alternative Health Insurance Services: 1-800-966-8467.)

Another plan is offered by American Western Life Insurance Co. in Foster City California: Prevention Plus. It covers a full range of alternative therapies. Enrollees use a naturopath as their primary care physician, or the gatekeeper who refers to other alternative practitioners. There is a $5 copayment for prescriptions, including herbal medicines. The company also has a 24-hour 800 Wellness Line staffed by naturopathic physicians, saving on doctor visits where possible. (American Western Life: 1-800-925-5323)

V.2.1 ALTERNATIVE TREATMENT

V.2.1a ACUPUNCTURE

Acupuncture is a form of medical therapy that involves inserting thin, solid needles into selective sites on the surface of the body. Recent studies have shown that HCV may be spread by acupuncture. Please make certain that your acupuncturist uses disposable needles and uses universal precautions. *(Visit http://en.wikipedia.org/wiki/Universal_precautions)*

V.2.1b CHIROPRACTIC

Chiropractic is a healing profession in which the spine, joints, and muscle tissue are manipulated in order to restore the proper function of the nerves. The chiropractor does not use drugs or surgery in treating diseases.

V.2.1c ENERGY HEALING (Reiki, Hands of Light, Touch Therapy, etc.)

The gentle energy of Reiki (ray-kee) is an ancient spiritual practice which enhances natural healing processes. Reiki is called by various names in different parts of the world: "prana" in India, "qi" or "chi" in China, "spirit" in Western traditions, etc., and simply translates as "life force". Reiki is a means of adding more energy to our "life force" battery to help "jump start" the healing process. A Reiki treatment is essentially the "laying on of hands," an ancient technique common to many spiritual traditions. In a typical Reiki treatment, the client lies down (fully clothed) on a padded treatment table. Energy is transferred to the client through the hands of the practitioner in a sequence of standardized positions where the hands are placed. In each position, the hands are simply rested on the client for 3-5 minutes. A full treatment usually takes about an hour. A Reiki treatment is a spiritual practice because it works directly with energy, or "spirit." There is no pressure applied and no manipulation of tissues (as in massage, for example).

V.2.1d REFLEXOLOGY

Reflexology is a specialized type of massage treatment which works on the theory that reflex areas on the feet and hands are linked to other areas and organs of the body. It is felt that blocked energy, congestion, or tension in one part of the body (generally the foot or hand) mirrors congestion or tension in a corresponding part of the body. Thus, when you treat the big toes there is a related effect in the head, and treating the whole foot can have a relaxing and healing effect on the whole body.

V.2.1e OZONE THERAPY

This is an experimental treatment, popular mostly in Europe, in which the blood is removed from the body, has ozone bubbled through it with the intention of killing the virus, and then the blood is returned to the body. I personally do not believe this is a safe practice, and would strongly recommend against it. Ozone bubbled through blood to kill viruses in vitro damages the living cells in it as well as removing the viruses. Ozone injected into your veins or aerated through your colon is a poison and has the very real potential of killing you rapidly. Ozone is very reactive and not stable in the lower atmosphere and does not remain ozone very long in any reactive media.

There have been reported cases of patients acquiring hepatitis C from improperly sterilized equipment

used during ozone therapy. ("Transmission of Hepatitis C by Ozone Enrichment of Autologous Blood," *Lancet*, *1996;347:541*)

V.2.1f HOMEOPATHY
Homeopathy offers several remedies for the treatment of hepatitis. They are Mercury and Natrum Sulfuricum. Natrum Sulfuricum has clinically been found a valuable remedy for spinal meningitis, and has also found to be quite useful as a liver remedy as well.

Kalium Phosphoricum, Gelsimium, Picricum Acidum, Strychinum, Oxalicum Acidum and *Zincum Phosphoricum* are said to be useful for peripheral neuropathy related to hepatitis C. (*Thanks to Dr Naseem Iqbal Ghumman, B.Sc, D.H.M.S,R.H.M.P. for this information).*

Homeopathy has people for and against it, and they feel very strongly about their beliefs. We suggest you do some investigation and check with your doctor before trying it. Try these sites:
Easy to understand explanation about what homeopathy is: *www.1023.org.uk/what-is-homeopathy.php*

Pro-homeopathy: *www.homeopathy.ca/ and http://news.nationalpost.com/2013/01/28/karen-wehrstein-homeopathy-offers-hope/*

Anti-homeopathy: *www.theguardian.com/lifeandstyle/2015/mar/11/homeopathy-not-effective-for-treating-any-condition-australian-report-finds*

V.2.1g TRADITIONAL CHINESE MEDICINE (TCM)
We feel it important to caution the reader about Chinese medicines. We know many persons who have found TCM to be very helpful, but there have been many instances of unscrupulous preparation of Chinese medicinal compounds, where herbs and substances other than those indicated were used in the preparation. In some cases this has led to death. Please seek out a reputable practitioner. If possible, get the names of the ingredients in English and check them out for safety. Always consult with your doctor first.

The following is from ("Complementary and alternative medicine in chronic liver disease," Hepatology September 2001 Volume 34 Number 3)

TCM has been practiced for roughly 2 millennia, with comprehensive records of Chinese medical theories dating back to 221 BC. CTM comprises multiple forms of ritualistic healing practices. These include the relatively well-known practices of acupuncture and herbal therapy and the lesser-known moxibustion (dermal counter-irritation therapy), massage, and exercise therapy (Qi Gong). Chinese herbal therapy comprises over 100,000 recorded treatments, roughly 80% being combination or herbal mixtures. Most herbal mixtures comprise 4 to 5 herbs with 1 to 2 major pharmacologically active compounds (King herb), the remaining herbs playing a "helper function," such as reducing toxicity, promoting delivery to the target site, or working synergistically with the "King."

Regarding chronic liver disease, a limited number of mixtures (approximately 76) have been identified by screening a Traditional Oriental Medicine Database (Tradi/Med DB). A hepatoprotective extract with the highest potency and the lowest toxicity is the Plantago asiatica seed, the active component being aucubin. Aucubin appears to inhibit hepatitis B virus (HBV) replication in vitro and in animals (100 mg/kg daily for 1 month). Its use in a human trial, 10 mg/kg administered intravenously for 4 weeks, led to a 10% to 40% decrease in serum HBV-DNA levels that returned to pretreatment values after stopping therapy.

A second combination of 10 herbs, termed "Herbal Medicine 861 (HM861)," was tested for antifibrotic activity in 3 controlled clinical trials encompassing 107 patients with hepatitis B. ALT levels fell into the normal range in 73% of patients, while spleen size, portal pressure, and serum procollagen peptide and laminin levels decreased in 53%. Liver biopsies, 6 months post-treatment, showed reductions in fibrosis and inflammatory infiltrates and quantitative decreases in tissue hydroxyproline. All patients remained hepatitis B surface antigen (HBsAg) positive. In vitro studies using human stellate cells and in vivo studies using animal models of fibrosis (CCl4 and albumin induced) showed that HM861 inhibited stellate cell activation by blocking cyclin/cyclin-dependent kinase activity in the cell cycle, and that fibrotic tissues were remodeled, with revascularization of liver sinusoids. Transforming growth factor and collagen type I, III, and IV gene transcripts were reduced while matrix metalloproteinase I was increased, suggesting a reversal of early stages of cirrhosis through the correction of imbalance in the dynamics of synthesis and degradation of the extracellular matrix.

CH-100 is a formulation of 19 different herbs developed for treatment of liver disease. In a double-blind, placebo-controlled trial involving patients with hepatitis C, treatment with the product was associated with a significant reduction in ALT levels, although no treated person cleared the virus. NCCAM is currently supporting a study of a 10-herb combination, referred to as 3AR. The trial will assess safety

and adverse events, as well as symptoms of fatigue, quality of life, liver function, and HCV-RNA levels in patients who do not qualify for standard therapy of hepatitis C. Thus, there is increasing interest in conducting rigorous testing of candidate CTM compounds (1) as alternatives to standard treatment, (2) to augment conventional treatments, or (3) to ameliorate the side effects of current therapies.

A very good overview of TCM and HCV can be found in Matt Dolan's book, *The Hepatitis C Handbook.*

V.21h RETICULOSE
Patients with Hep A and 18 patients with Hep B were treated with reticulose. Nine patients with Hep A and 17 patients with Hep B were given a placebo. The treated patients received reticulose for 15 days. Based upon prothrombin times, serum bilirubin, white blood cell count, and clinical observation, reticulose-treated patients appeared to show improvement. The bilirubin levels of 83% of patients with Hep B were in the normal range in 30 days. None of the patients given placebo was within normal range in 30 days. Of Hep A patients treated with reticulose, all showed normal bilirubin after 30 days. Of patients with Hep A taking a placebo, only 22% were in normal range after 30 days. In all of the reticulose-treated patients, the white blood cell count showed significant increase, indicating the immune system was stimulated. In all of the reticulose-treated patients, prothrombin times returned to normal range promptly while the controls did not. The results appear to demonstrate improvement in the patients treated with reticulose, especially those with Hep B. Further study is indicated. (*www.hepcprimer.com/inf/combos.html#G* December, 1992)

V.2.2 ALTERNATIVE MEDICINE: SUPPLEMENTS
WARNING: An investigation released on February 17, 2015 by the New York State Attorney General's office reported that GNC, Target, Walmart and Walgreens were ordered to stop selling their supplements, which did not contain those on the label, and there were other substances that were found, such as wild carrot, citrus, rice, beans, pine, citrus, houseplants, and other fillers, and weren't listed. That could be dangerous for people with allergies. One product had only 4% of the ingredient listed. Herbal substances are often not regulated. How do you know which ones to trust? There are websites with information, but many require a subscription. Consult with your doctor, especially if you are taking HCV treatment!
(www.ag.ny.gov/press-release/ag-schneiderman-asks-major-retailers-halt-sales-certain-herbal-supplements-dna-tests)

V.2.2a KNOWN FOOD-HERB-DRUG INTERACTIONS

Although the area of herb-drug interactions is under-researched, there are some interactions we do know about.

Echinacea, if used for more than eight consecutive weeks, could cause liver toxicity and should not be used with drugs such as anabolic steroids, amiodarone and methotrexate which are toxic to the liver as the effect may be additive.

Evening primrose oil and borage are contraindicated in patients taking anticonvulsants (e.g., clonazepam). Immunostimulants such as echinacea and zinc should not be given with immunosuppressants such as corticosteroids (like prednisone) and cyclosporine and are contraindicated in patients suffering from rheumatoid arthritis, systemic lupus erythematosus and autoimmune hepatitis.

Feverfew, garlic, ginger, ginseng, and ginkgo biloba all affect bleeding time and should not be taken by patients using warfarin or by patients that have decreased platelet counts.

Feverfew is most commonly used for the treatment of migraines. Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin or ibuprofen (Motrin, Advil) may reduce the effectiveness of feverfew. It can also inhibit platelet activity and should not be taken together with blood thinners such as Coumadin. Feverfew contains tannin, which has the ability to inhibit iron absorption, and should not be used for longer than four months without medical supervision. The recommended dosage is 125 mg daily; each dosage unit should contain at least 0.2% parthenolide.

Garlic: Most recent uses for garlic focus on its ability to treat high cholesterol and high blood pressure. Garlic can increase the risk of bleeding and should not be used concurrently with blood thinners. It has been reported to induce heartburn and flatulence, sweating, lightheadedness and allergic reactions. The German Commission E (Germany's equivalent to the FDA in the United States) recommends a dosage of 4 g of fresh garlic daily.

Ginger is often recommended for motion sickness, nausea and for loss of appetite. It has also been shown to prolong bleeding time and its use with aspirin or Coumadin should be avoided. Excessive

consumption of ginger may also interfere with cardiac and anti-diabetic therapy. It is usually well tolerated but may cause stomach upset or heartburn in some people. For motion sickness it is taken one hour before traveling. The total daily dose is 2-4 g.

Ginkgo biloba is one of the most popular plant extracts in Europe and has recently received approval in Germany for the treatment of dementia. There have been reports of spontaneous bleeding in people taking ginkgo and again, it should not be used with blood thinners. People who take anti-convulsant medications, such carbamazepine and phenytoin, or phenobarbital should not take gingko without the knowledge of a physician, because it reduces the efficacy of these medications. Ginkgo is generally safe and well tolerated with the most common adverse reactions being stomach upset, headache and dizziness. German Commission E recommends a dosage of 40 mg of ginkgo three times daily with meals for at least four to six weeks. Preparations should be standardized to contain 6% terpene lactones and 24% ginkgo flavone glycosides.

Ginseng is used to combat overall debility, as well as lack of energy and concentration. It has also been used as an aphrodisiac. There is tremendous variation in products labeled as ginseng; in one study, only 25% of the commercially available products actually contained ginseng. Nevertheless, ginseng enjoys widespread popularity. Siberian ginseng has been associated with falsely elevated digoxin levels (a heart drug used to treat congestive heart failure) by interfering with the test used to determine digoxin blood levels. Ginseng may also affect fasting blood glucose levels, so people who need to control their blood glucose levels should take ginseng with caution. Concomitant use with warfarin, heparin, aspirin and NSAID's should be avoided. Additionally, ginseng may cause headache, nervousness, and manic episodes in patients with manic-depressive disorders or psychosis or those on anti-depressants, particularly the monoamine oxidase inhibitors (MAOI) such as phenelzine (Nardil). Side effects include high blood pressure, restlessness, nervousness, insomnia, skin eruptions, edema and diarrhea. German Commission E recommends Asian ginseng be taken as 1-2 g of crude herb daily or as 100-300 mg of ginseng extract three times daily. Commercial products should contain at least 4%-5% ginsenosides.

Kava Kava is recommended for anxiety, as a sedative and as a relaxant. Excessive sedation may result when Kava Kava is taken with other sedatives (flurazepam, temazepam) or anti-anxiety drugs, particularly alprazolam (Xanax). The toxicity of kava is increased if taken with alcohol. Until the clinical significance of Kava's action on platelet activity is determined, its use with blood thinners should be cautioned. Long-term use is not advised and is characterized by dry, flaking, discolored skin and reddened eyes. The herb is contraindicated in patients with certain types of depression because it may increase the risk of suicide. The daily dosage is the equivalent of 60 mg to 120 mg kava pyrones. Heavy consumption of kava has been associated with increased concentrations of glutamyltransferase, suggesting potential hepatotoxicity. A case of recurring necrotising hepatitis has been reported

Licorice, plantain, hawthorn and ginseng may interfere with digoxin therapy and valerian root should not be taken when barbiturates are used because it could cause an increase in the barbiturate effects.
(Sources: Hans Larsen, Alive Magazine March 1999 with some changes by D. Morrow and *When medicine and herbs don't mix by Tammy Chernin, R.Ph. http://www3.healthgate.com)*

St. John's Wort: **WARNING: Don't take St. John's Wort if you are taking Harvoni or Holkira/Viekira Pak**! St. John's Wort can reduce the effect of those C drugs. St. John's Wort is most widely used to treat mild to moderate depression, anxiety and seasonal affective disorder. Adverse reactions reported include stomach upset, allergic reactions, fatigue and restlessness. Photosensitivity is usually rare and is associated with higher dosages. Fair-skinned people should be particularly cautious. Concomitant use with other photosensitizers, such as piroxicam (Feldene) or tetracycline should be avoided. St. John's Wort should not be used with MAOIs (phenelzine) or selective serotonin reuptake inhibitors (SSRIs) such as Prozac, Zoloft or Celexa. St. John's Wort has been reported to prolong narcotic-induced (codeine) sleeping times as well as decreasing barbiturate-induced sleeping times and caution is advised when combining these medications. The herb also contains tannin and may interfere with iron absorption. The usual dosage is 300 mg of standardized extract three times daily or 450 mg twice daily. It may take up to four to six weeks to see desired effect. St. John's Wort should not be taken with monoamine oxidase inhibitors or selective serotonin reuptake inhibitors like Prozac and Paxil until more information is available.

Valerian: German Commission E recommends valerian for use in the management of restlessness and nervous disturbances of sleep. Valerian may cause headache, hangover, excitability, insomnia, uneasiness and cardiac disturbances. Given its sedative property it would be wise to avoid barbiturates (phenobarbital), sedatives (flurazepam, temazepam) and alcohol while on valerian. Valerian is also a tannin-containing herb and may interfere with iron absorption. Persons currently taking antidepressants should take valerian only under medical supervision. The usual dosage of the extract is 2-3 g, one to several times per day.

V.2.2b ARTICHOKE (cynara scolymus)
The artichoke has a long folk history in treating many liver diseases. Recent evidence supports this longtime use. The active ingredient in artichoke is cynarin. This compound is found in highest concentrations in the leaves. Cynara extract has demonstrated liver-protecting and regenerating effects, and promotes the outflow of bile from the liver to the gall-bladder. This is very important because if the bile is not being transported adequately to the gallbladder, the liver has an increased risk of being damaged.

V.2.2c DANDELION (Taraxacum officinale)
The name dandelion is sometimes loosely applied to other milky-sapped weeds with fluffy yellow flowers. But true dandelion is that ubiquitous weed growing prolifically in millions of lawns, backyards and pastures throughout America. This perennial herb has deeply cut leaves forming a basal rosette in the spring and flower heads born on long stalks. All leaves and the hollow flower stems grow directly from the rootstock. The creator of the comic strip "Marvin" once had his adorable diapered hero surveying a clump of dandelions and then thinking to himself, "Dandelions are Nature's way of giving dignity to weeds!"

The late naturopathic physician, John Lust, stated in his Herb Book that dandelion root is good for all kinds of liver problems, including hepatitis, cirrhosis, jaundice and toxicity in general, as well as getting rid of gallstones. Bring 1 quart of water to a boil, reduce heat to low and add about 20 tbsp. of fresh dandelion leaves, stems and clean, chopped root. Simmer as long as it takes for the liquid to be reduced to just a pint, then strain. Dr. Lust recommended taking 3 tbsp. six times daily.

For those desiring something more convenient in capsule form, there is the AKN Formula from Nature's Way, which contains considerable dandelion root and other cleansing herbs. It can be obtained from any local health food store. - *Heinerman Encyclopedia of Fruits, Vegetables and Herbs*, John Heinerman, Parker Publishing Company
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V.2.2d GARLIC
Garlic is a natural antibiotic. It protects the body from infection, detoxifies the body, strengthens blood vessels, and lowers blood pressure. Garlic contains a natural antibiotic, antifungicide, and has many antiviral properties.

V.2.2e KOMBUCHA TEA
There have been quite a few warnings posted about serious adverse effects from Kombucha Tea in Australia and the United States.

V.2.2f LICORICE ROOT (glycyrrhiza glabra)
Studies have shown a component of licorice to be effective in treating viral hepatitis, particularly chronic active hepatitis. This is probably due to its well documented antiviral activity. A glycyrrhizin-containing product is widely used intravenously in Japan for the treatment of hepatitis. If licorice is used over a long time it is necessary to increase the intake of potassium rich foods. Caution should be exercised by anyone with high blood pressure or cirrhosis. ("Complementary and alternative medicine in chronic liver disease," *Hepatology* September 2001 Volume 34 Number 3)

V.2.2g REISHI/SHITAKE MUSHROOMS
Medicinal mushrooms may stimulate many aspects of the immune system, including the production of interferon. In the Orient, Reishi is considered a Fu Zhen herb (immune modulation). Presently, Reishi has various applications including lowering or raising blood pressure, stimulating liver actions, blood cleansing, and acting as an adaptogen in helping the body fight the effects of stress. Chinese herbalists prize it for its abilities to regenerate the liver. In high doses, and to some degree normal doses, Ganoderma may be classified as a liver detoxicant and protectant.

Toxicity studies show no toxic effects on humans. In research, patients are given much higher doses, as high as 10 grams of extract per day, with no ill effects.

The potency of Reishi mushrooms is usually based on its level of triterpenoids. One can determine the level of this by tasting it. The more bitter it is, the higher the level of triterpenoids.

Because Reishi is a polypore, (a group of hard, woody, bracket-like mushrooms) it is not eaten, but cut into pieces and made into a tea. In China, the average dose is 3 to 5 grams a day. Other popular forms of delivery are the water/alcohol extracts and powders. ("*Reishi: Ancient Medicine is Modern Hope*",

Linda McGlasson, Health Foods Business Consumer Education Series, January 1992).

A study of Ganoderma undertaken at Cornell University found that there was a good argument for the use of this substance in conjunction with other medicines in the treatment of cancer. There was no mention in the literature of HCV. (*Role of Ganoderma Supplementation in Cancer Management Meridian Medical Group at the Institute of East-West Medicine and Department of Medicine, Cornell Medical College Raymond Y. Chang, 1997*).

V.2.2h MILK THISTLE

Milk thistle (silymarin) is reported to be an anti-inflammatory and mast cell stabilizer that helps protect the liver against toxin, drugs, and the effects of alcohol (*Better Nutrition for Today's Living*, March 1993).

Use extract of milk thistle (Silybum marianum). "...European research shows that it stimulates regeneration of liver cells and protects them from toxic injury" Usually stocked in health food stores under the names milk thistle, silybum, or silymarin.

A serious study in test tubes, showed that milk thistle, widely used among Hep C sufferers, is an anti-inflammatory and possibly has antiviral effects. This study used standardized silymarin extract (MK-001). Better antiviral results were obtained by combining MK-001 with IFN-N1 than by using either alone. Silymarin bought in stores showed some antiviral effects, but not as much as MK-001. The most effective "ingredients" in milk thistle seem to be silybin A, silybin B, isosilybin A, and isosilybin B.22. *(www.natap.org Original article: Gastroenterology, May 2007, Volume 132, Issue 5, Pages 1925-1936)*

Results of a small study with 16 nonresponders to pegIFN/RBV who were retreated with 10 mg/kg silibinin monotherapy, an ingredient in milk thistle, intravenously during 4 hours a day for 7 consecutive days, showed a decline in viral load and ALT levels. This product may be beneficial for nonresponders, and more studies are needed. *(www.natap.org/2008/EASL/EASL_57.htm)*

In a 2011 study, silibinin was given intravenously to a patient post-transplant without any other antiviral. The patient still had un-detectable virus at his 5-month follow-up. The researchers believe that IV silibinin should be researched especially in non-responders to standard therapy or in those who cannot tolerate standard therapy, perhaps in combination with a protease inhibitor.
(www.natap.org/2011/HCV/021611_06.htm 02/16/11)

There still seems to be interest in milk thistle in 2015, and more researchers are dedicating themselves to better-designed clinical trials. Benefits reported have been decreased liver enzymes, longer survival, decreased GGT, increases in glutathione, decreased platelet MDA, increased antiviral effect, decrease in lipid peroxidation, decrease in insulin resistance, less fatigue, less nausea, less liver, joint and muscle pain, and in at least 3 studies, there were no significant benefits apparent. See more bout recent human clinical trials here: *www.cancer.gov/cancertopics/pdq/cam/milkthistle/HealthProfessional/page5*

V.2.2i SPIRULINA (BLUE-GREEN ALGAE)

Researchers report that spirulina, an extract of blue-green algae, contains a substance that shows antiviral activity against HIV. Studies have not yet been conducted on its effectiveness against the hepatitis C virus.

V.2.2j THYMIC FACTORS

Thymic Factors is a combination of drugs including thymus, Enzymatic Poly-Peptide Fractions, Crude Thymus Extract, Thymosin, Thymopoietin, Thymus Humoral Factor, other nutrients, herbs, vitamins, and enzymes, developed by Carson B. Burgstiner, M.D. after he contracted hepatitis B. He claims to have treated 83 cases of Hepatitis B, 23 cases of hepatitis C, 28 cases of Rheumatoid Arthritis, and arrested 12 cases of Systemic Lupus (some of whom were taking 22 different drugs and are now asymptomatic), 10 cases of Multiple-Sclerosis, 12 cases of Psoriasis, 7 cases of people with Squamous Cell Cancer of the skin. This formulation has not been studied through official clinical trials, and the claims have not been proven, but many listmembers on the HEPV-L mailing list report that they feel better and have more energy while taking Thymic Factors.

In 1996 a company Preventive Therapeutics, Inc. started manufacturing the original formula of Dr. Carson B. Burgstiner. The product is distributed by many health food stores. When Preventative Therapeutics was contacted, they gave the following advice: When first taking the Thymic Formula until stabilized 2-3 months, take 6 tablets twice daily (total 12 tablets) 12 hours apart. When stabilized, take 3 tablets, twice daily.

Preventive Therapeutics, Inc. has since been absorbed by Logos Nutritionals. The products can be obtained by calling 1-800-556-5530 in the US, or by going to their "contact" page at *http://logosnutritionals.com/aboutus/contactus/*.

Warnings have been issued against the use and consumption of raw animal parts (glands, testicles, brains) in herbal and alternative treatments, since there is fear that they may spread "mad cow disease."

V.2.2k VITAMIN A
A study from 2013 investigated the association between vitamin A deficiency and lack of response to IFN therapy. Researchers investigated 199 treatment-naïve HCV+ patients and measured their blood levels of vitamin A vitamin D. They used 119 healthy blood donors as controls. The average vitamin A levels in HCV+ patients were quite a bit lower than in controls: 256 ng/mL vs 742 ng/mL. 122/199 patients achieved SVR. Almost half were infected by difficult-to-treat HCV genotypes, of whom 37.5% were nonresponders. Factors believed to predict non-response included IL28b allele (non-CC), genotypes, viral load over 600,000 IU/mL, levels of vitamin A under 100 ng/mL, and a cumulative dose of RBV under ≤80%. The researchers found that many HCV+ are vitamin A deficient, and a combined vitamin A and D deficiency was a strong independent predictor of nonresponse to antiviral therapy.
(www.ncbi.nlm.nih.gov/pubmed/23213086)
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V.2.2l VITAMIN B12
Some hepatitis patients report having more energy when they take extra vitamin B12. It is important to note that Vitamin B12 is not effective when taken in tablet form. It must be injected. Studies have shown Vitamin B12 to improve SVR rates.

In 2011, an evaluation of levels of vitamin B12 levels was reported by researchers in Sweden. They reported that patients who achieved good treatment results had significantly higher baseline vitamin B12 levels compared to non-responders, and that end-of-treatment "non-detectable" response was achieved in 96.2% of patients with vitamin B12 levels over 360 pM, versus 68.5% of those with levels under 360. For SVR, the difference wasn't that good (65% vs 52%). Some would say every little bit helps.
(www.medscape.com/viewarticle/777087)

V.2.2m VITAMIN C
Linus Pauling the two time Nobel Prize winner said that vitamin C is very beneficial to hepatitis patients. He recommends a bare minimum of 10,000 milligrams = 10 grams a day. 20,000 - 50,000 milligrams a day is much better = 20 to 50 grams. Take pure vitamin C. Take the pills three to four times a day instead of once a day. Vitamin C is an antiviral agent. The only side effect known is diarrhea which should slow down and stop as you get used to the vitamin C. You can get Linus Pauling's books at your local library.

"In [a] large, national, population-based study, the risk for apparent liver injury was associated with increased iron and decreased antioxidants, particularly carotenoids *(Gastroenterology. 2003 Jun;124(7):1821-9)*.

V.2.2n VITAMIN D3
In 2011, researchers found that patients undergoing IFN/RBV treatment who had higher vitamin D levels seemed more likely to achieve SVR. To see if it was true, they treated 42 patients for 48 weeks, and measured vitamin D levels before treatment. Of the 42, 15 patients were given oral vitamin D3 supplements to stop further bone loss. SVR was observed in 13 patients. Supplementation, in patients with normal or near normal baseline vitamin D concentration, and possessing a genotype other than 1 were the only characteristics associated to SVR. They concluded that vitamin D supplementation improves the probability of achieving SVR. *(www.ncbi.nlm.nih.gov/pubmed/20649944)*

V.2.2o VITAMIN E
Vitamin E is reported to assist the liver in detoxifying the blood. Vitamin E works best when taken with Selenium, an antioxidant mineral. Too much Vitamin E thins the blood, so those with bleeding disorders should exercise caution.

V.2.2p NATURAL INTERFERON BOOSTERS
Studies indicate that many natural substances can activate the body's own production of interferon. Some better known natural interferon boosters are:
Astragalus: a Chinese herb that enhances the antibody reaction to foreign invaders of all types, including cancer.
Boneset: a Native American Indian herb with antiseptic, anti-viral properties used for the treatment of colds and flus, coughs, fevers, indigestion and pain.

Chlorophyll: a plant pigment which can be found in a long list of green leafy vegetables and algae like spirulina, chlorella and barley green.
Coenzyme Q10: an antioxidant involved in the electron transport chain needed for all energy dependent processes in the body. CoQ10 increases helper T-cells and reduces infection risk.
Echinacea: the most popular herb in North America used as a treatment for toothaches, bites or stings and all types of infections.
Ginkgo: a potent central nervous system antioxidant for the treatment of circulation disorders, memory problems, high blood pressure, depression, tinnitus and immune system disorders.
Melatonin: a hormone produced by the pineal gland with strong antioxidant and immune system boosting properties.
Ojibway tea or Essiac Tea is thought to cleanse the body of toxins and boost immunity, which some people have found to be helpful. (Personally, it seemed to make me sicker - Patti).

V.3.0 HEALTHY BODY AND MIND

V.3.1 EXERCISE
Exercise can help release tension and improve your level of health. It can help you increase your fitness level. You can do it even if you suffer from fatigue, but remember to not tire yourself too much. Symptomatic hepatitis patients may need to avoid stressful activities, and each person's tolerance for stress will be different, and can change. It is nonetheless important for people who can exercise to do so, up to their level of tolerance. This should be done with care, since crossing the "invisible line" of exercise intolerance may prompt a flare-up. That can be bad for your immune system.

Try these:

- Bicycle riding – ride a little further each day/week
- Commuting--Get off the bus one stop earlier and walk the rest of the way home
- Walking (increase the distance you walk each day/week) Invite a friend or get a dog.
- Swimming or water aerobics
- Play a game of golf
- Practice yoga
- Gardening – plant some herbs that are good for your liver. (Dandelion, milk thistle, artichokes…)
- Kick a ball around with kids or grandkids
- Walk on escalators instead of standing
- Choose an activity you enjoy and can participate in on a regular basis.

Please consult with your doctor before beginning any exercise program.
(www.hepcawareness.net.au/lifestyle/be_active.htm)

V.3.2 Tai Chi
For those with symptoms of Hep C, such as fatigue and muscle aches, doing exercise can be a problem, but it is so important to our health. When Wendy Mackay of British Columbia found that even walking was too much, she decided to try Tai Chi I 2004, and was able, with the help of the instructors, to participate in class, sitting out most of it at first, and even then, battling migraines and feeling sicker. Gradually, she was able to participate more and more, and she built up her strength and stamina.

During the second year, the pain started going away. She can now stay awake longer. Her digestion and respiratory function have improved. The more she does, the more she can do, and the better she feels. She says it helps her concentration and gets rid of the "brain fog." Cognitive function improves as one focuses on learning and remembering the moves in the Taoist Tai Chi set. This form of movement also provides a calming meditative aspect for the mind, which helps reduce stress and anxiety often associated with chronic illness.

"The reality of this disease is that many of us are unable to continue working or perform manual labour, let alone enjoy any sort of social life. By focusing on what we can do, rather than on what we can no longer do, we provide our body and mind with the tools to help us feel well," says Wendy.

Wendy is now an accredited Taoist Tai Chi instructor! You can read her story at
www.hepcaustralia.com.au/symptoms-news/hep-c-and-exercise-experience-tips.html,
and please visit her website at *www.wendyswellness.ca or her Facebook page at*
www.facebook.com/groups/222751877843182/

V.3.3 Yoga
One of the benefits of yoga is that it stills the mind, and this may help boost the immune system, reduce fatigue, and alleviate depression. The yoga won't get rid of the virus by itself, but it may help keep the liver healthy until a cure can be found.

- **Bikram Yoga**

People with Hep C may find benefits from Bikram Yoga. Bikram Yoga is performed in rooms heated to 85-105 degrees Fahrenheit and humidity of 60 to 70 percent. It incorporates a sequence of 26 poses, and is supposed to flush out the toxins accumulated in the body. Bikram Yoga might be used combined with—not instead of—standard treatment for hepatitis C. The heavy sweating that occurs may detoxify the body, and is also used at the clinic for post-chemo cancer patients. It is hoped that the yoga will increase blood circulation in the liver, thus reducing immune substances that react to the virus and cause liver inflammation.

"This is still hypothetical," says Standish, director of the Centre. "But the kind of aerobic exercise that would be most valuable to flushing the liver would be yoga, and especially yoga where there is increased blood flow as well as sweating."

Please consult with your doctor before beginning any exercise program. Trust your body. If it makes you feel sick, stop.
(*www.yogajournal.com/health/585*)

V.3.4 STRESS MANAGEMENT

Typically, one of the most beneficial things a person with hepatitis can do is to avoid stress and get lots of rest. Stress does not merely mean only unpleasant experiences, but rather any biological stressors, physical or emotional, which prompt a protective reaction in the body. Failure to avoid stress often leads to short-term and long-term set-backs which may be serious.

High-stress events sometimes seem to "trigger" the flare-ups of the virus and they will usually worsen the symptoms if the virus is already active. Medical studies show that stress plays an important role in several immune-mediated illnesses.

There are many sites on the Internet and on YouTube to help you de-stress. Beware: Sometimes you will find unscrupulous teachers or guides who may be involved in cults, and try to recruit you and your time or money. The techniques, however, can be excellent for stress reduction:
MEDITATION: *www.wikihow.com/Meditate*
VISUALIZATION/GUIDED IMAGERY*: www.youtube.com/watch?v=oIkJZ49DjIY*
www.youtube.com/watch?v=tXVD42LGC80

V.3.5 POSITIVE ATTITUDE

Laughter and a positive spirit are good for the body. They provide interferon, the body's natural infection fighter, and produce endorphins to combat depression and anxiety.

V.3.6 TIPS TO KEEP YOURSELF HEALTHY

- **Avoid exposure to chemical fumes, gasoline fumes, etc.**

Use the least toxic products (cleaning products, health and beauty aids, etc.) available in your home and on your body.

Some US researchers used data from 2003-2005 to find adults with pollutants in their blood or urine. 37.6% of the subjects had high ALT levels, even though those with Hep B and C, those who have abused alcohol, and those with iron overload were not counted. The results indicated that about 70 million adults in the US have liver problems not caused by the expected risk factors. Most are due to NASH (fatty liver). The researchers could blame some of the problem on pollutants like pesticides (some that were banned decades ago) and heavy metals. High levels of heavy metals and pesticides were associated with higher ALT. Subjects with the highest levels of mercury had double the risk of an elevated ALT. Two pesticides banned in the U.S. since the 1970s and 1980s, dieldrin and heptachlor epoxide, were also associated with more risk of liver disease. Most people are exposed to pollutants through food. Once in the body, they are not well metabolized. The pesticides are notorious for accumulating in fat tissue, so those who are overweight may have higher levels of pollutants in their bodies.
(www.medpagetoday.com/MeetingCoverage/DDW/14428 DDW 2009; Abstract 289. May 29, 2009)

- **Watch your weight!** NAFLD, non-alcoholic fatty liver disease, is any disease of the liver caused by fats in those who drink little or no alcohol. One of the causes can be hepatitis C. Much of the fat in the liver comes from your diet. It seems to be related to excess weight, diabetes and insulin resistance. No one knows why NAFLD occurs, but it is treated by weight loss, as well as medicine, insulin and/or diet to control diabetes. NAFLD is now known to be a stepping stone to cirrhosis in 25% of people. Fat from food is deposited into the liver, making it difficult for the liver to metabolize the fat resulting from carbohydrates. If insulin levels are high, the fat synthesis is turned on 24/7, but it is not known if that is

a cause or an effect. Diet may correct the fat buildup. Antioxidants and exercise may help, too, as may the Mediterranean Diet.
(www.hepatitisneighborhood.com/content/in_the_news/archive_2332.aspx 05-04-05 John C. Martin, Fatty Liver: Your Diet is Partially to Blame, Says Study)

PART VI - DRUGS AND ALCOHOL

VI.1.0 WHAT ARE THE EFFECTS OF RECREATIONAL DRUGS?

If you are HCV+, alcohol and other drugs are likely to put added strain on your already stressed liver. And even if you already have HCV, you are still open to re-infection if you expose yourself to the virus through unsafe drug use. There are several different types and variations of HCV, and every time you catch a different type, it is like you have been infected for the first time. People with multiple infections of HCV are often the ones who become sicker. It is advisable to avoid alcohol and all street drugs. If users are opiate-dependent, methadone may be an alternative in this phase of infection, simply because it is available in pure form.

Hepatitis generally increases the chances of overdosing (especially on alcohol, and benzodiazepine tranquilizers such as Serepax, Rohypnol, Valium, Mogadon and Temazepam) because the liver cannot handle the doses of drugs to which the user was formerly accustomed. Serepax is better than other benzodiazepines but it still presents problems.

Heroin is relatively harmless during hepatitis infection, but all drugs present problems, whether in pure or impure forms. Amphetamines and benzodiazepines are moderately destructive and alcohol is the worst.

In as far as drug use is concerned, purer forms of drugs are advisable in all cases (for instance methadone is better than street heroin, pharmaceutical amphetamines are better than street amphetamines) but this is only a minor improvement, for it is the liver's function of removing drugs from the body which is affected by the hepatitis C virus. It is best to be aware of any possible problem in this area and the specific relationship between specific drugs and the liver.

It is best to be entirely drug free during the acute phase of hepatitis infection so that the liver can repair itself. Drug-taking presents fewer problems if you have a healthy liver. *(New South Wales Users and AIDS Association "Hepatitis C and Drug Use")*

VI.1.1 ALCOHOL

There is no question that alcohol should be off limits for those with HCV. Studies have shown that patients who drink have a higher incidence of cirrhosis. But not only that, patients who drink also have a faster rate of progression to cirrhosis and higher mortality rates. As well, because alcohol interferes with the effect of interferon, those with a history of drinking problems may be denied treatment.

EFFECT OF ALCOHOL ON HCV REPLICATION: A critical question is whether or not alcohol and hepatitis C infection are synergistic in a combined liver injury. In some patients, there are both histologic features of alcoholic liver injury and chronic viral hepatitis, but in most studies the predominant pattern is chronic hepatitis.
Alcohol may enhance the replication of hepatitis C and produce a more severe injury independent of the direct alcohol-induced toxic injury. There is a correlation between HCV RNA levels and amount of alcohol consumed. Alcoholic patients with HCV infection have higher hepatic iron concentrations, which may be germane to increased HCV replication. Clinical evidence of hepatic activity and viral levels is significantly greater in those consuming greater than 10g of alcohol per day.

EFFECT OF ALCOHOL ON PROGRESSION OF CHRONIC VIRAL C HEPATITIS TO CIRRHOSIS AND HEPATOCELLULAR CARCINOMA: There is a more rapid development of cirrhosis and hepatocellular carcinoma in the alcoholic with chronic HCV infection. The period from transfusion to the diagnosis of cirrhosis is shorter in the heavy drinker. As well, recent studies demonstrate that alcohol consumption in cirrhotics can lead to increased bacterial infection (*American Journal of Gastroenterology*, Editorial, May 2000, Volume 95, Number 5, Pages 1124-1125).

The risk for the development of hepatocellular carcinoma in alcoholic cirrhotics is 8.3 times higher in the HCV(+) patients than HCV(-) patients, and the prevalence of anti-HCV among alcoholics with HCC is 50-70 percent. Therefore, alcohol may modify the replication of HCV as well as the oncogenicity of HCV in hepatocellular carcinoma.

I**NTERFERON THERAPY IN ALCOHOLIC PATIENTS WITH CHRONIC HEPATITIS C**: Among alcoholic patients with chronic hepatitis C who remained abstinent during therapy with interferon, there was a significantly lower rate of HCV RNA clearance in those who consumed 70g/day of ethanol as compared to 70g/day up to the time of interferon therapy. - "Hepatitis C and Alcohol," by E.R. Schiff,

abstract submitted by the author to the National Institute of Health Conference on Hepatitis C, held March 24-26, 1997, in Bethesda, Maryland.

An important cofactor of disease severity appears to be alcohol and alcohol should be avoided in those with chronic HCV infection." - "Natural History and Clinical Aspects of HCV Infection." H.J. Alter. Department of Transfusion Medicine, National Institutes of Health, Bethesda, Maryland. *Cancer Biotechnology Weekly*, *01-29-1996, pp 20.*

VI.1.2 TOBACCO

Cigarette smoking combined with the hepatitis C virus is known to be a heavy risk factor in developing primary hepatocellular carcinoma. (*Int J Cancer* 2000 Feb;85(4):498-502).

While many people are aware of smoking's negative effect on the lungs, less consideration is usually given to its effects on the liver. Tobacco and marijuana smoke are rich airborne stews of toxic benzpyrene, polycyclic aromatic hydrocarbons, cyanide, acetaldehyde, tars, acrolein, etc. Since these get into the bloodstream through the lungs, the liver must detoxify them. And virtually all the constituents of smoke are known to be at least mildly liver-damaging (*The Liver: Master Organ for Optimal Nutrition*).

A 2001 study biopsied 310 Hep C patients. 176 were current smokers (who were more often males, younger, alcohol consumers, and more often had a history of IVDU than those who had never smoked). The results were adjusted to consider these factors. The authors concluded that "Smoking increases the severity of hepatic lesions in patients with chronic hepatitis C." Source: *Hepatology* 2001;34:121-125, "Cigarette smoking and hepatic lesions in patients with chronic hepatitis C."

A Japanese study presented at the DDW 2008 concluded that "when combined with IFN-a, nicotine disturbed the antiviral effects of IFN on HCV replication," *(www.natap.org/2008/DDW/DDW_08.htm)*

VI.2.1 MARIJUANA

There are plenty of conflicting studies on the benefits/dangers of marijuana use by the chronically ill. Recent studies show that marijuana can be beneficial for those with AIDS. The results of a study released at the XIII International AIDS Conference reports that smoking marijuana helps people with AIDS gain weight, without causing adverse virologic effects (July 2000). But HCV is not HIV. Nor is it cancer. Nor is weight gain recommended for people with HCV because of the possibility of fatty liver.

Other studies (May 2000) speak of the synthetic marijuana derivative CT-3 as an anti-inflammatory and analgesic therapy intended as a safer alternative to nonsteroidal anti-inflammatory drugs (NSAIDs), the most commonly prescribed analgesic and anti-inflammatory therapy for long-term treatment of arthritis.

One study states that marijuana use increases tumor growth. Another links it to emphysema.

A report from the New South Wales Users and AIDS Association "Hepatitis C and Drug Use" states that marijuana presents no problems for the liver; another report warns that marijuana may interact adversely with antidepressants.

It has been shown that marijuana interferes with the effectiveness of interferon alpha-2a in the treatment of genital warts due to drug-induced impairment of cellular immunity. ("Genital Warts do not respond to systemic recombinant interferon alpha-2a treatment during cannabis consumption," Gross G; Roussaki A; Ikenberg H; Drees N., *Dermatologica*, 1991, 183(3):203-7) Whether this is also true for marijuana use during interferon alpha-2b treatment for hepatitis is unknown.

A presentation made in the Fall of 2004 at the 55th Annual Meeting of the American Association of Liver Diseases showed that HCV + people who smoke marijuana daily have a rapid rate of liver scarring (fibrosis). In this study, 66% of those who smoked daily for an average of 16 years progressed rapidly, compared to 40% of those who smoked about once every 2 weeks, and 41% of those who never smoked marijuana. "Patients with ongoing chronic hepatitis C should be advised against daily cannabis use, since regular use over the span of the disease is an aggravating factor regarding fibrosis progression." Another researcher commented that Hep C patients have many CB1 receptors in their livers, so that smoking marijuana is a co-factor, and not directly responsible for the fibrosis. *(Source: Mark L. Fuerst, AASLD: Smoking Marijuana Raises Fibrosis Risk in Patients With Chronic Hepatitis C Infection Nov. 2, 2004 Abstract 67]*

A recent study (Oct 2006) showed that use of cannabis might help some Hep C patients stay on treatment, but some experts voiced their worries, basing their concern on a French study of untreated Hep C patients showing those who used cannabis daily had more liver scarring and were more likely to have their fibrosis progress than those who used marijuana little or not at all. At the EASL meeting in Barcelona, that team reported that cannabis sativa binds to two receptors, one of which activates the accumulation of fat, according to a study of 311 treatment-naïve patients, 59% of whom were non-

users, 15% smoked fewer than 1 joint daily, and 26% daily users. Fatty liver was found in 16.3% in non-users, 10.9% in occasional users, and 30.9% in daily users. Steatosis was also linked to body mass index of 27 kg/m2, use of maintenance treatment, alcohol consumption of 30 g/day, genotype 3, hyperglycemia, fibrosis stage 2 or more. Still, the authors report "a strong link between daily cannabis use and steatosis severity in patients with chronic hepatitis C," and state, **"Patients with untreated chronic hepatitis C should be advised to refrain from daily cannabis use."**
(www.hivandhepatitis.com/aboutus2.html#liz) (www.natap.org/2006/HCV/091506_02.htm)

VI.2.2 AYAHUASCA
Ayahuasca has been promoted by Dr. Gabor Maté in his book "*In the Realm of Hungry Ghosts,*" as a means to wean people off opiates. It is a traditionally ceremonial drug, like the psychodellics, peyote and "magic mushrooms." Our question is, can it benefit those suffering from hepatitis C, other than ridding them of addictions? Can it harm their livers?

Some research has been done by scientists in the form of brain scans on users, with no follow-up. In a more recent study, 12 participants were questioned before and after about aspects of quality of life several times over 6 months. Promising results published in *"Current Drug Abuse Reviews"* showed decreased use of tobacco, alchohol, and cocaine, and improvement in quality of life. They say the psychelelic drug is relatively safe if taken in moderation. Brain scans show no neurotoxic effect. The risks are more psychological. Some shamans serve counterfeit brews. There are horror stories, and possible dangerous interactions with prescription drugs.
(www.riverfronttimes.com/2013-11-28/news/the-vine-of-the-soul)

Ayahuasca is metabolized mostly in the liver. People with Hep C are affected more by ayahuasca, and should take smaller doses, along with a good diet and anti-inflammatories, and products to protect and purify the liver, along with lab tests to verify liver functions.
(https://books.google.ca/books?id=49i8-CzmY_oC&pg=PA238&lpg=PA238&dq=ayahuasca+hepatitis+c&source=bl&ots=67eOa647OM&sig=t1YLpmGUHFHiNz1gqX97goZc_yU&hl=en&sa=X&ei=eM0EVcXdNcG3ogSDqICIBQ&ved=0CEsQ6AEwCA#v=onepage&q=ayahuasca%20hepatitis%20c&f=false)

VI.3.1 COCAINE
A study of blood donors who showed traces of past infection with the liver-damaging disease hepatitis C has uncovered a possible link between the infection and snorting cocaine. Snorting "could be an unrecognized route" for the hepatitis C virus to get into the body, said a team of medical researchers led by Dr. Cathy Conry-Cantilena of the National Institute of Allergy and Infectious Diseases. But the researchers noted that cocaine abuse may not be the actual cause of the hepatitis. Cocaine users may simply be more prone to other behaviors that make them vulnerable to the infection. Hepatitis C is usually passed via contaminated blood. The researchers said it was possible the straws used to snort the drug could be tainted with blood and the virus could get into a user's body through the wall of the nose, which is often damaged in cocaine snorters.

VI.3.2 METHADONE AND HEPATITIS C
The effects of methadone can alleviate possible painful symptoms of hepatitis C. Although this may be helpful, it can camouflage early signs of liver damage (if it develops). Flu-like hepatitis C symptoms may give the impression that you are on prescription pills. If this causes problems at the clinic where you receive your methadone, it may be useful to remind them of the complicating effect of hepatitis C symptoms.
If you experience flu-like symptoms of hepatitis C, these symptoms should not be misinterpreted as withdrawal symptoms from opiates.
People should be careful with methadone dosages and aware of their real tolerance for drugs. This is especially important if liver damage is severe. - *Hepatitis C Council of NSW*

VI.4.1 INTRAVENOUS DRUG USE PRECAUTIONS
When injecting drugs, the best protection is to never re-use injection equipment. Cleaning injection equipment is not guaranteed to kill the hepatitis C virus.
To avoid getting or spreading hepatitis C when injecting:
- Have a syringe, spoon, water, filter, swab and tourniquet.
- Wash your hands with warm soapy water before and after injecting.
- Clean the spoon with a fresh swab.
- Keep all your utensils separate from your friend's utensils.
- Inject yourself - but if someone else does inject you, make sure he/she has washed his/her hands.
- If you get blood on your hands, go and wash them before you touch anything on the table. If someone

asks you to pass them something, tell them to wait.
- If you do touch something before you're able to wash your hands, treat it as contaminated.
- Dispose of your used syringes, filters, swabs, etc., properly by putting them into a sharps container, or use an empty plastic drink bottle or detergent container. (Look for the letters PET on the bottom of the plastic bottles, as these are especially strong). Be careful not to dispose of your fits in aluminum cans or glass bottles. Kids collect cans for recycling and could get needle sticks, and glass bottles can easily break.
- Remember - use new equipment every time. Cleaning equipment doesn't always kill the hepatitis C virus.
- Remember - wash your hands with soap and water before and after injecting. You can't always see minute amounts of blood.
- Remember - make the bench or table where you're injecting as clean as possible.

VI.4.2 CLEANING SYRINGES

We don't know that disinfection or cleaning really works so be safe and use all new equipment every time you hit up. Reusing fits should be a last option only. If you're cleaning syringes, remember the following guidelines:

- Immediately after use, rinse the syringe in cold water until signs of blood are gone. Squirt water down sink or into an old drink bottle.
- Do this as soon as you've used the syringe since dried or clotted blood is hard to wash out and can block the syringe. Always use cold water as hot water will clot blood in the syringe and block it.
- Fill the syringe with fresh high-strength bleach. Use the strongest bleach available (which is usually the most expensive). With the syringe full of bleach, replace the cap over the needle and shake it for 30 seconds or more. Time this on a watch or count it out slowly. Then squirt the bleach out into the sink or an old drink bottle. Now repeat the bleach process, again shaking for thirty seconds.
- With another container of fresh clean water, rinse out the syringe at least two times. Again, squirt the water down the sink or into an old drink bottle, not into your containers of bleach or clean water. Empty all your containers down the sink when you are finished.

Remember that this way of cleaning syringes can't be guaranteed to kill the hepatitis C virus. - *Hepatitis C Council of NSW*

PART VII - HOW CAN HCV AFFECT MY EMOTIONAL LIFE?

VII.1.0 HOW IS DEPRESSION RELATED TO HEPATITIS?

Many emerging illnesses, before they have gained acceptance by the medical community, have initially been discounted as being hysteria, depression, etc. Before the hepatitis C virus was identified in 1989, many of its symptoms were correlated to depression, and many un-read physicians today still believe that HCV is normally asymptomatic.

Another issue is that HCV patients can get "secondary depression" if their lives have been disrupted because their illness has interfered with their job or their social or family life. This indirect consequence of the illness may be taken by some medical professionals as indicating a cause rather than an effect of the observed symptoms. An article in *Hepatology*, June 2000, p. 1207-1211, Vol. 31, No. 6, "Hepatitis C, Interferon Alpha, and Depression," the authors note that "two separate lines of evidence support an association between HCV and depression. First, patients with psychiatric disorders have a higher prevalence of HCV infection. Second, patients with chronic hepatitis C may have a higher prevalence of psychiatric disorders including depression."

VII.2.0 DEALING WITH A CHRONIC DISEASE

Many people never fully appreciate their health until they suddenly have to face the fact that they now have an illness that is not going away. This new state of affairs can make you feel angry and depressed, and it's hard to get beyond the question "Why me?"

People commonly work through what Dr. Elisabeth Kubler-Ross has identified as the five stages of adjustment as they learn to accept a chronic illness. There are feelings of denial, anger, depression, bargaining and acceptance. All of these feelings are natural, and there is no fixed time schedule for your passage through the stages, and many times the stages overlap.

Know that it's not you. It takes a lot to adjust to your new, lessened capabilities, and the adjustment is made more difficult by the expectations of you and those around you who have been long accustomed to dealing with your "normal, healthy self".

- Patients often find an equilibrium point at which they can function. As in combating any chronic illness, a positive hopeful attitude is essential.

- Be prepared for a possible lack of acceptance from some from whom you might expect support. This may be a shock, but when you cannot regularly "go bowling" with the gang, or you increasingly depend on being accommodated at home or on the job, and when you have a condition that your doctor may not certify or that other people have already heard of as "that disease that junkies get", then your emotional world will become quite different.
- Find new sources of support. It will be important to create a new family-and-friends support structure. This can be done through HCV support groups, electronic networking, pen pals, and other means.
- You will need to take the time to create a new self-image for yourself, to know that your new physical limitations do not limit you as a person, as a soul, no matter what other people are thinking. And take some advice from those who have traveled this difficult road before you—consider reading from books like the ones listed in Section XII.1.5: Bibliography: Suggested Readings.

VII.2.0a ACCEPTANCE

- Realize that you have to experience the pain in order to work through it. Don't try to hide the physical and emotional hurt. Experience the pain and then let it go. Don't be afraid to express the hurt you feel.
- Learn to laugh; try to see humor in your situation, and to enjoy the simple pleasures of life.
- Keep the lines of communication open. It helps to know that someone understands how you're feeling and can help bear the load.
- Don't neglect your personal "self-time." Being alone can provide a personal perspective from which calm, wise judgments, opportunities for personal growth, and a new optimism about life can emerge.
- Don't hesitate to seek counseling for your special situation.
- Some problems are too big to work through on your own.
- Take responsibility for yourself and realize that you DO play a role in your illness.

VII.2.0b DEALING WITH A LACK OF ENERGY: See "FATIGUE".

VII.2.0c IRRITABILITY

Anger is a known side effect of liver disease. And just being sick and tired and achy just about all the time does not help. What helps is slowing down, but most of us can't. If we do, we won't be able to eat and pay the rent.

People with symptomatic HCV should be on disability pensions. They should have home care, and day care provided for their children. They should have help cleaning their homes and doing the shopping and cooking.

When you are tired and achy and nauseous and dizzy, getting caught up in the day-to-day aspects of life becomes increasingly difficult. Often you feel like you have cement in your blood. You feel so heavy.

So when you feel overwhelmed by the welfare system, or a doctor, or a bank clerk or whomever, it's no wonder you just might explode.

The best thing is to have a friend who understands. Joining a local support group really helps.

VII.3.0 HOW CAN HCV AFFECT MY SEX LIFE?

What sex life? ☺ See "Loss of Libido" above.

VII.4.0 HELPING A FRIEND OR FAMILY MEMBER WITH HEPATITIS C

TIPS FOR COPING WITH HAVING A FAMILY MEMBER WITH HEPATITIS C

Remember:

1. You cannot cure your family member.
2. Despite your efforts, symptoms may get worse, or may improve.
3. If you feel much resentment, you are giving too much.
4. It can be as hard for you to accept the illness as it is for the ill family member.
5. Acceptance of the disease by all concerned may be helpful but not necessary.
6. You may learn something about yourself as you learn about a family member's journey through illness.
7. Separate the person from the virus. Love the person, even if you hate the virus.
8. Separate medication side-effects from the disease/person.
9. It is not OK for you to be neglected. You have needs and wants, too.
10. Your chances of catching hepatitis C from casual contact or sexual contact with a family member is extremely low, providing proper precautions are taken to avoid contact with blood.
11. The illness of a family member is nothing to be ashamed of. Reality is that you may encounter

discrimination from an apprehensive public.
12. No one is to blame.
13. Don't forget your sense of humour.
14. It may be necessary to revise your expectations.
15. Acknowledge the remarkable courage your family member may show dealing with the illness.
16. Your family member is entitled to his own life journey, as you are.
17. Survival-oriented response is often to shut down your emotional life. Resist this.
18. Inability to talk about feelings may leave you stuck or frozen.
19. The family relationships may be in disarray in the confusion around the disease. It may be necessary to renegotiate the way things have been done in your relationship, both emotionally and physically.
20. Recognize that a person has limited capabilities should not mean that you expect nothing of them.
21. You may experience grief issues about what you had and lost, or about what you never had.
22. After denial, sadness, and anger comes acceptance. The addition of understanding yields compassion.
23. Diseases are a part of the varied fabric of life.
24. It is absurd to believe you may correct a physical illness such as hepatitis with talk, although addressing social complications may be helpful.
25. Symptoms may change over time, while the underlying disorder remains.
26. The disorder may be periodic, with times of improvement and deterioration, independent of your hopes or actions.
27. Don't shoulder the whole responsibility for your ill family member.
28. Forgive yourself and others for mistakes made.
29. Physicians have varied degrees of competence.
30. If you can't care for yourself, you can't care for another.
31. The needs of the ill person do not necessarily always come first.
32. It is important to have boundaries and set clear limits.
33. Chronic illness affects the entire family, not just the person who actually has the disease.
34. It is natural to experience a cauldron of emotions such as grief, guilt, fear, anger, sadness, hurt, confusion, etc. You, not the ill member, are responsible for your own feelings.
35. You are not alone. Sharing your thoughts and feelings with others in a support group is helpful and enlightening for many.
36. The chronic illness of a family member is a trauma for the entire family. You pay a price if you do not receive support and help.
Support your local hepatitis C group and the search for a cure!

VII.4.0a WHAT SHOULDN'T I SAY?
People with hepatitis C tend to hear a lot of - well...there's no nice way to say it - "Crap" from usually well-meaning people. We understand that most people really do want to help, but sometimes they just don't seem to think before they speak.
Here are a few of the "Worst" things you can say to your HCV-positive friend:
1. "Will you stop that constant whining"?
2. "You just need to get out and exercise more."
3. "It's all in your head."
4. "No one ever said life was fair."
5. "Stop feeling sorry for yourself."
6. "There are a lot of people worse off than you."
7. "You think **you've** got problems..."
8. "Maybe you should eat better/take vitamins."
9. "There is always somebody worse off than you are."
10. "Cheer up!"
11. "You're always feeling sorry for yourself."
12. "Have you been praying/reading the Bible?"
13. "You don't **look** sick!"
14. "Everybody knows HCV doesn't have any symptoms. You're just looking for attention."
15. "That which does not kill us makes us stronger."
16. "Believe me, I know how you feel. I was sick once."
17. "So, you feel sick. Don't you always?"
18. "Oh, cheer up!"
19. "Go out and get some fresh air... that always makes me feel better."
20. "It doesn't matter what your experience was with biopsy, interferon, side effects of treatments, you HAVE to get the treatment/procedure done. I don't care about your excuses."
21. "Gosh... I would love to be a couch potato and not work all the time; it's not such a hard life that

way."
22. "I only want to hear good news."

VII.4.0b WHAT CAN I SAY?

Do you really want to help? Here are a few of the "Best" things you can say to your HCV-Positive friend:

1. "I love you!"
2. "I Care"
3. "You're not alone in this"
4. "I'm not going to leave/abandon you"
5. "Do you want a hug?"
6. "Don't say anything, just hold my hand and listen."
7. "I'm sorry you feel so bad. I am not going to leave you. I am going to take care of myself so you don't need to worry that your pain might hurt me."
8. "I listen to you talk about it, and I can't imagine what it's like for you. I just can't imagine how hard it must be."
9. "If you need a friend....." (and mean it)
10. "Is there anything I can do to help?" (and mean it)
11. "I am going food shopping tomorrow. Give me your list and I will pick up everything for you and bring it home to you and put it away."
12. "I don't care if you get tired and cranky. I love you and spending time with you is still fun."
13. "I will be over in half an hour with (you put it in) dinner, a video, and then I will leave so you don't have to entertain me."
14. "It's okay, you don't have to be brave for me. Let me be the strong one for a while."
15. "It is a gift to me that you permit me to help and support you. I know how hard it is for you to ask for help."

PART VIII - DEALING WITH INTERFERON AND OTHER THERAPY

"'Tis better to suffer the slings and arrows of outrageous interferon, than to be sawed in half for a transplant." - *Cindy Torchin* *cindyt@cpcug.org*

The good news is that the new DAA treatments have few, if any, side-effects. Some people still have to take interferon-based therapies, so this section is for their benefit. And of course, many of these symptoms are experienced from time to time.

Taking care of yourself during your interferon therapy is important. It can lessen some of the physical side effects you may experience.

A few simple tips can make a big difference in how you feel, and knowing some ways to take care of yourself can give your emotions a boost at a time when you may be feeling that much of what's happening to you is out of your control.

This feeling can be easier to deal with when you discover how much you can contribute to your own well-being. Remember though, that self-help is never a substitute for professional medical care. Be sure to ask your doctor and nurse any questions you may have about your medication, and tell them about any side effects you may experience.

VIII.1.0 GENERAL TIPS FROM MERCK

To help relieve some of the side effects of Intron A (interferon alpha-2b, recombinant) for Injection therapy, follow this simple A-B-C approach:

- A nalgesics such as acetaminophen or ibuprofen can be used to prevent or partially alleviate the fever and headache.
- B edtime administration of Intron A therapy will allow you to sleep through the "flu like" symptoms of therapy.
- C onserve your energy; try to get plenty of rest.
- D rink plenty of fluids; keep yourself well hydrated before and during therapy.
- E at balanced meals; make sure your are getting an adequate amount of calories in your diet.
- F ocus on the positive; maintain a healthy mental outlook.

The most common side effects associated with Intron A therapy are mild to moderate flu-like symptoms, which usually diminish after the first few weeks of therapy. These may include fever, headache, fatigue, weakness, chills, and muscle and joint pain.

Other frequently occurring symptoms are nausea, loss of appetite, diarrhea, and hair loss. They are common at the start of therapy and should not alarm you. If you have any questions about your side effects or medication, make sure to call your doctor.

VIII.2.0 HOW DOES INTERFERON WORK?

Alpha interferon works differently in the various diseases it is used to fight. In hepatitis C the virus invades and destroys liver cells; interferon lowers the virus population to a level where it no longer causes injury. Interferon helps by stimulating immune cells that in turn repel the invasion. Some hepatitis patients don't respond to interferon at all; others do, but some of them relapse when they stop taking it, or even during treatment.

VIII.2.1 WHAT WILL INTERFERON ACHIEVE?
Even when the interferon does not cure the disease, it can help to put the virus into remission for a while, giving your liver a much needed break, and helping you to live longer and more comfortably.

A study presented at the AASLD 50th Annual Meeting (Nov 1999) showed that even non-responders to interferon treatment have positive results. Interferon has been shown to halt and even reverse fibrosis in non-responders, and to slow down the rate of progression by reducing the rate of inflammation, and lowering the viral load.

VIII.2.2 WILL I BE ABLE TO CONTINUE WORKING WHILE I'M ON TREATMENT?
Most people are able to continue working while they are being treated, even with interferon. It may be possible to schedule your shots late in the day or right before the weekend, (or whenever you determine your worst side effects - if any - occur) so they interfere with work as little as possible.

If your interferon treatment makes you very tired, you might want to think about adjusting your work schedule for a while. Speak frankly with your employer about your needs and wishes at this time. You may be able to agree on a part-time schedule, or perhaps you can do some of your work at home. Under federal and state laws, some employers may actually be required to allow you to work a flexible schedule to meet your treatment needs.

DAAs typically have comparatively few side effects. There are exceptions.

VIII.2.3 HOW WILL I KNOW IF THE INTERFERON IS WORKING?
Your doctor and nurse will use several methods to measure how well your treatments are working. You will have frequent physical exams and blood tests. Don't hesitate to ask the doctor about the test results and what they show about your progress. I like to keep copies of my tests.

While tests and exams can tell a lot about how the interferon is working, side effects tell very little. Sometimes people think that if they don't have side effects, the drugs aren't working or that if they do have side effects, the drugs are working well. But side effects vary so much from person to person, that having them or not having them usually isn't a sign of whether the treatment is effective. If you do have side effects, there is much you can do to help relieve them. The next section of the FAQ describes some of the most common side effects the people may experience while taking interferon, and gives you some hints for coping with them.

If you are reading this section before you begin taking interferon, you may feel overwhelmed by the wide range of side effects it describes. But remember: Not every person gets every side effect, and some people get few, if any. In addition, the severity of side effects varies greatly from person to person. Whether you have a particular side effect, and how severe it will be, depends on your own particular dosage and injection schedule, and how your body reacts. Be sure to talk to your doctor and nurse about which side effects are most likely to occur for you, how long they might last, how serious they might be, and when you should seek medical attention for them.

VIII.3.0 SIDE EFFECTS

VIII.3.0a NAUSEA
Nausea and vomiting can often be controlled or at least lessened. If you experience this side effect, your doctor can choose from a wide and ever-growing range of drugs that help curb nausea and vomiting. Different drugs work for different people, and it may be necessary to use more than one drug to get relief.
Don't give up. Continue to work with your doctor and nurse to find the drug or drugs that work best for you.
You can also try the following ideas:
- Avoid big meals so your stomach won't feel too full. Eat small meals throughout the day.
- Drink liquids at least an hour before or after mealtime, instead of with your meals.
- Eat and drink slowly.
- Stay away from sweet, fried, or fatty foods.
- Eat foods cold or at room temperature so you won't be bothered by strong smells.

- Chew your food well for easier digestion.
- If nausea is a problem in the morning, try eating dry foods like cereal, toast, or crackers before getting up.
- Drink cool, clear, unsweetened fruit juices, such as apple or grape juice, or light-colored sodas, such as ginger ale, that have lost their fizz.
- Suck on ice cubes, mints, or tart candies.
- Try to avoid odors that bother you, such as cooking smells, smoke, or perfume.
- Prepare and freeze meals in advance for days when you don't feel like cooking.
- Rest in a chair after eating, but don't lie flat for at least 2 hours.
- Wear loose-fitting clothes.
- Breathe deeply and slowly when you feel nauseated.
- Distract yourself by chatting with friends or family members, listening to music, or watching a movie or TV show.
- Popsicles
- Sea Bands are elastic bands worn around the wrist, with a small built-in "bump" which presses against an acupressure point on your wrist. Many people find these to be extremely helpful for both nausea and dizziness. Sea Bands can be found in most Sporting Goods departments, or fishing supply stores.
- Peppermint tea works wonders for nausea, as does a **small** (very small) drop of peppermint essential oil on the tip of your tongue.
- Many people find chewing on candied ginger helpful. You can find candied ginger available in the spice department, or in the Oriental foods section of your grocery store. Or you can put a pinch of dried ginger in powder on the tip of the tongue or chew a piece of the root. Or drink a tea: boil one cup of water with a slice of fresh ginger root (or 1/2 teaspoon of dried ginger powder) for 10 minutes. Strain it and add a few drops of lemon.

VIII.3.0b HAIR LOSS

Some people experience hair loss as a side effect of interferon, but it doesn't always happen. It may range from a slight to moderate amount of hair loss, but I have never seen anyone become completely bald from the dosages given for hepatitis. The hair grows back after the treatments are over. When your hair does begin to grow back in, it may come in thicker, curlier, or straighter than it did before your interferon therapy. Hair loss can occur on all parts of the body, not just the head. Facial hair, arm and leg hair, underarm hair, and pubic hair may all be affected. Hair loss usually doesn't happen right away; more often, it begins after a few weeks. At that point, hair may fall out gradually or breaks at or near the skin, and the scalp may become tender. Any hair that is still growing may become dull and dry.

To care for your scalp and hair:

- Use mild shampoos.
- Use soft hair brushes.
- Use low heat when drying your hair.
- Don't use brush rollers to set your hair.
- Don't dye your hair or get a permanent.
- Have your hair cut short. A shorter style will make your hair look thicker and fuller. It will also make hair loss easier to manage if it occurs.

There is a special type of shampoo and conditioner designed specifically for people undergoing chemotherapy. Many people have reported good results using it while taking interferon. The brand name is "Nioxin" and it is sold only in salons.

VIII.3.0c FATIGUE

Fatigue is a common symptom of hepatitis, and it can become worse while you are taking interferon. Here are some things you can do to help yourself feel better:

1. Get plenty of rest. Sleep more at night and take naps during the day if you can. Try to schedule regular rest periods each day.
2. Limit your activities: Do only the things that are most important to you.
3. Delegate tasks. Don't be afraid to get help when you need it. Ask family and friends to pitch in with things like child care, shopping, housework, or driving.
4. Eat well, and be sure to include plenty of healthy foods.
5. When sitting or lying down, get up slowly. This will help prevent dizziness.
6. Don't stand when you can sit.
7. Plan your activities and assemble everything before you start.
8. Reschedule daily tasks so you do some only 3 or 4 times a week so you have time to rest each day.
9. Use a cart, wagon or basket to carry things from one part of the house to the other to eliminate retracing your steps.

10. Sit on a stool in the bathroom while shaving or applying makeup. Prop elbows up on counter if you can.
11. Use warm, not hot water for baths or showers. Hot water increases muscle fatigue.
12. If your fatigue is severe, think about asking your doctor for a handicap sticker for your car.
13. Shop when you are at your peak energy.
14. When shopping alone, ask a grocery clerk to carry out groceries.
15. If you arrive home from grocery shopping tired, put away only the perishables. A family member or friend can do the rest.
16. Shop by phone whenever possible.
17. Avoid peak shopping/traffic hours.

VIII.3.0d MOUTH PROBLEMS

If mouth dryness bothers you or makes it hard for you to eat, try these tips:

- Ask your doctor if you should use an artificial saliva product to moisten your mouth.
- Drink plenty of liquids.
- Suck on ice chips, popsicles, or sugarless hard candy. You can also chew sugarless gum.
- Moisten dry foods with butter, margarine, gravy, sauces, or broth.
- Dunk crisp, dry foods in mild liquids.
- Use lip balm if your lips become dry.
- Avoid food with a lot of condiments (chilies, salt, acidity).
- If possible, see your dentist before you begin taking interferon to have your teeth cleaned and to take care of any problems such as cavities, abscesses, gum disease, or poorly fitting dentures.
- Brush your teeth after every meal. Use a soft toothbrush and a gentle touch; brushing too hard can damage soft mouth tissues.
- If your gums are too sensitive for even a soft toothbrush, use a cotton swab or gauze. Use nonabrasive toothpaste or a paste of baking soda and water.
- Rinse your toothbrush well after each use and store it in a dry place.

MAGIC MOUTHWASH

Magic Mouthwash was developed at Duke, and consists of the following ingredients (any pharmacist can do this):

NDC Number	Metric Quantity
00143-1254-01	6.00 Hydrocortisone 20 mg tablet
000536-1220-85	60.00 Nystatin 100000 U/mL Susp (an antifungal)
99999-9999-99	420.00 Benadryl

More mixtures from Peppermint Patti:

First Magic Mouthwash Recipe

1/3 Maalox
1/3 liquid Benadryl
1/3 lidocaine viscose 2% solution

(You can buy Benadryl and Maalox at the pharmacy, over the counter. I easily got a prescription for Lidocaine at walk-in clinic when they saw my mouth).

Second Magic Mouthwash Recipe

1/3 liquid prednisone syrup 5mg/5mL
1/3 liquid Benadryl
1/3 liquid Nystatin

VIII.3.0e INFECTIONS

Interferon can decrease your white blood cell count (these are the cells that fight infections). Your doctor will check your blood cell count often while you are taking interferon, and if your white cell count falls too low, your doctor may lower the dosage of interferon for a while to give your body a chance to rebuild its defenses.

When your white count is lower than normal, it is very important to try to prevent infections by taking the following steps:

- Wash your hands often during the day. Be sure to wash them extra well before you eat and before and after you use the bathroom.
- Clean your rectal area gently but thoroughly after each bowel movement. Ask your doctor or nurse for advice if the area becomes irritated or if you have hemorrhoids.
- Stay away from people who have diseases you can catch, such as a cold, the flu, measles, or chickenpox. Also try to avoid crowds.
- Don’t cut or tear the cuticles of your nails. Use cuticle cream and remover instead.

- Be careful not to cut or nick yourself when using scissors, needles, or knives.
- Use an electric shaver instead of a razor to prevent breaks or cuts in your skin.
- Use a soft toothbrush that won't hurt your gums.
- Don't squeeze or scratch pimples.
- Take a warm (not hot) bath, shower, or sponge bath every day.
- Pat your skin dry using a light touch. Don't rub.
- Use lotion or oil to soften and heal your skin if it becomes dry and cracked.
- Clean cuts and scrapes right away with warm water, soap, and an antiseptic.
- Wear protective gloves when gardening or cleaning up after animals.
- Do not get any immunization shots without checking first with your doctor to see if it's all right.

Even if you take extra care, you may still get an infection. Be alert to the signs that you might have an infection and check your body regularly for its signs, paying special attention to your eyes, nose, mouth, and genital and rectal areas. The symptoms of infection include:

- Fever over 100 degrees F.
- Chills.
- Sweating.
- Loose bowels
- A burning feeling when you urinate.
- A severe cough or sore throat.
- Unusual vaginal discharge or itching.
- Redness or swelling, especially around a wound, sore, pimple, or boil.

Report any signs of infection to your doctor right away.

VIII.4.0 IMPORTANCE OF WATER

It is extremely important to drink all of the water that you can stand (and then drink some more) when you are taking interferon. It not only dramatically decreases the severity of side-effects, but there is also a danger of serious kidney infections if you do not drink enough. Milk/soda/coffee/tea don't count. You need genuine water. See more about **Water**

VIII.5.0 TRAVELING WITH INTERFERON

When flying with interferon, it won't be affected by going through the x-ray machine. If you are worried about it, you can always just stick it in your pocket and walk through the metal detector. Since the horror of September 11th, it might be advisable to carry your prescription with you, as proof as to why you are carrying syringes. In order to keep the interferon cool, you can pack it in a Thermos bottle, or freeze a blue ice pack and put it into a soft thermal lunch bag, and wrap the interferon in newspaper so that it doesn't sit directly on the ice. This should last you for a few days. **Do Not** put ice in a glass Thermos. It can break the glass (personal experience). If possible get a stainless steel Thermos. I don't know if they're as good, but they don't break. When in a hotel you can just fill the ice bucket and then put a glass with the interferon bottles on top so if the ice melts the interferon will not get wet.

VIII.6.0 TIMING OF INJECTIONS

Merck (the manufacturers of Intron-a) recommend giving yourself the injections in the evening so that you can sleep through the worst of the side effects. A better idea is to keep track of when your worst side effects occur, and then time your shots so that they occur when you are asleep. For some people, this may even mean giving yourself the injections in the morning.

VIII.7.0 INJECTION HINTS

1. Clean the surface of your work area.
2. Have an alcohol swabs, bandage, a needle, your sharps container and your instructions handy.
3. Take one syringe or vial to where you inject, leaving the rest in the refrigerator.
4. Warm the syringe or vial by rolling it between your hands for approximately one minute.
5. Wash your hands with soap and water.
6. Attach the needle to the syringe (if it isn't, already) and twist it to lock it. Set it down on your work area.
7. Choose an injection site; clean it with an alcohol wipe, starting at the spot where you are going to inject and using a circular motion clean from that point out a few inches.
8. Wipe the vial top with an alcohol wipe also.
9. When you're ready to inject, pull the safety cover off the needle.
10. PRE-MIXED SYRINGES: ***(Skip to the next paragraph if you have a mix-it-yourself kit)***

Point the needle up towards the ceiling and flick the syringe near the vial with your finger to get the air

bubbles to the top. Push them out with the plunger.
10. POWDERED MIX-IT-YOURSELF KIT:
Fill the syringe: Pull the top off the syringe. Holding the vial in one hand, have the syringe in the other and brace both hands together so you can pierce the center of the vial without blunting the needle. Turn the vial upside down and draw in the IFN. Push out the air (vial and syringe still upside down). Then draw to the full dose, occasionally pushing out air bubbles. I draw a little more past the fill level, so if it's a 3mil dose instead of the .5cc I go to a couple of small marks beyond 0.5cc. Take the needle out of the vial. Holding the syringe needle up, push the plunger to the correct level (e.g., .5cc). This gets rid of any air in the needle.
11. Hold the syringe like you hold a pencil, with the opening of the needle facing up.
12. With one hand pinch the skin/fat layer at the injection site. As fast as possible push the needle into the layer with the syringe at a 45 degree angle to the skin. The faster the needle goes in, the less pain there is. (Another way is to pretend the needle is a thumb tack. Place the needle against your skin, and then tell yourself that the nerves are on the surface of the skin, and the needle is already there. Pushing it in won't make it hurt any more than what you feel with the needle against your skin. Push. It works for me. I don't worry about "missing". --Joan)
Pull the syringe straight back. You get less bleeding if you don't play twister. Drop the syringe in the sharps container. Cover the area with a bandage.

Things that happen after injection:
Sometimes there will be a tiny bit of blood after an injection. This just means you've probably popped some capillaries or punctured a small vein. It's nothing to worry about; just cover it up with a bandage and let it clot.
Bruising is also very common after shots. You may be able to avoid bruising and bleeding if you choose a spot with no visible red or blue veins.
The day after a shot, a red area is quite normal. They can range from dime size to silver dollar size and may feel hot and tender. A small area is fine, but if it gets much bigger and hotter, or you see something that looks infected, contact your doctor.
Sites: Most people use their thighs for injections. Some people find the lower abdominal area (*not* around the belly button) to be the least painful spot for injections.
Sharps containers: You should be provided with one, either from where you get your interferon (pharmacy or home delivery) or your doctor's office. If you have a problem getting one, puncture-proof soda bottles can be used to temporarily hold the used syringes until you can take them to your doctor's office and ask them what to do with them. If you do this enough times, eventually, someone might get the idea you need a real sharps container. If you have children and/or cats, keep your sharps container locked up. The hole is inviting to small hands and paws.
Some find it helpful to numb the injection site beforehand. An icepack (or a bag of frozen peas) placed on the injection site a few minutes ahead of time will make the shot relatively painless.
To help prevent bruising, some people recommend using only half of the diluent provided (This does not apply to the pre-mixed syringes).

If you are having a problem giving yourself a shot, ask your pharmacist for a B-D Automatic Injector, Inject-Ease. They cost about $25.00, and are well worth every penny. You simply load the syringe into the automatic injector, place it on the injection site, and push a button. It is virtually painless, and also makes it much easier to choose a site to inject, thereby giving you more sites per thigh or tummy.

VIII.8.0 HELP! I THINK I HIT A VEIN!
It's almost a sure thing that at least once you will pull the needle out and find blood and bruises. Unless you are injecting into your neck and hit the jugular you have no problem! And even then, with the size of needles we use, it would be real hard to have a bleeding problem. The skin is "rich" with blood supply, so it's just a matter of time before you "nail" something that bleeds or shows up as a bruise (not just the normal interferon reaction).
Normally, if you hit an actual vein, there will be no doubt in your mind, as the blood tends to come up into the needle very quickly. If you only see bruising or a small drop or two of blood, chances are that you only went through some capillaries and it's nothing to worry about.
The only important thing to do if you are bleeding after an injection is to cover it with a Band-Aid. Even for long-term interferon users there is enough clotting factor to stop the bleeding in a few minutes. The Band-Aid is to stop making a mess. Interferon is given intramuscularly and intravenously for other conditions, so even if you are "lucky" enough to find a real vein or vessel the interferon won't hurt you.
The caution against injecting the interferon intravenously is because interferon is very irritating and can cause a slight phlebitis (inflammation of the vein). Also it will be painful once the reaction starts, with swelling and redness. If that ever happens to you first apply cold compresses to keep the swelling down and take your favorite painkiller. If after 24 hours the swelling becomes worse, along with increased pain and redness, apply warm compresses and call your doctor or go to the emergency room.

VIII.9.0 WHAT DO I DO WHEN I CAN'T AFFORD TREATMENT?

Merck, the manufacturer of Intron-A recombinant alpha-interferon 2b, has a cost sharing program called "Commitment to Care" designed to help those in need of interferon therapy who are unable to afford it. The program is based on a sliding-scale based on your income, with the cost to you ranging from free in some cases, to whatever their scale says you can afford. They will first try to find programs in your State that may help, and if none are found they will determine what you are able to pay and absorb the rest of the cost.

In the US: The number to call for the "Commitment to Care" program is 1-800-521-7157, ext 147.

The interview will take approximately a half hour. Some of the questions you will be asked are:

- Name and address of the prescribing doctor -dosage you will be using
- When you were diagnosed
- Your income (need to send them tax forms or pay stub to verify)
- Number of people in household
- Why you are unable to pay
- Cost of your rent or mortgage
- Any outstanding loans
- Amount of credit card debt
- Any savings

In Canada:

MerckCare™ is a program to help people who have been prescribed PEGETRON™, VICTRELIS™ or VICTRELIS TRIPLETM. The program provides:

- assistance with reimbursement and/or insurance claims.
- financial assistance for co-pay/
- deductible for people who qualify.
- 24/7 nursing support by phone.
- multilingual assistance.
- home delivery of medication.

MerckCare™ provides all of these services free of charge.

To enroll in MerckCare™, you can call 1-866-872-5773 or your doctor or nurse can submit an enrollment form for you. Reimbursement specialists are available from 8:00 a.m. to 8:00 p.m. EST Monday to Friday, excluding statutory holidays.

AbbVie Care

With the approval of HOLKIRA™ PAK, AbbVie is launching AbbVie Care, which is a program that will provide best-in-class solutions to improve outcomes for people living with hepatitis C.

Canadians prescribed HOLKIRA PAK will have the opportunity to request to be enrolled in AbbVie Care. The signature care program is designed to provide a wide range of customized services including reimbursement assistance, education and ongoing disease management support. AbbVie Care will not only support health care professionals but people living with genotype 1 hepatitis C throughout their treatment journey to achieve high cure rates in the real world.

For enquiries: 1-844-471-2273.

Janssen's GALEXOS™: **BioAdvance®** program can assist you in many ways during your treatment. This includes compiling and submitting, on your behalf, all the forms and documents required by your insurance company to request coverage of GALEXOS™, and following up with your insurer to get you the best coverage possible. If you don't have private insurance, the GALEXOS™: BioAdvance® program will investigate public assistance programs that can help pay for your treatment. Whichever type of coverage you have, if your insurance does not fully cover the cost of treatment, the GALEXOS™: BioAdvance® program can usually coordinate and provide financial assistance to help you get treated. Finally, the program can offer many other types of support and your doctor and members of your healthcare team will work with the GALEXOS™: BioAdvance Program to develop a customized approach to best support you throughout the course of your treatment. Contact: 1-855-512-3740.

Pendopharm has established the **IBAVYR™** Patient Support Program. The program will assist patients who have been prescribed IBAVYR™ (ribavirin tablets) with reimbursement navigation, financial assistance and pharmacy services. Case managers will support patients with insurance-related matters and assess eligibility for financial support. Pharmacy services include adherence support, medication delivery and counselling.

To enquire or to enroll, you may call 1-844- 602-6858 Monday – Friday 7am to 11pm EST. IBAVYR™

Vertex's **Incivek Care Patient Assistance Program** supports patients with the reimbursement process for Incivek (telaprevir) treatment (Incivek, pegIFN, ribavirin). It will give you an efficient

assessment of your options and eligibility. You may qualify to receive co-payment and other financial assistance to supplement your private and provincial drug program coverage. The program also provides dispensing and home delivery options, and expert treatment advice. Call the Support Line at 1-877-574-4298. (Select option 2 for English, then 2 for Incivek Care).

Mometum Support. To learn more about SOVALDI™ or the Momentum Program in Canada, the patient should speak to his/her doctor or nurse or call the Gilead Sciences Canada medical information line at 1-866-207-4267. Eligible patients may receive an integrated offering of support services for patients and healthcare providers throughout the entire treatment journey, including:

- Access to dedicated case managers/reimbursement navigators to help patients and their providers with insurance-related needs, including identifying alternative coverage options through private, federal and provincially-insured programs.
- The SOVALDI™ Co-pay assistance program, which will provide financial assistance for eligible patients who need help paying for out-of-pocket medication costs.
- Medication delivery services.
- Compliance and adherence programs

The **PegAssist** Reimbursement Assistance Program provides reimbursement coordination assistance for patients who have been prescribed Pegasys or Pegasys RBV. The program will assist in securing funding for patients to ensure that they can start, stay on, and complete their treatment successfully. PegAssist Reimbursement Specialists are available (Monday to Friday, 10 AM - 6 PM EST) by calling: 1-877-PEGASYS or 1-877-734-2797. Patients can also obtain a program enrollment form from their nurse/physician to gain access to the program. The program provides financial aid to qualified patients, alleviating financial barriers which may prevent patients from starting treatment, i.e., deductibles and/or co-payments. In partnership with CALEA Pharmacy, the program can conveniently deliver the medication directly to patients' homes or to the clinics.

Concerns like these will be answered:

- I don't know who is supposed to pay for my treatment.
- I don't think I have coverage.
- I have no coverage and I can't afford to pay for it myself.
- I have insurance but I can't afford my co-pay or deductible.
- I have insurance but they won't pay for Pegetron.
- My government plan is too complicated for me to understand.
- My government plan only pays for a portion of my treatment and I can't afford the rest.
- They tell me that my treatment is not covered. What do I do now?

OTHER THINGS YOU CAN DO:

- Make sure you sign up for BC's FairPharmacare or its equivalent throughout the rest of Canada. Your deductible is decided using your tax return information.
- Check with any extended medical insurance you or your spouse may have. That may take care of part or all of the deductible.
- If you are on disability or EI, that may be taken into consideration, as well.
- Explore the possibility of a clinical trial. See **CLINICAL TRIALS**
- Ask your specialist if you are eligible to receive a medication otherwise unavailable by means of Special Access. (See www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/index-eng.php)

Also, in the US: IV ONE (800) 892-9622
Call for help with interferon costs. This operation will accept whatever your insurance company will pay as full payment in most cases. For dosages above 3 million units, your physician must write a special request to your insurance company first. They send your prescription in pre-mixed dosage syringes, alcohol swabs, Band-Aids and a sharps biohazard container for the used syringes, each month by FedEx. They deliver nationally, so their office location does not preclude anyone from using their service. The staff is available 24 hours a day to answer any questions or give you any assistance you may need.

PART IX - EMPLOYMENT AND DISABILITY

IX.1.0 INCOME SECURITY: JOB AND/OR DISABILITY BENEFITS

Canadians, see **HEPATITIS C AND DISABILITY BENEFITS IN BRITISH COLUMBIA**, below, and also this link: *www.servicecanada.gc.ca/eng/services/pensions/cpp/disability/benefit/*
Please, please! Get advice from an experienced disability advocate before you submit your forms. Get your doctor to provide the records you need, but send them in personally, not through your doctor, AFTER you go over them with the advocate. Some of the advice below for the US may apply to Canadians, as well.

IX.1.1 HOW DO I HANDLE PROBLEMS ABOUT MY JOB?

- If your work is, or will likely be, affected by your illness, educate your boss about your condition. Do this soon.
- You may need their support later when more problems may arise, and it will be easier to educate them while you are still relatively productive and "credible".
- Understand that you might have to make some severe changes: a change of job, or perhaps an involuntary loss of your job and a shift to disability benefits.
- Beware of the trap of losing important disability benefits if you switch to part time work. Many HCV patients whose health was spiraling downwards had switched to part-time work to preserve their place with their employer. Later, when their health deteriorated even more and they needed to seek disability benefits, they found out too late that those benefits for a part-time employee did not include a livable income, whereas if they had gone straight from full-time to disability, the disability payments were much more livable. Be careful.

IX I.1.2 WHAT PROBLEMS DO I FACE IN SEEKING DISABILITY BENEFITS?

You can order a Disability Workbook for Social Security Applicants for $20.00 from: **Physicians' Disability Services, Inc., P. O. Box 827, Arnold, Maryland 21012**

IX.1.3 APPLYING FOR SSI / SSDI

According to the Social Security Administration's SSA Pub. No. 05-10029 April 1995, the definition of "disability" is as follows:

"Disability under Social Security is based on your inability to work. You will be considered disabled if you are unable to do any kind of work for which you are suited and your disability is expected to last for at least a year or to result in death."

1. Are you working? If you are and your earnings average more than $500 a month, you generally cannot be considered disabled.
2. Is your condition severe? Your impairments must interfere with basic work-related activities for your claim to be considered.
3. Is your condition found in the list of disabling impairments?
   We maintain a list of impairments for each of the major body systems that are so severe they automatically mean you are disabled. If your condition is not on the list, we have to decide if it is of equal severity to an impairment on the list. If it is, your claim is approved. If it is not, we go to the next step.
4. Can you do the work you did previously? If your condition is severe, but not at the same or equal severity as impairment on the list, then we must determine if it interferes with your ability to do the work you did in the last 15 years. If it does not, your claim will be denied. If it does, your claim will be considered further.
5. Can you do any other type of work? If you cannot do the work you did in the last 15 years, we then look to see if you can do any other type of work. We consider your age, education, past work experience, and transferable skills, and we review the job demands of occupations as determined by the Department of Labor.

   If you cannot do any other kind of work, your claim will be approved.
   If you can, your claim will be denied.
   To get information from the Social Security Administration, call 1-800-772-1213.

IX.1.4 WINNING YOUR SOCIAL SECURITY DISABILITY CLAIM: 15 Mistakes You Cannot Afford to Make! *by Scott E. Davis, Esq. and Scott M. Harris, Esq.*

This article reprinted with permissions from the Hep C Connection in Denver Colorado. Although written with the US population in mind, the issues raised below apply equally to filing for disability in Canada. In Canada, however, there is a network of community advocates, paralegals and legal aid lawyers in place who will represent you for free if your finances are limited.

Mistake #1: Assuming that what SSA tells you is true.

Unfortunately, some of the advice that Social Security Administration (SSA) employees provide to the public is incorrect. So if you aren't happy with what SSA told you over the telephone, you'll be glad to know it may not be correct. The problem is, many people don't file a disability claim for years (and go without benefits they deserve) simply because an SSA employee gave them bad information.

Advice: Don't give up on your claim until after you have reviewed your case with a disability lawyer. Disability lawyers know more about the law than SSA employees and will give you correct information.

Mistake #2: Assuming the Social Security Administration will approve your claim.

Many people believe that because they have paid into SSA, their claim should easily be approved when they apply for disability benefits. Many people believe it's just a matter of filling out the forms and going through the process. But this isn't true. SSA denies 70 to 75% of first-time claims. SSA denies 82% of claims that are appealed for Reconsideration. However, the good news is that when cases are heard before judges, nationwide over half (53%) are approved.

Advice: Appeal every denial within 60 days of receipt. Build a strong case by understanding what information Social Security requires. Make sure to present your case properly.

Mistake #3: Assuming the disability forms you fill out will win your case.

Usually they will not. Claimants hurt their case by overstating what they can do. In most cases, SSA and judges rely heavily on medical records as well as your doctor, psychiatrist, and/or psychologist's opinion about your ability to work full-time. If the judge isn't happy with you, if he doesn't believe what you're saying, or if he is looking for a reason to deny your claim, he may look for inconsistencies in answers you provided earlier on the forms. For example, if you answer one way on the form and testify at a hearing to something else, the judge may use the answer on the form to undermine your credibility and support a denial of your claim.

Advice: When completing the forms, be honest, accurate, and brief! You should always answer the question in the space provided--do not attach additional sheets of paper or write in the margins. Also, it is important to assume you are back working full-time on a sustained basis (8 hours per day, 5 days per week) when answering questions about what you are capable of doing.

Mistake #4: Assuming that your medical and/or psychological symptoms will be enough for the judge to approve your claim.

Not true. You need detailed medical records, which document your symptoms and limitations and specific opinions from your doctor, psychiatrist, and/or psychologist if you hope to win your case. Their opinions will only be given weight by the judge if you have received continuous and consistent medical treatment. If you are not meeting regularly with your doctor, you are jeopardizing your case!

Advice: It is critical that you receive continuous and consistent medical treatment and care so you can provide SSA and a judge with current and complete medical records which support your doctors' opinions.

Mistake #5: Assuming your diagnosis will win your claim.

It won't. It's true that SSA needs a diagnosis. But SSA also needs medical proof that your diagnosis causes limitations that are so significant and severe that they preclude your ability to work full-time on a sustained basis.

Advice: Disability cases are won based on your limitations, not your symptoms. Make sure you provide detailed medical records from your doctor that reflect your symptoms, the diagnosis, and your limitations.

Mistake #6: Assuming SSA will be persuaded by any type of medical treatment you choose.

It will not. You can choose any alternative therapies and holistic treatments you desire. After all, you should do whatever it takes to try to get better. However, be aware that SSA and judges are most persuaded by mainstream doctors (M.D., D.O., and psychologists) and how you respond or fail to respond to mainstream treatment. If you are not taking medications or are not receiving mainstream treatment by a mainstream doctor, you may be jeopardizing your claim.

Advice: To win your claim, try to exhaust every medical treatment your mainstream doctors recommend, so you can prove that in spite of doing so, you continue to be unable to work full-time on a sustained basis.

Mistake #7: Assuming your family doctor's opinion is the only one you need.

This may not be a good choice depending upon your diagnosis. If your diagnosis is usually made and treated by a specialist (M.D., D.O., Ph.D.), you should treat with both a board-certified specialist and your family practitioner. From a legal standpoint, you want to show the judge your diagnosis is correct and that you are receiving the best possible medical care. You have a stronger case when your doctor is a specialist who is skilled and experienced at treating people who have your condition. Social Security law generally gives more weight to the opinions of a specialist than a general practitioner. As a result, SSA and the judge will look more closely at the credentials of the doctor who is providing the opinion.

Advice: Get your medical treatment from a specialist because the more skill and experience your doctor has, the more likely you are to win your claim. Note: If you are a member of an HMO and they will not allow you to go to a specialist, consult with your disability lawyer, who can help you get appropriate treatment.

Mistake #8: Assuming your doctor will support your claim for disability benefits.

He may not. Some doctors refuse to help patients with their disability claims. Many doctors do not know SSA's definition of disability and believe that one has to be bedridden to qualify. In general, doctors are very conservative in their opinion about a patient's ability to work. Because SSA and a judge will want to know if your doctor supports your claim, it is critical you know the same information! After you have established a relationship with your doctor you should discuss with them the fact that you have filed a claim for disability. Ask if they will support your claim, and if they will not, you should consider finding another doctor because their opinion is not likely to change! It is critical your doctor supports your inability to work full time on a sustained basis!

Advice: As soon as practicable, you should learn whether your doctor supports your disability claim. If not, consider finding a more compassionate doctor who will. One place to find a referral is to attend a local support group for individuals who share your diagnosis.

Mistake #9: Assuming you have to go to SSA's doctor for a medical examination.

Often, SSA wants to a claimant to go a disability examination with a doctor/psychiatrist/ psychologist it chooses. Unfortunately, the doctor is not really "independent" and probably performs many of these examinations for SSA each month. In my experience, the majority of the time the doctor will conclude you are not disabled and can return to work. Once this opinion is included in your file SSA and a judge will have sufficient evidence to deny your claim. Here's the good news: SSA rules allow your doctor to perform the disability exam and SSA should pay for all or at least part of it. Naturally, if your doctor supports your disability claim he will probably conclude your condition precludes your ability to work. Once your doctor's exam report is in your file with a conclusion that you are disabled, SSA and a judge may have sufficient medical information to approve your claim.

Advice: This strategy is only possible if you are certain your doctor supports your claim and is willing to do the examination. If you do not have a doctor, or your doctor will not perform the examination, you must go to SSA's doctor or risk having your claim denied or closed out. This strategy really should only be employed by a disability lawyer because complex regulations are involved and must be complied with.

Mistake #10: Assuming an entire year has to pass before you can file a disability claim.

Not true. SSA law requires that before you can be approved one of the following must be true: (1) you have already been disabled and out of work for one year, or (2) your doctors expect that you will be unable to work for a minimum of one year from the date you last worked, or (3) your medical condition is expected to result in death. Too many people have told me that an SSA employee said they could not file a claim until one year had passed since they last worked. This information is totally incorrect and if followed, will almost certainly cost you disability benefits and medical insurance!

Advice: Apply for disability benefits as soon as you or your doctors believe your medical and/or psychological condition will preclude you from working for at least one year. Waiting to file will only cost you benefits that you may not be able to recover.

Mistake #11: Assuming that if you lose before a judge at a hearing, you can simply file another claim.

When you have a hearing before a SSA judge, you do not want to lose. This is because, practically speaking, your best chance at winning is at your first hearing before a judge. True, you can file a second application if you lose at a hearing; however, the second time you go through the process, SSA and a judge will know your first claim was denied. In my opinion, this may have a detrimental effect on your second claim as the second judge will know.

Advice: Make sure your case is properly prepared so you can present your strongest case at the first hearing.

Mistake #12: Assuming you can handle your case without a disability lawyer.

Most people can't. SSA disability laws are complex; even many lawyers do not understand them. To win your claim, you need to very carefully prepare your case from the very beginning. In addition, it is critical to understand what you need to prove legally in order to win your case; if you do not know what you need to prove, why would you risk going before SSA or a judge without knowing how to win your case? The fact that you and your doctor agree you are disabled is not enough to win your case.

Advice: Retain only an experienced disability lawyer. They will help build your case, develop a case strategy, and obtain a complete set of your medical records and critical opinions from your doctor that will maximize your chances of success. More often than not, your doctor will not be familiar with the stringent criteria that SSA and a judge will utilize in determining whether you meet their definition of disability.

Mistake #13: Assuming any lawyer can help you win your claim.

Not true. You want a disability lawyer who is familiar with SSA laws and regulations. Similar to doctors, attorneys generally specialize in a certain area of the law. You wouldn't go to a dentist for a physical examination, so do not pick just "any" attorney to represent you in your disability claim.

Advice: Choose a disability lawyer whose practice is dedicated to representing clients because your odds of winning will increase. A seasoned disability attorney will understand the strategy and tactics that are crucial to helping you win your claim.

Mistake #14: Assuming you should not hire a lawyer until your case has initially been denied.

Not true. You can hire a lawyer any time you wish. Unfortunately, many employees at SSA will tell you that it is not necessary to hire an attorney until you have been initially denied. Following this advice could be fatal to your claim! Why? Because in general, SSA will begin preparing a case against you from the day you file your application!

Advice: You should consult with and/or hire a disability attorney as soon as possible after you file your application. The attorney can explain how the process really works and lay the proper foundation for your case by developing a case strategy. The attorney can also guide your case through the myriad of rules and regulations that are certain to have an effect on your entitlement to benefits.

Mistake #15: Assuming that you cannot afford a lawyer.

Not true. In almost every case, you will only pay the attorney a fee if and when you have won your case and received benefits. SSA law limits the amount of money your lawyer can earn from your disability claim. Generally, by the time you win your claim you will have accrued back benefits. The law mandates the fee can only be 25% of your past benefits and is capped at $4,000. In other words, if your back benefits total $1,000.00, the attorney's fee would be $250.00. The law does not allow your lawyer to charge a fee on your future benefits. What may be at stake? By way of example, assume a claimant is 45 years old and their monthly disability benefit is $1,000.00. If the person never returns to work before age 65, their disability benefits would total $240,000.00! This amount does not include the value of the lifetime health insurance they would also receive through Medicare or Medicaid.

Advice: Because the amount of the benefits can be staggering, the truth is, you can't afford not to hire an experienced disability attorney!

Scott E. Davis and Scott M. Harris are attorneys who specialize in Social Security and long-term disability claims. More than 50% of their disability practice is devoted to individuals with FMS and/or CFIDS. Mr. Davis and Mr. Harris are located in Scottsdale, Arizona and represent clients throughout the United States. They invite your questions and inquiries about representation by email harris.davis@azbar.org *or FAX at (602) 482-4300.*

IX.1.5 HEPATITIS C AND DISABILITY BENEFITS IN BRITISH COLUMBIA

Your Doctor(s):

If you have been diagnosed with hepatitis C you should be under the care of a specialist. If you are not, ask your family doctor to recommend one. Your doctors should be your closest allies, both in your battle with hepatitis C and also in obtaining your disability benefits, should you qualify.

Disability Benefits:

There are several types of disability benefits available to residents of BC: Canada Pension Disability Benefits; Disability Benefits from the BC Government; Worker's Compensation; and various private plans. All have very different qualifications, and procedures, which your local advocate can explain to you.

Advocates:

Advocates are community workers who have a great amount of experience fighting for citizens' rights in many areas: housing, income assistance, disability benefits, and so forth. Often advocates can be found at community organisations, such as AIDS organisations, or organisations for the disabled, such as the BC Coalition of People with Disabilities, TAPS or the ACPD. They can also be found at various Legal Services Society offices throughout the province. For help in locating an advocate nearest you, you can call the **Advocacy Access Project** at 1-800-663-1278, or HepCBC at (250) 595-3892.

Often people feel their case is so clear cut that they can take care of it themselves. Big Mistake! Unfortunately, the decision to award disability is not based on how you feel, or even on how you look, but on very special criteria that each disability plan has established. Unless you meet these criteria, you will not get your disability—no matter how deserving you may feel that you are.

Arguing your own case is exhausting. If you are ill, this is the last thing you need. Advocates know the ropes and they are there to help you.

Qualifying for Disability Benefits:

If you are applying for Canada Pension Plan Disability benefits, the most important aspect, aside from

your condition, is whether or not you have made enough contributions to the Canada Pension Plan, and when you have made them. If you have not paid into this plan because you have not been working, or have not worked recently, you may not be eligible. Your advocate, or a lawyer from Legal Services, can help you understand whether or not you should apply for CPP Disability. If you are applying for BC Disability Benefits, it can help if you have applied for and received your CPP, but not having CPP Disability will not disqualify you from getting BC Disability Benefits.

Some of the Issues:

The Run-around:

Getting disability even if you are really sick is not easy. Often you will need to have lots of papers and doctors' appointments and interviews. When you are feeling really sick and tired, it is very frustrating to have to go to one appointment after another, all the while not knowing how you are going to eat, let alone pay the rent.

Hep C and Doctors:

Perhaps the single most important document you will need when making your disability claim is your doctor's letter. Unfortunately, many doctors, no matter how sympathetic they may be to your plight, do not know how to fill in the form properly. Your advocate can provide you with guidelines that you can give to your doctor, to help him or her fill out the form more effectively, or you may wish to compose a sample letter with your advocate to give to your doctor as a guide.

Sadly, there are still many doctors out there who do not understand the nature of hepatitis C. Many continue to think that it is only a liver disease, and that, unless you are suffering from end-stage liver disease (cirrhosis, ascites, bleeding), you cannot be disabled.

Many doctors and specialists are beginning to understand that hepatitis C, while it does cause liver disease, also causes a host of other problems related to autoimmunity. In fact an article in the American Journal of Gastroenterology states that "up to 70% of patients with chronic hepatitis C" may suffer from autoimmune related disorders.[1]

It is the presence of autoimmune activity (your body fighting the hepatitis C virus) that causes the fatigue, muscle aches, confusion, bone aches, feverishness, nausea, itching and mood swings from which people with hepatitis C suffer. Often, none of this can be established by a specific blood test, although some autoimmune disorders do have special "markers" in the blood.

When the Federal Government decided to compensate certain individuals who received tainted blood between 1986 and 1990, they concluded that those under the plan with grade 2 liver fibrosis (a stage of scarring in the liver) would be eligible for "loss of income" payments. In making this decision, the government set a precedent which should make it much easier for anyone with grade 2 fibrosis (non-bridging fibrosis) to qualify for long term disability benefits, which is what "loss of income" payments are.[2]

Those under the compensation scheme with grade 3 fibrosis (bridging fibrosis) or cirrhosis have been awarded even more because the government recognizes that the more heavily scarred the liver is, the more disabled the person will be.

However, in order for anyone to know to what extent your liver is scarred, you must undergo a liver biopsy, which is not the most pleasant of experiences, or possibly a FibroScan will be accepted.

Notes:

1. American Journal of Gastroenterology, Vol 96 number 2, 2001: 910-911.

2. Hepatitis C : January 1, 1986-July 1, 1990 Class Actions Settlement, p. 18.

PART X - IMPORTANT INFORMATION

X.1.0 WHAT ELSE IS IMPORTANT FOR ME TO KNOW ABOUT HCV?

Medical research and acceptance of the illness will develop only if our national support organizations which promote them are strong. Be sure to support your national groups, and when your national group calls for letters and phone calls to be sent to public officials and media, please get your family and friends to assist you in responding to those requests. We may be able to make greater achievements if we act in unison.

In the USA, the largest source of research money comes from government allocations. Therefore, contacting your Congressman about the importance of hepatitis research is very important.

Standard treatment is not successful in treating all HCV patients, since many are not eligible for treatment or cannot tolerate it. Many doctors are not happy with treatment, which they see as too expensive, and as carrying too many side effects. Remember, to the drug companies, profits are the first objective, so question all statistics carefully.

HCV is the leading indication for liver transplants.

According to the New York Blood Center, as many as 25% of people receiving blood transfusions in the early 1960s were being infected with contagious diseases and the majority were infected with hepatitis.

Many hepatitis C cases result from unknown sources. This means someone does not have to be among the high-risk groups to become infected with the virus.

X.2.0 HCV INFORMATION RESOURCES AND SUPPORT GROUPS
To add a group or correct information, please contact info@hepcbc.ca
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X.2.1 USA

- The American Liver Foundation has very nice, down-to-earth pamphlets on treatment and stuff, which they will send to you by calling their number: (212) 668-1000. The American Liver Foundation also provides physician referrals. American Liver Foundation, 39 Broadway, Suite 2700, New York, NY 10006. Helpline: 1-800-465-4837 For programs and support services: *www.liverfoundation.org/contact/programsandsupport/*
- The American Liver Foundation Liver Transplant Fund Program provides liver transplant patients with fundraising guidance; trusteeship and administration of patients' funds at no charge; educational information about liver diseases and transplantation; information brochures as well as brochures on policies, procedures and fundraising.
  For more information, including application form, resources list, and patient agreement form, please contact the ALF Liver Transplant Fund Program:
  www.healthcharities.org/chc.asp?bid=4&OrgID=20
  1-800-GO-LIVER (465-4837) Fax (201)256-3214 Email txfund@liverfoundation.org
- The Hepatitis Foundation International toll free line for email: callers in North America is 1-(800) 891-0707 www.hepfi.org info@hepatitisfoundation.org
- The CDC Hepatitis Branch Hotline number is 1-(800) 232-4636 The voice mail allows you to request Faxed information to be sent to you or you can listen to a recording, 8am-8pm ET/Monday-Friday
- American Chronic Pain Association, Inc., P.O. Box 850, Rocklin, PA 95677, (916) 632-3208. Email: ACPA@theacpa.org Several hundred chapters in the United States, Canada, Great Britain and many other countries. Provides a support system for those suffering chronic pain. www.theacpa.org
- U.S. Medic Alert: Medic Alert, P.O. Box 381009, Turlock, CA 95381-9009,1-800-432-5378
- Canadian Medic Alert: 1-800-668-1507 Tax deductible. Buy your medical ID jewelry. Join for $5.00/month. 24-hour emergency hotline has all your info, notifies your family. www.medicalert.ca/
- The Well Spouse Foundation, *www.wellspouse.org/* Support groups; gives emotional support to spouses of the chronically ill; raises consciousness of professionals to the plight of the well spouse; advocates for legislative changes in insurance coverage for respite care and long-term care; produces a bi-monthly newsletter, WSF Newsletter.
- Agency for Health Care Administration, HMO/Managed Care Hotline
  www.fdhc.state.fl.us/mchq/Managed_Health_Care/
- A good source of patient contacts is narcotics anonymous groups or drug-abuse recovery groups. Many people in these groups have Hep C and they meet regularly and pass information around a lot.

US SUPPORT GROUPS: Why reinvent the wheel? HCV Advocate keeps a great database of support groups in the US. You can access it here: *http://linux.hcvadvocate.org/cgi-bin/sw_lookup1.cgi*

X.2.2 CANADA

HEPCBC

Phone: (250) 595-3892
Fax: (250) 483-4041
Email: info@hepcbc.ca
Website: http://www.hepcbc.ca/

HepCBC is an organization dedicated to educating and advocating for those infected and affected by HCV. HepCBC provides information, education and support to people infected with Hep C as well as to the organizations caring for them. HepCBC is the home of the *hepc.bull*. HepCBC distributes and updates the FAQ and other materials. HepCBC maintains the most comprehensive community Hep C library on Vancouver Island, and one of the best in the province of British Columbia. Full text access to major medical journals and other services are available to member organizations.

HepCAN

The online support group for Canadians and everyone else. Check us out on the Web at http://health.groups.yahoo.com/group/hepcan/. To subscribe send an email message to hepcan-subscribe@yahoogroups.com

hepc.bull
The *hepc.bull* is a monthly Canadian newsletter about hepatitis C. The newsletter provides support information primarily in BC but also from across Canada and contains articles on many different aspects of the disease. You can browse or download it here: http://hepcbc.ca/hepc-bull-monthly-newsletter/
To subscribe to the email version, send a message to info@hepcbc.ca

CANADIAN SUPPORT GROUPS:

BRITISH COLUMBIA/YUKON: (Updates appreciated: info.hepcbc@gmail.com)

Armstrong HepCURE Phone support 1-888-437-2873

AIDS Vancouver Island The following groups provide info, harm reduction, support, education and more:
¨ **Campbell River**: Drop in, harm reduction, needle exchange, advocacy. 1371 C - Cedar St. Contact *leanne.wingert@avi.org* 250-830-0787
¨ **Comox Valley** Harm reduction, counselling, advocacy. 355 6th St., Courtenay. Contact Sarah *sarah.sullivan@avi.org* 250-338-7400
¨ **Nanaimo AVI Health Centre**. Counseling, advocacy. **NEW: 102-**55 Victoria Rd Contact Anita for details. 250-753-2437
anital.rosewall@avi.org
¨ **Port Hardy** (Port McNeil, Alert Bay, Port Hardy, Sayward, Sointula and Woss) Drop-in kitchen. 7070 Shorncliffe Rd. Contact Shane, 250-949-0432 *shane.thomas@avi.org*
¨ **Victoria** Access Health Centre, drop in, disability applications, peer training. Support group Tues 12:30 PM, 713 Johnson St., 3rd floor, 250-384-2366 *Hermione.jefferis@avi.org*

ANKORS Hepatitis C Project
Hep C Info, support for prevention, testing, treatment and living well with Hep C.
¨ **Boundary, Nelson, West Kootenay** Women's gathering monthly. 101 Baker St, Nelson. Contact Laura 1-800-421-2437 250-505-5506 *ankorshepc@ankors.bc.ca*
¨ **East Kootney** 209 16th Ave N, Cranbrook, Contact Michelle 250-426-3383 1-800-421-2437 ankorshcv@gmail.com

Castlegar Contact Robin 250-365-6137 *eor@shaw.ca*

Chilliwack PCRS Hep C Prevention, harm reduction. 45904 Victoria Avenue, Chilliwack. Contact Kim Lloyd 604-798-1416. *lbirdsall@pcrs.ca* *www.pcrs.ca*

Comox Valley Positive Wellness North Island Treatment/Pre & Post-treatment Support Group 2nd & 4th Wed., 615-10th St, **Courtenay**. Lunch. Contact Cheryl 250-331-8524.
Cheryl.taylor@viha.ca

CoolAid Community Health Centre, **Victoria.** Meetings each Wed 10 AM and Thu **1:30** PM. 713 Johnson St. Support for all stages of treatment (deciding, during, after). Contact Roz *rmilne@coolaid.org* for treatment or group info.

Courtenay HCV Peer Support and Education. Contact Del 250-703-0231 *dggrimstad@shaw.ca*

Cowichan Valley HCV Support Contact Leah
250-748-3432 *r-l-attig@shaw.ca*

Haida Gwaii support. Contact Wendy
wendy@wendyswellness.ca *www.wendyswellness.ca*

HepCBC *info@hepcbc.ca, www.hepcbc.ca* Call for office hours.
¨ **Victoria Peer Support**: 4th Tues. monthly 7-8:30 PM, Victoria Health Unit, 1947 Cook St. Contact 250-595-3892 Phone support 9 AM-10 PM.
¨ **Fraser Valley** Support**/**Info: 604-576-2022

Kamloops ASK Wellness Centre. Chronic illness health navigation/support.
info@askwellness.ca 250-376-7558 1-800-661-7541 ext 232 or Merritt health housing & counseling 250-315-0098
www.askwellness.ca

Kamloops Hep C support group, 2nd and 4th Wed monthly, 10-1 PM, Interior Indian Friendship Society, 125 Palm St. Kamloops. Contact Cherri 250-376-1296 Fax 250-376-2275

Kelowna Hepkop: Phone support, meeting info. Contact Lisa 1-866-637-5144 *ljmortell@shaw.ca*

Nanaimo - Central Island Hepatitis Service: Nurses & doctors available for info, support, treatment. Clinic located in Nanaimo. Doctor or self-referral. Contact 1-855-740-2607, sarah.hughes@viha.ca or shelby.munk@viha.ca

New Westminster Stride with Purpose "HepC" Support Group 1st&3rd Fri monthly 10:30-11:30. BBP Nursing Team, refreshments/lunch. Contact: Stride Workers 604-526-2522, *mail@purposesociety.org*

Positive Wellness North Island-North Island Liver Service Info, support, treatment/pre-post treatment groups. Doctor or self-referral. 1-877-215-7005 250-850-2605.

¨ **Courtenay**: 2nd Fri monthly 1PM, Drop-in, Comox Valley Nursing Centre (nurse)

¨ **Campbell River:** Treatment/pre&post-treatment support group 1st&3rd Thu monthly 10-11pm, Discovery Room, Sunshine Wellness Centre, Campbell River Hospital. Jody Crombie at 850-2620, jody.crombie@viha.ca

Penticton & District Community Resources Society, Harm Reduction Program, Meetings every 2nd Tues, 12:30-1:30 PM. 330 Ellis Street. Contact Melanie: 250-488-1376 or 250-492-5814

Positive Haven Info, harm reduction, support, drop in, clinic. 10697 135A St. Surrey. Contact Monika 604-589-9004.

Positive Living Fraser Valley (Abbotsford) Hep C support, Drop-in centre #108-32883 S. Fraser Way, M-F 10:30 AM-4:30PM. Info, support worker, rides to appointments in surrounding areas. Contact 604-854-1101 or *plfvcentre@plfv.org*

Powell River Hepatology Service Powell River Community Health, 3rd Floor–5000 Joyce Ave. Contact Melinda 604-485-3310 *Melinda.herceg@vch.ca*

Prince George Hep C Support Contact Ilse *ilse.kuepper@northernhealth.ca*

Sunshine Coast-Sechelt Healthy Livers Support Group Information/resources
Contact Catriona 604-886-5613
catriona.hardwick@vch.ca or Brent
604-740-9042 *brent.fitzsimmons@vch.ca*

VANDU The **Vancouver** Area Network of Drug Users. 380 E Hastings St. M-F 10-4 Contact 604-683-6061
vandu@vandu.org *www.vandu.org*

Vancouver HCV Support Contact Beverly 604-435-3717 *batlas@telus.net*

Vancouver Hepatitis C Support Group Contact 604-454-1347 or 778-898-7211, or call 604-522-1714 (Shelley), 604-454-1347 (Terry), to talk or meet for coffee.

Vernon telephone buddy, M-F 10-6 Contact Peter, *pvanbo@gmail.com* Tel. 250-309-1358.

YouthCO HIV and Hep C Society of BC. Call for appts or drop in M-F 10-6. 205-568 Seymour St,

Vancouver 604-688-1441, 1-855-YOUTHCO Stewart *info@youthco.org*,
www.youthco.org

Whitehorse, Yukon—Blood Ties Four Directions Contact 867-633-2437 1-877-333-2437
admin@bloodties.ca

OTHER PROVINCES:

ONTARIO:
Barrie Hepatitis Support Contact Jeanie for info/appointment
jeanievilleneuve@hotmail.com

Hamilton Hepatitis C Support Group 1st Thurs. monthly, 6-7 PM, Hamilton Urban Core Community Health Centre, 71 Rebecca St, Hamilton. Contact Maciej Kowalski, Health Promoter 905-522-3233
mkowalski@hucchc.com

Hep C Team, AIDS Committee of North Bay & Area. Education, outreach, treatment, individual & group support, harm reduction, needle exchange. 269 Main St. W, Suite 201, North Bay. Contact 705-497-3560, 1-800-387-3701 or *hepccommcoord@gmail.com, www.aidsnorthbay.com*

Hepatitis C Network of Windsor & Essex County Last Thurs. monthly, 7 PM, Teen Health Centre-Street Health Program Office, 711 Pelissier St., Suite 4, Windsor. Contact Andrea Monkman

519-967-0490 or
hepcnetwork@gmail.com.
http://hepcnetwork.net

Kingston Hep C Info HIV/AIDS Regional Service. Contact 613-545-3698, 1-800-565-2209
hars@kingston.net
www.hars.ca

London Hepatitis Hep C Support 186 King St, London. For those infected as well as affected by Hep C. Contact: 519-434-1601,
1-866-920-1601
www.hivaidsconnection.com

Niagara Health System – Hepatitis C Care Clinic (HCCC) Clinics:
New Port Centre-Port Colborne, 4 Adams Street - St Catharines, Niagara Falls Hospital. Education, counseling, individual/group support, treatment, outreach, and harm reduction. Contact 905-378-4647 ext 32554 and HCCC@niagarahealth.on.ca
www.niagarahealth.on.ca/services/hepatitis-c-care

Oshawa Community Health Centre Hepatitis C Team Drop-in, lunch provided each Thurs. 12-1 PM, 79 McMillan St. *www.ochc.ca* Contact 1-855-808-6242

Owen Sound Info, support. Contact Debby Minielly
dminielly@publichealthgreybruce.on.ca
1-800-263-3456 Ext. 1257, 519-376-9420 Ext. 1257,
www.publichealthgreybruce.on.ca

Peel Region (Brampton, Mississauga, Caledon)
905-799-7700
healthlinepeel@peelregion.ca

St. Catharines Contact Joe 905- 682-6194

Toronto CLF 1st Mon. monthly Oct.—June, 7:30 PM, North York Civic Centre, 5100 Yonge Street. Contact Billie 416-491-3353, ext. 4932.
bpotkonjak@liver.ca *www.liver.ca*

Thunder Bay Hep C support. Contact Sarah Tycholiz 807-345-1516 (or for 807 area only 1-800-488-5840)

Unified Networkers of Drug Users Nationally
undun@sympatico.ca

York Region Hepatitis C Education Group 3rd Wed. monthly, 7:30 PM, York Region Health Services, 4261 Hwy 7 East, B6-9, Unionville. Contact 905-940-1333, 1-800-361-5653
info@hepcyorkregion.org
www.hepcyorkregion.org

QUEBEC:

Quebec City Region
Contact Renée Daurio
418-836-2307
reneedaurio@hotmail.com

CAPAHC support group meetings 3rd Thurs. monthly 6-8PM, 5055 Rivard St., Montreal) Contact 514-521-0444 or 1-866-522-0444

ATLANTIC PROVINCES

Hepatitis Outreach Society of NS. Info and support line for the entire province.
Call 1-800-521-0572,
902-420-1767
Online Peer Support:
info@hepns.ca *www.hepns.ca*

PRAIRIE PROVINCES:

Manitoba Hepatitis C phone and email support and outreach. Contact Kirk at info@mbhepc.org.
Direct line: 1-204-231-1437

Manitoba CLF each Thu 1:30-3. 375 York Avenue, Suite 210, Winnipeg, Contact Bianca 204-831-

6231 bpengelly@liver.ca

Medicine Hat, AB Hep C Support Group 1st & 3rd Wed. monthly, 6:30 PM, HIV/AIDS Network of S.E AB Assoc, 550 Allowance Ave. Contact 403-527-7099
bettyc2@hivnetwork.ca

X.2.3 SUPPORT GROUPS AND ORGANIZATIONS WORLDWIDE
The World Hepatitis Alliance organizes the annual World Hepatitis Day, and has a good list of organizations throughout the world that you can access here:
www.worldhepatitisalliance.org/en/membership.html

X.3.0 WHAT HCV RESOURCES ARE AVAILABLE ON THE INTERNET?
There is a Hepatitis support discussion group (mailing list) called HEPV-L. Its address is HEPV-L@listserv.icors.org. To subscribe, send an e-mail message to: listserv@listserv.icors.org and in the body of the message type: SUBSCRIBE HEPV-L FIRSTNAME LASTNAME (that's **your** first and last name)

Parents of Kids with Infectious Diseases (PKIDs) has a great website. For more information, contact pkids@pkids.org http://www.pkids.org

Residents or citizens of Canada dealing with Hepatitis C may join HepCAN the online support group for Canadians and everyone else. Check it out on the Internet at http://groups.yahoo.com/group/hepcan To subscribe, send an email message to hepcan-subscribe@yahoogroups.com

For a list of recommended World Wide Web sites, see Appendix C.

X.4.0 BIBLIOGRAPHY: SUGGESTED READING

General Info

Progress in Molecular Basis of Viral Infection Vol. 129 (2015) Edited by P.J. Klasse
Hepatitis C. Virus: From Molecular Virology to Antiviral Therapy by Ralph Bartenschlager (Hardcover - Jan 1 2013) A compilation of the most recent scientific advances.

Zakim and Boyer's Hepatology: A Textbook of Liver disease. (Elsevier 2012)
https://books.google.ca/books?id=zjYof6MJZkkC&printsec=frontcover&dq=books+about+hepatitis+C+2015&hl=en&sa=X&ei=M8LjVMfaBtjcoASwuIGIAQ&ved=0CFQQ6AEwBzge#v=onepage&q&f=false

Handbook of Liver Disease, 3rd edition by L.S. Friedman, E.B. Keeffee (Elsevier 2012)
Quick reference to the most recent diagnostic and treatment options for patients with liver disorders.

Free from Hepatitis C: Your Complete Guide to Healing Hepatitis C (Square One Publishers, 2011) by Lucinda K. Porter

Personal Stories
Hepatitis C, Cured by Johnny Delirious (AuthorHouse 2009) One man's journey.

My Mom Has Hepatitis C by Hedy Weinberg (Hatherleigh Press, 2000) Explaining to children what is happening to their mother/father.

Natural Liver Therapy
The Hepatitis C Help Book, Revised Edition: Program Combining Western and Eastern Medicine by Misha Ruth Cohen, Robert Gish, and Kalia Doner (Paperback - May 15, 2007)

Hepatitis C by David Drum Cardinal Publishers Group (Paperback - Mar 1 2012) A Do-It-Yourself Guide for Health explains how people who have Hepatitis C can help themselves enhance their body's natural ability to maintain and heal.

Hepatitis C Free: Alternative Medicine VS, The Drug Industry, The People Speak by Lloyd Wright (Paperback - Mar 20, 2002)

Herbs for Hepatitis C and the Liver (Medicinal Herb Guide). by Stephen Harrod Buhner (Paperback - Jul 1, 2000)

Healing Hepatitis C with Modern Chinese Medicine by Qingcai Zhang (Paperback - May 1, 2000)

Spontaneous Healing: How to Discover and Embrace Your Body's Natural Ability to Maintain and Heal Itself by Andrew Weil Paperback - April 4, 2000)

Hep C: Practical, Medical, Spiritual Guidelines for Daily Living, 2000. Mark Jenkins. ISBN 1568383681.

The GastroIntestinal Sourcebook, 1998. M. Sara Rosenthal. $16.95 (paperback). ISBN: 0737300817. Overview on GI conditions such as ulcers, GERD, heartburn, pain, cramps, H. Pylori, NUD, dysmotility,

bowel problems, eating disorders, more. Discusses correct diet, testing and therapies. Glossary of terms.

Liver Cleansing Diet: Love Your Liver and Live Longer,1998 (revised). Dr. Sandra Cabot. ISBN 0646277898.

Miracle Cures: Dramatic New Scientific Discoveries Revealing the Healing Powers of Herbs, Vitamins and Other Natural Remedies, 1998. Jean Carper. ISBN: 0060984368.

Prescription for Dietary Wellness: Using Food To Heal, 1998. Dr. Phyllis A. Balch, MD and Dr. James A. Balch, MD. ISBN: 0895298686.

Foundations of Health: Healing with Herbs and Foods, 1994. Christopher Hobbs. ISBN 0961847085.

The Encyclopedia of Natural Medicine by N.D.s Michael Murray and Joseph Pizzorno. (pub: 1991, Prima Publishing in Rocklin, California). It has a good chapter on "Liver Support" and another on Hepatitis, with a suggested daily regimen of nutritional supplements and botanical medicines.

Herbs and Other Natural Remedies For a Healthy Liver (with a chapter on Hepatitis C). By: Christopher Hobbs. ISBN: 0961847026.

Hepatitis C Cookbook (200 recipes, diet tips) Romona L. Jones, CNC, Vonah Stanfield. To order: Nature's Response, 22 Fairview Lane, Shawnee, OK 74804. 1-800-216-5195. Email to tealady1@aol.com

How to Reverse Immune Dysfunction. By: Mark Konlee. To inquire about ordering at: Keep Hope Alive, Ltd. PO 27041 West Allis, WI 53227. (414) 548-4344. Email at Keephope@execpc.com. KEEP HOPE ALIVE http://www.execpc.com/~keephope/keephope.html. Mark Konlee is also the Editor of newsletter *Positive*

Health News ($15), and *Progressive Health News* ($20).
Stedman's Pocket Medical Dictionary (ISBN0-683-07921-2) - $22. A good general companion.

Transplantation
Transplantation of the Liver, 3rd Edition by R.W. Busuttil, G.B. Klintmalm (Elsevier Jan. 16, 2015)

Greg: A Liver Transplant Recipient by Gregory Gaines Jr. (Paperback - Jan 18, 2007)

Medical Care of the Liver Transplant Patient: Total Pre-, Intra- and Post-Operative Management by Paul G Killenberg and Pierre-Alain Clavien (Hardcover - May 26, 2006

Manual of Liver Transplant Medical Care by Abhinav Humar (Spiral-bound - May 15, 2002)

I'm Glad You're Not Dead: A Liver Transplant Story, 2nd edition by Elizabeth Parr (Paperback - Jan 20, 2000)

Pennies, Nickles and Dimes, 1999. Elizabeth Murphy Melas. ISBN 0929173325.

Strings: The Miracle of Life, 1998. John B. Robbins. ISBN 1880823179.

Defying the Gods, Inside the New Frontiers of Organ Transplantation. Scott McCartney. ISBN 0025828207.

This Is The Story About God: The True Account of Two Men, an Impossible Surgery and The God of the Universe. Ann Kiemel Anderson. ISBN 0834117312.

The Puzzle People - An autobiography of Dr. Tom Starzl, the pioneer who developed the techniques that made liver transplantation possible. It's available from the American Liver Foundation. It's a great read about one of the most compassionate and human of physicians/surgeons on the face of the earth. Given some of the horror stories we read daily on the HEPV-L list, this one will really give you a positive boost!

Coping, Personal Loss & Grief
Site listing books on personal loss and grief http://www.GriefWorks.com/GriefBooks.html

In The Country of Illness: Comfort & Advice for The Journey, 1998. New York Times Writer Bob Lipsyte $24.00. ISBN: 0679431829. Book for anyone facing a challenging illness or caring for ill loved one.
Mainstay: For the Well Spouse of the Chronically Ill, 1988. M. Strong, New York: Penguin Books.

In Search of the Sun: How to Cope with Chronic Illness, 1988. H. Aladjem, New York: Macmillian.
Living with Chronic Illness: Days of Patience and Passion, 1987. C. Register, New York: Free Press.

We Are Not Alone: Learning to Live with Chronic Illness, 1987. S.K. Pitzele, New York: Workman.

Sick and Tired of Feeling Sick and Tired by Donoghue and Seigel. ISBN 0-393-03408-9. Published in New York by W.W. Norton. $23. - A WONDERFUL book, for patients and caregivers alike. If you can only get one, get this one!

Also try reading or listening to any of the material from Bernie Siegal, the cancer surgeon cum motivational speaker from Yale. Good stuff! His organization is ECAP (Exceptional Cancer Patients)

X.5.0 WHAT NEWSLETTERS, MAGAZINES AND VIDEOS ARE AVAILABLE?

Newsletters:
The *hepc.bull*, Canada's most widely-read Hep C bulletin is available via snail mail and online as well www.hepcbc.ca. It is edited by Joan King. Contact info@hepcbc.ca if you would like to subscribe. Read the bulletin online at www.hepcbc.ca.

The HCV Advocate. An excellent newsletter out of San Francisco. Check them out at www.hcvadvocate.org

HepNews: Another excellent newsletter out of Seattle. Check them out at www.scn.org/health/hepatitis

Magazines:
Hepatitis Magazine. Check them out at www.hepatitismag.com. They do a really fine job.

Videos
Hepatitis Foundation International 30 Sunrise Terrace, Cedar Grove, NJ 07009 Phone: 1.800.891.0707 or 1.973.239.1035 Fax: 973.857.5044 - *Respect Yourself - Protect Yourself: Teens Talk to Teens about Liver Wellness - **Greg: A Liver Transplant Recipient* by Gregory Gaines Jr. (Paperback - Jan 18, 2007)

Medical Care of the Liver Transplant Patient: Total Pre-, Intra- and Post-Operative Management by Paul G Killenberg and Pierre-Alain Clavien (Hardcover - May 26, 2006

Manual of Liver Transplant Medical Care by Abhinav Humar (Spiral-bound - May 15, 2002)

I'm Glad You're Not Dead: A Liver Transplant Story, 2nd edition by Elizabeth Parr (Paperback - Jan 20, 2000)

Greg: A Liver Transplant Recipient by Gregory Gaines Jr. (Paperback - Jan 18, 2007)

Medical Care of the Liver Transplant Patient: Total Pre-, Intra- and Post-Operative Management by Paul G Killenberg and Pierre-Alain Clavien (Hardcover - May 26, 2006

Manual of Liver Transplant Medical Care by Abhinav Humar (Spiral-bound - May 15, 2002)

I'm Glad You're Not Dead: A Liver Transplant Story, 2nd edition by Elizabeth Parr (Paperback - Jan 20, 2000)

Silent Stalker: High Risk Video Hepatitis and Abuse Prevention - *Hepatitis C: Cutting Edge Medical Report - http://www.hepfi.org/

HepCBC: HepCBC has a host of videos in its library. They may be borrowed. HepCBC also has on hand videos of the First Provincial Roundtable, with guest speakers, Dr. Frank Anderson, Dr Stephen Sacks and more, and from the Hepatitis C and Your Rights Workshop. To borrow these items, please call (250) 595-3892 or email info@hepcbc.ca.

The San Francisco Support Project (HCV Advocate) has fantastic resources available. Please give Alan Franciscus a shout at (415) 978-2400. The Hepatitis C Support Project is the home of the HCV Advocate, a great newsletter. Please visit their site at www.hcvadvocate.org or email them at sfhepcat@pacbell.net.

In the Seattle area: Contact HEP. They can be reached at (206) 732-0311, or email hep@scn.org
"Hepatitis C Video," $39 American Liver Foundation , 1-201-256-2550 or 1-800-223-0179

APPENDIX A: WHERE CAN I GET THE CURRENT VERSION OF THIS FAQ?
E-Mail: send a message to Joan King at jking.hepcbc@gmail.com, and say "Send me the FAQ please!" or download it from www.hepcbc.ca, or write to HepCBC, #20-1139 Yates Street, Victoria, BC V8V 3N2 or call 250-595-3892. There are Spanish version and French versions, as well, not yet updated.

APPENDIX B: COMMON ABBREVIATIONS and MEDICAL TERMS
Below are shown common medical abbreviations that HCV people often come across.

ALT - Alanine aminotransferase - a protein (liver enzyme) which, when found in the blood in elevated quantities, generally indicates liver damage. Also sometimes called SGOT.
ANTIBODY - A protein secreted by cells of our immune system in response to infection. The antibody binds to an "enemy" molecule, in this case, a specific part of the hepatitis C virus. This is meant to prevent the virus from infecting other cells or destroy it. As with other viral infections, the presence of antibodies does not necessarily mean a virus will be eliminated from the body.

ASCITES - The accumulation of fluid in the abdominal cavity.
AST - Aspartate aminotransferase - A protein which, when found in the blood in elevated quantities, generally indicates liver damage (although less specific for liver damage than ALT). Also sometimes called SGPT.
BLOOD & BLOOD PRODUCTS - Components of blood including red cells, platelets and plasma which are separated out by blood banks. Plasma is processed and purified to produce specific medical purposes, e.g., Factor VIII.
BREAKTHROUGH - Relapse during treatment, in spite of a complete initial response.
CARRIER - Practically all people who are HCV+ "carry" the virus. The term "carrier" is often misused, though, to mean someone who has the hepatitis C virus yet is in good health. In regard to hepatitis C, the term "carrier" is used less and less. Better definitions of illness status include "antibody positive" or "antibody negative"; "symptomatic" or asymptomatic". Most important to note is that all people who are hepatitis C antibody positive need to be aware of potentially passing on the virus.
CBC - complete blood count
CDC - Centers for Disease Control and Prevention (USA agency), responsible for estimating prevalence rates and making epidemiological studies
CIRRHOSIS - A condition where scar tissue develops in the liver - to the extent where such scaring becomes extensive and permanent. Cirrhosis interferes with the normal functioning of the liver.
COQ10 - co-enzyme Q10, a naturally occurring substance which some patients find helpful; available without prescription
DHHS - Dept. of Health and Human Services (USA agency)
EVR – Early Virological Response. Undetectable viral load at 12 weeks of treatment
FATTY LIVER - Abnormal lipid increase in the liver, probably related to reduced oxidation of fatty acids or decreased synthesis and release of lipoproteins, causing inadequate lipid clearance from the liver.
FDA - Food and Drug Administration; a USA agency which regulates drug approvals, nutritional supplements, and food quality and labeling
FIBROSIS - Scar formation resulting from the repair of tissue damage. If it occurs extensively in the liver it is called cirrhosis.
GENOTYPE - Different genotypes or strains of the Hep C virus are similar enough to be regarded as the same virus but have some minor differences in their RNA composition. These differences in the genotypes may mean the virus reacts differently to our immune response or to drug treatments and natural therapies.
HCC - Hepatocellular carcinoma, or liver cancer.
HCV - Hepatitis C Virus
HEMOCHROMATOSIS – An excess of iron absorption and presence of iron-containing deposits (hemosiderin) in the liver, pancreas, kidneys, adrenals, and heart. It may be associated with hepatic enlargement and insufficiency, and esophageal bleeding from varices.
HEPATIC COMA, CHOLEMIA – A peculiar syndrome characterized by slow or rapid onset of bizarre behavior, disorientation, flapping tremors of extended arms, and hyperactive reflexes, and later lethargy and coma. It seems to be caused by intoxication with ammonia, a product of protein digestion that the diseased liver fails to convert into urea.
HEPATIC ENCEPHALOPATHY - A serious complication of advanced liver disease probably caused by cerebral toxins, including ammonia, certain amines, and fatty acids. It is clinically manifested by personality changes and impaired intellectual ability, awareness, and neuromuscular functioning.
HEPATIC FAILURE, FULMINANT – A clinical syndrome caused by extensive necrosis of the liver, which may be induced by hepatoxic drugs and may lead to progressive encephalopathy and a fatal prognosis.
HEPATIC NECROSIS - Destruction of functional liver tissue.
HEPATITIS, VIRAL - Acute or chronic inflammation of the liver caused by the hepatitis virus A, B, C, D, E, G
HEPATOMA - Tumor of the liver.
IFN – Interferon
INTRAHEPATIC BLOCK - block within the liver, or - EXTRAHEPATIC BLOCK: block within the portal vein.
IVDU - Intravenous drug use or user
IVIG - Intravenous gamma globulin
NUCLEOSIDE ANALOGUE – a synthetic antiviral drug that interferes with the activity of the viral enzyme reverse transcriptase
NIH - National Institutes of Health (USA agency); largest medical research institution in the world
NON-A NON-B HEPATITIS - The old term for hepatitis not caused by the A or B viruses. In 1988, this form of hepatitis was shown to be mainly caused by HCV.
NON-RESPONDER - A person who previously failed to suppress HCV RNA
NSAID - Non-steroidal anti-inflammatory drugs; examples: naproxen, ibuprofen; used for pain
PCR - polymerase chain reaction; a DNA technique used for identifying viruses and other life forms
Peg-IFN - Pegylated interferon (also pegIFN)

pegIFN/RBV – Pegylated interferon plus ribavirin
PORTAL HYPERTENSION - A portal venous pressure greater than 20 mm Hg is associated with an enlarged spleen, increased collateral circulation, varicosity, bleeding and ascites.
PR – Pegylated interferon plus Ribavirin
RBV – Ribavirin
RECOMBINANT DNA - DNA molecules formed by laboratory methods of genetic re-combination, combining genetic materials from different sources.
RELAPSER - A patient who experienced a re-emergence of HCV RNA following discontinuation of therapy
RVR – Rapid Virologic Response. Undetectable virus at week 4.
SGOT - (See ALT)
SGPT - (See AST)
SSA - Social Security Administration (USA agency), responsible for retirement and disability benefits
SSDI - Disability benefit program form the SSA (USA)
STANDARD THERAPY – As of 2011, standard therapy is pegylated interferon, ribavirin, and a protease inhibitor.
STEATOSIS – Fatty liver. Abnormal lipid increase in the liver, probably related to reduced oxidation of fatty acids or decreased synthesis and release of lipoproteins, causing inadequate lipid clearance from the liver.
SVR – Sustained Virological Response, or undetectable virus 6 months after the end of treatment
VECTOR – Something that delivers a virus or other biological material from one place to another. A vector containing foreign DNA is called recombinant DNA.
T-CELL – A type of white blood cell essential for the immune system, protecting the body from infections.
VIRAL LOAD - The amount of virus present in a person's bloodstream. It is usually measured by the PCR quantitative test and the result is given in number of virus particles per mL of blood.

APPENDIX C - SOME RECOMMENDED WEBSITES ARETHE FOLLOWING:

Alternative Medline: http://www.nlm.nih.gov/medlineplus/alternativemedicine.html
American Association for the Study of Liver Diseases (AASLD):http://www.aasld.org
American Journal of Gastroenterology: www.nature.com/ajg/index.html
American Liver Foundation (ALF) Homepage: www.liverfoundation.org
BC Transplant http://www.transplant.bc.ca/index.asp
British Medical Journal: www.bmj.com/thebmj
Canadian Liver Foundation: www.liver.ca
CATIE - www.catie.ca/en/hepatitis-c
CenterWatch Clinical Trials Listing Service: www.centerwatch.com
Clinical Trials www.clinicaltrials.gov
Columbia University Diseases of the Liver: http://cpmcnet.columbia.edu/dept/gi/disliv.html HCV Advocate: www.hcvadvocate.org
Hepatic Pathology Index: http://library.med.utah.edu/WebPath/LIVEHTML/LIVERIDX.html
Hepatitis C Association www.hepcassoc.org
Hepatitis Education Project: www.HepEducation.org
Hepatitis Foundation International Online (NJ): www.hepfi.org/
Hepatitis Information Network: http://www.hepnet.com
Hepatology: http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1527-3350
HepCAN: http://groups.yahoo.com/group/hepcan
HepCBC: www.hepcbc.ca, Email: info@hepcbc.ca
Hep C in Queensland: www.hepqld.asn.au
HIV and Hepatitis.Com: www.hivandhepatitis.com
Journal of the American Medical Association: http://jama.ama-assn.org/
Medline Plus: http://www.nlm.nih.gov/medlineplus/hepatitisc.html
Medscape Hepatitis C Resource Centre: www.medscape.com/resource/hepc
Merck Manual: http://www.merckmanuals.com/professional/
NATAP http://natap.org
New England Journal of Medicine: http://content.nejm.org/
PovNet: www.povnet.org
Reuters Health Information: www.reutershealth.com/
RxMed: http://www.rxmed.com/
RxList - The Internet Drug Index: www.rxlist.com
Sandi's Crusade Against Hepatitis C: http://creativeintensity.com/smking/
UNOS Website (Transplant): www.unos.org
Wendy's Wellness http://www.wendyswellness.ca

Oh yes: If you go to this Facebook site you should be able to see the three Hep C quilts. We've been having trouble tracking them down: www.facebook.com/groups/337506719604773/

If you want to find out about contributing a square, email Marie: *marie.stern@GMAIL.COM*
"On a 12" x 12" red or yellow cotton cloth, trace your hand in the opposing color of the background and apply it in any medium you like. (Make sure it's waterproof!) Please write your name, state you live in, date you think you contracted the disease and the date you were diagnosed with Hep C. Feel free to write anything else you'd like and be as creative as much as you'd like. If you want to eliminate the hand and do something different, please do so. I will do the backing. I will not turn anyone's square away. When you are finished send it to the following address:

Marie Stern
14119 Via Corsini
San Diego, CA 92128

If you'd like a picture of your square after it's put on the quilt please include an email address, let Marie know in your letter if you'd like a hard copy.

APPENDIX D FOLLOWS ON THE NEXT PAGE:

APPENDIX D* – *A List of Canadian Clinics and Doctors specializing in the treatment of HCV. *Please let us know if you know of a doctor or a clinic that is missing or if you wish your name to be removed. This year, we have added institutions and/or doctors that may do* **clinical trials** *or have done so in the past. These appear in* **bold** *type. Doctors and clinics are not allowed to advertise, so this is obviously not a complete list. We have put this list together thanks to word of mouth and educated guesswork. There is no official list of clinical trials, so we would appreciate your input. If you have a doctor who does clinical trials for Hep C patients, please contact us.*

ALBERTA

Calgary

Calgary Heart Centre
403 3280 Hospital Dr. NW
Calgary AB T2N 4Z6
403-521-2227

CUPS Health Care Clinic
128 7 Ave SE
Calgary AB T2G 0H5
403-221-8797

Foothills Medical Centre
3330 Hospital Drive NW
Calgary AB T2N 4N1
403-944-6555

Heritage Medical Research Clinic
3330 Hospital Drive, NW
Calgary AB T2N 4N1
403-220-6898

University of Calgary
Health Research Innovation Center
3280 Hospital Drive NW
Calgary AB T2N 4Z6
403-220-7118

University of Calgary
Health Sciences Centre
Christopher Andrews 403-210-9325
Alexander Aspinall 403-210-9327
Ronald Bridges 403-210-9356
Sylvain Coderre 403-210-9837
Carla Coffin 403-220-5767
Jeanne Catherine Dube, 403-210-9825
Jose Geraldo Ferraz 403-210-8575
Robert Hilsden 403-210-9355
Jennifer Jones 403-210-8575
Maitreyi Kothandaraman 403-220-5767
Kevin Rioux 403-220-8457
Alaa Mostafa Kamal Rostom 403-220-5767
Eldon Shaffer 403-210-9363
Martin Storr 403-210-9350
Guido Van Rosendaal 403-210-9325
3330 Hospital Dr NW
Calgary AB T2N 4N1

University of Calgary GI Medical Clinic
Saleh Alqahtani, 403-210-9325
Kelly Burak 403-210-9837
Gilaad Kaplan 403-210-9363
3350 Hospital Dr NW
Calgary AB T2N 4N1

Fatin Adams 403-244-4844
209-320 23 Ave SW
Calgary AB T2S 0J2

Sydney Bass 403-270-9555
415 14 St NW
Calgary AB T2N 2A1

Paul Beck 403-220-4500
1403 29 St NW
Dept of Medicine
Calgary AB T2N 2T9

Tara Chalmers-Nixon 403-244-4844
209-320 23 Ave SW
Calgary AB T2S 0J2

Martin Cole 403-244-2624
419-5920 1A St SW
Calgary AB T2H 0G3

Terry Fridhandler 403-259-3729
870-10201 Southport Rd SW
Calgary AB T2W 4X9

Noel Hershfield 403-240-4084
1025-1122 4 St SW
CalgaryAB T2R 1M1
Haussmann, Jessica 403-277-7321
1031 Russet Rd NE
Calgary AB T2E 5L2

Munaa (Mani) Khaliq-Kareemi 403-277-7321
1031 Russet Rd NE
Calgary AB T2E 5L2

Penina Hanna Krongold 403- 944-1110
Div. of GI
1403 29 St NW
Calgary AB T2N 2T9

Gisela Macphail 403-221-8797
128 7 Ave SE
Calgary AB T2G 0H5

Lawrence (Lorne) Price 403-283-6613
711-3031 Hospital Dr NW
Calgary AB T2N 2T8

James Shepherd 403-221-4448
320-401 9th Ave SW
Calgary AB T2P 3C5

Thomas A. Sherman 403-259-3729
870-10201 Southport Rd SW
Calgary AB T2W 4X9

Lloyd Sutherland
A902-500 Eau Claire Ave SW
Calgary AB T2P 3R8

Robert Thompson 403-259-3729
870-10201 Southport Rd SW
Calgary AB T2W 4X9

Iwona Wrobel 403-955-7721
2888 Shaganappi Tr NW
Calgary AB T3B 6A8

Edmonton

Community Services Centre
Isabelle Chiu, 780-944-2706
James Osinchuk (Dept of Psy) 780-735-4564
Stuart Rosser 780-735-5491
10240 Kingsway Ave NW
Edmonton AB T5H 3V9

Grey Nuns Community Hospital
1100 Youville Drive West
Edmonton AB T6L 5X8
780-735-7000

Hepatitis Support Program
Alberta Health Services
Division of Infectious Diseases
University of Alberta
8440–112 St
Edmonton AB T6G 2B7
780-407-1620

Hys MedicalCentre
James Ferguson 780-421-1031
Kata Matic 780-421-1029
Jill McDermid 780-421-1029
Brian O'Brien 780-496-1390
301-11010 101 St NW
Edmonton AB T5H 4B9
780-421-1029

Kaye Edmonton Clinic
11400 University Avenue
Edmonton AB T6G 1Z1
780-407-1650

Royal Alexandra Hospital
10240 Kingsway Avenue
Edmonton AB T5H 3V9
780-944-2706

University of Alberta
Division of Gastroenterology
519 Newton Bldg
11315, 87th Ave
Edmonton AB T6G 2C2

University Of Alberta Hospital
Liver Unit
205 College Plaza
8215-112th St
Edmonton AB T6G 2C8
780-492-8128

Zeidler Ledcor Centre
GILDR Group
130 University Campus
University of Alberta
Edmonton AB T6G 2X8
780-492-8602

Zeidler Ledcor Centre
Justin Cheung 780-492-8243
Denny Demeria 780-492-8393
Levinus (Leo) Dieleman 780-492-1888
Gutfreund, Klaus 780-492-0388
Lalor, Eoin 780-492-7700
Mang Ming Ma 780-492-8146
Andrew Mason 780-492-8176
John Patrick McKaigney 780-492-8151
Eric Semlacher 780-492-8152
Richard W. Sherbaniuk 780-492-8157
Puneeta Tandon 780-492-9844
Alan Thomson 780-492-6490
Sander Veldhuyzen van Zanten 780-492-9840
Zbigniew Wankowicz 403-257-9075
Christopher Noel Williams 780-492-8242
Winnie Wong 780-492-8134
Marilyn Zeman 780-492-8245
130 University Campus
Edmonton AB T6G 2X8
780-492-0388

Anand Bala 780-485-5515
214-6203 28 Ave NW
Edmonton AB T6L 6K3

Karen Doucette 780-407-1620
2E4.20-8440 112 St NW
Edmonton AB T6G 2B7

Constantine Karvellas 780-492-4390
WCM Centre
U. of Alberta
8440-112 St NW
Edmonton AB T6G 2B7

Mario Millan 780-455-1382
346-10230 142 St NW
Edmonton AB T5N 3Y6

Connie M Switzer 780-450-1807
217-3017 66 St NW
Edmonton AB T6K 4B2

Dennis Todoruk 780-488-6867
401-11523 100 Ave NW
Edmonton AB T5K 0J8

David Lorne Tyrrell 780-492-6018
750 HMRC
107 University Campus
Edmonton AB T6G 2S2

Brennan Walters 780-930-1915
408-8708 155 St
Edmonton AB T5R 1W2

Ronald Wensel 780-483-6146
13912 92 Ave NW
Edmonton AB T5R 5A9

Grand Prairie

Hepatitis Clinic, Queen Elizabeth II Hospital
Suite # 167, 1 East Mackenzie Place
10409 98 St
Grande Prairie Alberta T8V 2E8
780-830-2844

Red Deer

Red Deer Regional Hospital Centre
Medical Specialty Clinic
3942 50A Ave
Red Deer AB T4N 4E7
403-406-5503

Syed Farrukhb Amanullah 403-314-0355
707A-5010 43 St
Red Deer AB T4N 6H2

Sidney (Doug) Simmonds 403-343-6955
810-5010 43 St
Red Deer AB T4N 6H2

BRITISH COLUMBIA

Abbotsford

Anurag Markanday
Gateway Health & Wellness Centre
301-2051 McCallum Rd
Abbotsford BC V2S 3N5
604-853-8800

Burnaby

Gregory Monkewich 604-677-1624
200-3825 Sunset St
Burnaby BC V5G 1T4

Campbell River

North Island Liver Services
Campbell River District Hospital
375 2nd Avenue
Campbell River BC V9W 3V1
Clinic Phone: 250-850-2605 (self-referral)
Toll free: 1-877-850-2605

Courtenay

Percuro Clinic
104-1350 England Avenue
Courtenay BC V8V 8V8
250-382-6270 (Head office in Victoria)

Dawson Creek

Arulanandam Varadarasa
Dawson Creek & Dist. Hlth. Care
11100 13 St
Dawson Creek BC V1G 3W8
250-782-8501
or
816 103 Ave
Dawson Creek BC V1G 2G1

Fernie

Patricia Burnett 250-423-4442
PO Box 670
Fernie BC V0B 1M0

Kelowna

Dwight Alfred Nicholas Ferris
Kelowna General Hospital
2268 Pandosy St
Kelowna BC V1Y 1T2
250-862-4157

Kamloops

Kamloops Health Unit, Liver Clinic
519 Columbia Street
Kamloops BC V2C-2T8
250-851-7300
Toll free Clinic Line: 1-866-847-4372
Ask for "Liver Clinic Nurse" (self-referral)

Taralyn Picton 250-374-1898
405-275 Lansdowne St
Kamloops BC V2C 1X8

Twila-Faye Hazel Burgmann
405-275 Lansdowne St
Kamloops BC V2C 1X8

Christopher Stabler 250-372-9600
201-595 Columbia St W
Kamloops BC V2C 1K7

Bruce Yacyshyn 250-314-2533
Royal Inland Hospital
311 Columbia St
Kamloops BC V2C 2T1

Kelowna

Kelowna Gastroenterology Associates
Shane Agnew
Adrian Bak
Bruce Borthistle
Pina Michieletti
Robert Penner
Kenneth Render
564 Leon Ave
Kelowna BC V1Y 6J6
250-763-6433

Maple Ridge

Devin Spittel 604-467-5030
205 11743 224th St
Maple Ridge, BC V2X 7G2

Mission
Missiosn Health Unit
1st Floor-7298 Hurd St
Mission BC V2V 6C7
604-814-5500

Nanaimo

AVI Health Centre
Methadone and Hepatitis C Clinic
216-55 Victoria Rd
250-754-9111

New Westminster

Columbia Medical Bldg
Kenneth Atkinson
Kwok Yik
Henry Chung
Cassie Lin
Brock Pullen
Stacey Shapira
410-301 Columbia St E
New Westminster BC V3L 3W5
604-525-0155

North Vancouver

Michael Hahn 604-984-4138
204-135 15 St E
North Vancouver BC V7L 2P7

William Haniak 604-988-2855
209-125 13 St E
North Vancouver BC V7L 2L3

Jin Kee Ho 604-904-0810
1110-160 East 14th Street

North Vancouver BC V7L 2N3

Leila Keyvani 604-996-9989
Lions Gate Hospital
231 15 St E
North Vancouver BC V7L 2L7

William Zohrab 604-980-5731
520-145 17 St W
North Vancouver BC V7M 3G4

Penticton

Terence Maguire 250-493-1117
12-477 Martin St
Penticton BC V2A 5L2

Prince George

Prince George Health Unit
1444 Edmonton St
Prince George BC V3M-6W5
Clinic: 250-565-7387

Paul M. Murray
106-2155 10th Ave
Prince George BC V2M 5J6
250-563-5111

Dr. A A Hamour 250-563-8284
925 Vancouver St
Prince George, BC V2L 2P6

Richmond

Martin Fishman 604-273-4447
250-6091 Gilbert Rd
Richmond BC V7C 5L9

Gilwest Clinic
The Richmond Hospital
7000 Westminster Hwy
Richmond BC V6X 1A2
604-233-3135 (self-referral)

Victor Wong 604-273-4447
250-6091 Gilbert Rd
Richmond BC V7C 5L9

Saanichton

Kathie Koziol 250-652-7912
3-7865 Patterson Rd
Saanichton BC V8M 2C7

Surrey

North Surrey Health Unit
#220 – 10362 King George Highway
Surrey BC V3T 2W5
604-587-7900

Positive Haven
10697 135A St
Surrey BC V3T 4E3
604-589-9004

Positive Health Services
Jim Pattison Outpatient Centre
3rd floor – 9750 140 St
604-582-4581 (self-referral)

Marcia Prest 604-584-2033
4-13665 96 Ave
Surrey BC V3V 1Z1

Henry Wong 604-951-9186
203-13798 94A Ave
Surrey BC V3V 1N1

Vancouver

BC Children's Hospital, ACB
Pediatrics/Gastroenterology
Collin Barker - K4-180
Eric Hassall - K4-182
Kevan Jacobson - K4-181
Richard Schreiber - K4-183
4480 Oak St
Vancouver BC V6H 3N1
604-875-2332

Centre for Drug Research and Development (CDRD)
Suite 364–2259 Lower Mall
University of British Columbia
Vancouver BC V6T 1Z4
604-221-7750

Downtown Infectious Diseases Clinic
Osamah Alenezi
Robert Reynolds
201-1200 Burrard St
Vancouver BC V6Z 2C7
604-642-6429 ext 304

LAIR Centre
Edward Tam
Leila Keyvani
Stuart Zeng
305-750 Broadway W
Vancouver BC V5Z 1H2
604-876-5122

Pacific Gastroenterology Associates
Alnoor Ramji
Jack Amar
Brian Bressler
Robert Allan Enns renns@interchange.ubc.ca
Lawrence Halparin
Hin Hin Ko
Eric Lam
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Ganguli Provash 306-664-2021
202-514 Queen Street
Saskatoon SK S7K 0M5

S. Sanche
Positive Living Program
Royal University Hospital
103 Hospital Drive
Saskatoon SK S7N 0W8
306-655-1783

T A Sylwestrowicz 306-477-2800
182 Wall Street
Saskatoon SK S7K 1N4

YUKON

Whitehorse General Hospital
5 Hospital Rd
Whitehorse YT Y1A 3H7
867-393-8700

Yukon Medical Health Officer
Brendan Hanley
PO Box 2703
Whitehorse YT Y1A 2C6
867-667-5716, 867-667-5771

APPENDIX E: History of Blood Safety, Canada's Track Record, and Compensation Issues

1940's - Late in the 1940's a study was released warning of the greatly increased dangers of Post Transfusion Infection (PTI) with hepatitis in commercially purchased blood and blood sourced from prisons. They determined this by using elevated bilirubin levels to detect the hepatitis. This is a surrogate test.

1955 - Dr.'s Wroblewski and Ladue publish extensive paper on PTI hepatitis using elevated ALT and AST values. Surrogate testing.
Test to detect hepatitis B is developed. Surrogate testing shows that PTI of hepatitis is still present and it is called Non B hepatitis.
Test to detect hepatitis A is developed and surrogate testing confirms that there is still PTI of hepatitis. There are now three classes of hepatitis: A, B and Non-A/Non-B. PTI of NON-A/NON-B hepatitis turns out to be a collection of viruses of which Hep C comprises 90%.

1965 - West Germany adopts surrogate testing (testing for elevated ALT and AST levels) to screen out hepatitis Non-A/Non-B from their blood systems. Other European countries follow suit over the next 15 years.

1971 - The Canadian Red Cross bans use of prison blood. (this is significant when you read about "clause 32," Continental Pharmaceuticals in Montreal, and the USA prison blood).

1974/75 - Term hepatitis C first coined by Prince but was quickly discarded because they soon realized it consisted of more than one virus.

1979 - Canadian Medical Association journal publishes complete instruction guide on how to use surrogate testing to detect PTI of NON-A/NON-B hepatitis.

1981 - Such world experts in virology as Dr. Harvey J. Alter push for surrogate testing on all blood products in the U.S.A. and while the authorities drag their feet some centers like the New York blood center adopt screening on their own.

1985 - In the spring of 1985 the federal government licensed as an anti-hemophilia agent a product called Haemate P. It was heat treated using the "wet method" which killed both enveloped and non-enveloped viruses and was for treating both hemophilia A (factor VIII) and Von Willebrand's disease (Von Willebrand factor and factor VIII). This product sat on the shelves. It does not show up in Nova Scotia until 1992-93 and I didn't hear about until the spring of 96 after I was told I was infected. Sadly I know a young man who was diagnosed with hemophilia A in the fall of 86 over a year after this product was licensed but the Nova Scotia medical profession responsible for his treatment put him on untreated cryo-precipitate for the first four years of his life with the result that he has chronic hepatitis C—when there was no need whatsoever.

1986 - With a supply of HIV tested product in their possession, but unable to get anybody to guarantee payment to cover the cost of destroying the untested dangerous product they have in stock, the Canadian Red Cross puts the untested product in the front to be used before the safer product will be dispensed. I add this HIV incident to the Hep C story to illustrate how, in my opinion, little things have changed.
The U.S.A. becomes the latest and the last of the industrialized nations to adopt surrogate testing to screen their blood supply for Non-A/Non-B hepatitis. Canada joins Spain and Japan in refusing their citizens this extra measure of safety.

1988 - Tests by Harvey J. Alter show PTI of hepatitis Non-A/Non-B to be twice as high in Canada as in the United States despite the USA's use of commercially purchased blood.

1992 - A test for the Hep C virus is introduced. Prior to this they were looking for surface antigens and or antibodies to the disease to detect it in blood. Both of these are surrogate tests in that they use the presence of something other than the virus in to diagnose Hep C.

1992/93 - Hamate P is finally introduced into the treatment plan for Nova Scotian Von Willebrand's disease carriers. Despite being licensed in 1985 as an anti-hemophilia treatment, young Nova Scotian

hemophiliacs born and diagnosed well after the spring 85 date have been kept on Cryoprecipitate, resulting in PTI of hepatitis C.

1993 - Federal government announces the creation of the Commission of Inquiry on the Blood System in Canada.
Preliminary public hearings begin for Krever Inquiry.
First Krever Inquiry witnesses are heard.

1995 - Public hearings end.

1996 - Federal Court hearings begin.
Federal Court rules that Judge Krever is free to assign blame, if he wishes, to 14 Red Cross officials and three from the federal government. It forbids the inquiry from making allegations against 47 other people.

Nov. 1996 - The first lawsuit against the Federal Government, The Nova Scotia Government and the Red Cross is launched in Halifax Nova Scotia by five individuals including young hemophiliacs kept on Cryoprecipitate when haemate P was available.

1997 – The Krever Report is published. In it Justice Horace Krever recommends compensation for all victims of tainted blood in Canada, without prejudice. The report is ignored.

1998 - Then Justice Minister Allan Rock announces a compensation package, which excludes pre-86 and post-90 people and is riddled with clauses that require the victims to accept all responsibility for the package while forgiving all past and future wrong doings by the government and its agencies. The process involved in filing a claim is so complicated that it exhausts and confuses the victims.
Class Action lawyers suddenly appear and the victims vanish. The lawyers come out from behind closed doors with a package that will enrich them by $50,000,000 plus. Payment to the lawyers occurs well before any victim sees a penny.
September – The Canadian Red Cross files petition for bankruptcy

1999 - A one billion dollar lawsuit launched against the federal government, Connaught and Continental Pharma Cryosan for importing and manufacturing US prison plasma and exposing thousands to HIV and HCV. (Mike McCarthy, lead plaintiff)
Crawford appointed as administrator for the 86-90 settlement
Spring - National convention on CJD infected blood products is held in Toronto. Federal Department of health decides to re-release the contaminated products, despite the World Health Organization's recommendations of 1998.
Summer - Canadian Blood Services CBS tells people that they may have to pay for safer blood products out of their own pockets
Summer- Canadian Blood Services request permission to be added to the lengthy list of those allowed to dip from the Hep C compensation pool. It seems like everybody except the victims with Hep C are in the pool.
Despite the above (spring 1999) Canadian government states that that the blood system is as safe as can be. Supreme Courts of BC and Ontario hear arguments for and against proposed '86-'90 settlement.
Quebec announces pre-86/post-90 compensation.

2000 - Quebec starts to pay out pre-86/post-90
Lawyers go to court to request payout of $52.5 million (already advanced 4 million). Request approved in all three jurisdictions.
Claim forms sent out to '86-'90 potential claimants.
Ontario ups aid to pre-'86/post-'90 hepatitis C victims to $25,000.
Red Cross pre-'86/post-'90 victims vote on $79 million package

2001 - Manitoba announces pre-'86/post-'90 compensation of $10,000
RCMP announce no charges in destruction of documents
The Supreme Court of Canada upholds guilty verdict against the Canadian Red Cross
John Hamm of Nova Scotia tells victims of tainted blood that he will not spend the "care not cash" money on them; rather it will go to general revenue
Health Canada hosts 1st Canadian Hepatitis C Conference in Montreal, Quebec
$79-million Red Cross-led settlement for Hep C tainted blood victims approved by Ontario judge

2004 - Federal Health Minister Dosanjh announced that the federal government would negotiate with representatives of people infected with HCV through tainted blood received "outside the window".

2005 - The Canadian Red Cross was formally sentenced for distributing blood products contaminated by donors who suffered from HIV and hepatitis C. A court in Hamilton, Ontario, fined the agency the C$5,000, the maximum allowed.

2006 - The trial of Dr. Roger Perrault, the doctor at the centre of the tainted blood scandal, being in Toronto after months of legal wrangling and delays.

2007 - Feds offer $1 billion to compensate the forgotten Hep C victims
Judge Mary Lou Benotto acquits Former Canadian Red Cross director Dr Roger Perrault, Dr John Furesz, Dr Donald Wark Boucher, Dr Michael Rodell and Armour Pharmaceutical on all counts in Ontario Superior Court.

To protect ourselves from a lawsuit, we could not go into further detail here about these shocking matters. This information was kindly submitted by Bruce DeVenne.

COMPENSATION IN CANADA

LOOKBACK/TRACEBACK

Canadian Blood Services
Lookback/Traceback & Info Line: 1-888-462-4056

Lookback Programs, Canada: 1-800-668-2866

Canadian Blood Services, Vancouver, BC
1-888-332-5663 (local 3467) or 604-707-3467

Lookback Programs, BC: 1-888-770-4800

Hema-Quebec Lookback/Traceback & Info Line:
1-888-666-4362

Manitoba Traceback: 1-866-357-0196

Canadian Blood Services, Ontario
1-800-701-7803 ext 4480 (Irene)
Irene.dines@Blood.ca

RCMP Blood Probe Task Force TIPS Hotline
1-888-530-1111 or 1-905-953-7388
Mon-Fri 7 AM-10 PM EST
345 Harry Walker Parkway, South Newmarket, ON L3Y 8P6 Fax: 1-905-953-7747

CLASS ACTION/COMPENSATION

Class Action Suit Hotline: 1-800-229-5323 ext. 8296
Health Canada Compensation Line: 1-888-780-1111
Red Cross Compensation pre-86/post-90 Registration: 1-888-840-5764 HepatitisC@kpmg.ca
Ontario Compensation: 1-877-222-4977
Quebec Compensation: 1-888-840-5764

CLAIMS ADMINISTRATOR

1986-1990

Claimants may be reimbursed for costs of treatments and accepted hepatitis C medications not covered by public or private healthcare plan while they wait for reimbursement from the 1986-1990 plan. The upfront payment can cover the other drugs which would be part of the combined treatment regimen.
Ref: http://www.hemophilia.ca/en/hcv-hiv/hcv-treatment-support-for-1986-1990-claimants.
Pamphlet: http://www.hemophilia.ca/files/Hep8690%20Brochure_E%208%205x14.pdf

Administrator 1-877- 434-0944
www.hepc8690.com info@hepc8690.com

There are special support programs for accessing Hep C treatments through the Hepatitis C January 1, 1986 - July 1, 1990 Class Actions Settlement.
More information here:
www.hemophilia.ca/files/HT%20March%202015.pdf

If you are an approved claimant under the Hepatitis C January 1, 1986 - July 1, 1990 Class Actions Settlement, you may be eligible to be reimbursed for the cost of treatment and accepted hepatitis C (HCV) medications that are not reimbursed by any other health care plan, private or public.
Thanks to a collaborative effort between the CHS and Gilead Sciences Canada, Inc., until the claimants receive reimbursement from the 1986-1990 plan, treatment is being offered upfront to those able to physically qualify for **Sovaldi**, through the Gilead Momentum HCV Support Program. **Harvoni** (ledipasvir and sofosbuvir combined in a single tablet), approved in October 2014, is now included as well under the Gilead Momentum HCV Support Program (1-855-447-7977).
Holkira Pak (paritaprevir/ ritonavir + ombitasvir + dasabuvir) was approved for sale in December 2014, and the CHS has collaborated with AbbVie Canada to make the treatment available to 1986-90 class action claimants, as well, through the AbbVie Care Program. (1-844-471-2273).

Janssen's Galexos (simeprevir), which received Health Canada approval back in November 2013, is providing financial assistance and other support through the Galexos' BioAdvance Patient Support Program (1-855-512-3740). (WARNING: Do not take Amiodarone with Sovaldi or Harvoni).

These programs provide many services: reimbursement assistance, health care professionals and patients during their quest to achieve a cure. This assistance may cover the whole treatment regimen prescribed by your doctor, including drugs from other pharmaceutical companies that you might need to complete your treatment. The programs help you and your doctor see if you qualify for reimbursement through the 1986-1990 Class Actions Settlement. Once the plan issues reimbursement cheques to the patients, the patients must reimburse the pharmacy directly. To enrol in a program, ask your doctor or nurse or call the numbers above for more information.
For more information, see *www.hemophilia.ca/en/hcv-hiv/hcv-treatment-support-for-1986-1990-claimants*

Pre-86/Post-90

Administrator 1-866-334-3361
preposthepc@crawco.ca
www.pre86post90settlement.ca

Settlement Agreement:
www.pre86post90settlement.ca/PDFs/SA/

APPENDIX F: The Double Challenge of HIV/HCV Co-infection

By Brian D. Klein, MA, LMSW
Hepatitis C Action & Advocacy Coalition
For the ACT-UP Golden Gate Writers Pool

Approximately 40% of people living with HIV are co-infected with hepatitis C (HCV). At least twice that rate (80%) has been found among injection drug users and people with hemophilia. Compared to HIV and hepatitis B, HCV is not easily transmitted sexually, but, because of its higher rate of replication, it is much more easily transmitted blood-to-blood. HIV produces billions of new virons (virus particles) each day, while HCV produces trillions daily.

An accelerated rate of HCV progression occurs in people co-infected with both viruses compared to those living with HCV alone. One European study of 547 patients with HCV showed that among the 431 who were HIV-, the average time to development of cirrhosis (nonfunctioning scar tissue) was 23.2 years; for the 116 HIV+ individuals, the average time to cirrhosis was 6.9 years. Co-infected individuals also run an increased risk of developing liver cancer and liver decompensation. Many co-infected individuals are surviving HIV only to die due to HCV complications. These complications are the leading reasons for liver transplants. Fortunately, new information is emerging to better understand and treat HIV/HCV co-infection and to increase survival.

Research from UCSF indicates that when an individual with HIV has a CD4 rate <200 cells/mL, HCV is able to mutate more easily. It gets around the defenses of the weakened immune system and evolves new quasispecies (variants) that can survive and multiply, leading to further disease progression. Other research shows that older age and greater consumption of alcohol also lead to increased fibrosis (early scarring which can lead to cirrhosis) in co-infected individuals.

Progress has been made at U. of Pittsburgh regarding liver transplants in a few co-infected individuals. These people were far along in their HCV disease, but early enough in HIV progression to survive both the surgery and the immune suppressing drugs needed for recovery. Securing funding for this work is

due in large part to the work of community activists.

Only a year ago, researchers were debating which disease to treat first—HIV or HCV. People with HIV have higher HCV viral loads than those with HCV alone. Most research suggests that HCV does not affect HIV viral loads or CD4 counts. The consensus is growing that, other things being equal, it is best to get HIV stabilized first, then treat HCV if serious liver disease is seen.

Some HIV medications such as protease inhibitors (PIs), most notably ritonavir and, to a lesser extent, indinavir, are toxic to the liver. Co-infected individuals tend to be more sensitive to this toxicity. Most research shows that co-infected individuals see increased liver enzyme levels for up to several months after beginning HIV treatment. Most can ride it out and tolerate a regimen containing one of the less hepatotoxic PIs. There is evidence that people using a PI tend to slow the rate of liver fibrosis. The reason for this bonus has not yet been explained. If another combination is needed, different non-protease containing combinations can be used, using current HIV treatment guidelines and always looking for combinations likely to be easiest on the liver.

The only way doctors can tell the extent of liver disease is by liver biopsy. Unlike common blood tests for HIV, common HCV blood tests such as viral load and liver enzyme levels (ALT, AST) do not correlate with disease progression. A liver biopsy is an outpatient procedure. The doctor inserts a needle to take a tiny sample of liver tissue to look at. It is actually easier and less painful than it sounds. If the patient does not have any liver inflammation or fibrosis, and all liver enzymes are in normal ranges, just monitoring your status and waiting for better treatments is one viable option to discuss with your doctor.

Studies have examined the response of co-infected individuals to interferon therapy, an immune system modulator that is the most common treatment for HCV. Interferon is usually self-injected under the skin three times a week. Results have universally shown that getting a "sustained response" (maintenance of HCV viral load below the level of detection 6 months after treatment has ended) is more difficult for co-infected people than for singly HCV infected individuals. CD4 counts can drop significantly during interferon therapy, so this treatment is not recommended for individuals with CD4 counts below 200. Other co-factors that challenge response to treatment include increased age, increased alcohol use, higher baseline viral load, genotype 1a or 1b (the most common variants of HCV in the US), being male, and being African American. We do not know why African-Americans respond more poorly to HCV treatments than other ethnic groups. Higher doses of interferon and/or daily dosing increase sustained response rates, but usually no more than 28% of those studied with genotypes 1a or 1b. Results are somewhat better for other genotypes.

Combination treatments using interferon with ribavirin in co-infected people are being looked at. Ribavirin seems to make interferon work better. Early reports last November from a small ongoing study by Dr. Douglas Dieterich at NYU showed that, after 12 weeks of treatment, 50% of the individuals taking the combination had undetectable HCV viral loads compared with only 9% of the interferon monotherapy group. Laboratory research early on indicated that ribavirin might interfere with zidovudine (AZT) or stavudine (D4T). This has not been a problem with people using these HIV treatments in this study, but more analysis is needed. Half of the participants on the combination developed hemolytic anemia (low red blood cell count), a side effect of ribavirin. Co-infected people tend to be more susceptible to this effect. Either they need other expensive treatments such as Procrit or Epogen (erythropoietin) for the condition or they need the ribavirin dose reduced. Some studies from singly infected individuals indicate that 600-800 mg/day of ribavirin (as opposed to the common 1000-1200 mg/day) may actually be equally effective and less toxic.

Dr. Bennet Cecil, a clinician and hepatitis researcher with the VA and Hepatitis Treatment Centers, Inc., in Louisville, KY, makes the following comments regarding co-infection treatment and cirrhosis in his experience:

"If a patient has a platelet count below 150,000 or a prolonged prothrombin time they may have cirrhosis. These are simple blood tests that indicate the amount of damage each patient has. They are not perfect but they are very good and I use them every day treating hundreds of hepatitis C patients. I usually start with 600 mg of ribavirin each day and all of my patients do daily interferon because it has fewer side effects (1.5 MU on Intron is easier than 3 MU). Frail patients and cirrhotics usually start with 500,000 units daily of Intron or Roferon. I treat decompensated cirrhotics successfully with low titrated doses of interferon and ribavirin."

Studies are also underway in co-infected people using pegylated interferons. The two versions being studied (Pegasys from Roche, Peg-Intron from Merck) are designed to be long acting interferons that only have to be injected once a week and, ideally, maintain an even blood level of interferon in the body. Studies are looking at using these drugs +/- ribavirin. These drugs should be available later this year. Most research with them has been done to date in individuals infected with HCV alone. Merck has

released little data on their drug yet. Roche has released study results that show Pegasys monotherapy resulted in a 36% sustained response rate vs. 3% for standard interferon. A small Pegasys + ribavirin study in Europe showed an 80% sustained response rate. This is the highest rate shown in any HCV study to date. This looks promising for co-infected individuals as well.

Investigations are underway with a variety of other drugs. Ribozymes are natural enzymes that can be synthesized to selectively inhibit disease-causing proteins by interfering with RNA production. These are being investigated for use in HIV and HCV. Several pharmaceutical companies are also targeting other enzymes important in the life cycle of HCV (protease, helicase, and polymerase) for development of inhibiting drugs.

The goals of HCV treatment are now changing as well. Even if treatments that use interferon do not achieve complete viral suppression or eradication, such treatment should not be labeled a "failure" as these treatments often slow and sometimes reverse the development of fibrosis. The liver is an amazing organ with the ability to regenerate itself unlike other organs of the body. Dr Thierry Poynard, a leading hepatitis researcher, says:

"The true goal of therapy is to reduce the rate of liver fibrosis progression—this may be accomplished even without reducing the HCV viral load—some patients who have a virologic response to treatment even have regression of fibrosis. **The fibrosis progression rate is for HCV what the CD4 count is for HIV infection"**

A health care provider who knows HIV really well doesn't necessarily know HCV. And vice versa! It is important for co-infected individuals to have doctors with expertise in each disease and urge them to talk to each other to coordinate their medical care.

Research in co-infection is slower than for either HIV or HCV alone, as drug companies look to make sure their new treatments work in the least complicated populations first. Patient and treatment advocates need to urge healthcare providers, public health officials, and local drug company representatives to work for more clinical studies and access to treatments for people living with HIV/HCV co-infection.

For current information on viral hepatitis and HIV/AIDS check out www.HIVandHepatitis.com.

APPENDIX G: What is a Clinical Trial? by Viola Vatter, Victoria, BC

There are several ways that research studies may be conducted. Some give better results than others.

Randomized Clinical Trial: This is one of the best ways to conduct research and is considered the Gold Standard. Investigators randomly assign participants to one of two groups. One group receives the experimental drug/treatment, while the other gets a placebo. When the participants do not know which treatment they receive, this is called a blind study. This is to prevent any influence of the expectations of the treatment. A double-blind study is when neither researchers nor participants know who receives which treatment.

Non-randomized Study: Sometimes a randomized trial is not feasible. This may occur when one treatment is compared to another, and the participants do know which drug they are taking. This would be used when the participants don't want to discontinue all treatment.

Retrospective Study: Information is gathered from looking back on participants' histories to study the risk factors that may have led to the onset of the disease.

Meta-Analysis Study: Results are pooled from several smaller studies that have examined the same issue, to reach a larger and more statistically relevant conclusion. This will only be as good as the original studies. The Cochrane Library does reviews like this. This is an excellent site for researchers as it can be time-consuming to keep up on research in any one field. Here is their site:
www.cochrane.org/index.htm

The US National Institutes of Health (NIH) divides clinical trials into groups according to their purpose: diagnostic, prevention, treatment, screening and quality of life. Clinical trials are also divided into phases. After a drug/treatment is studied on animal models in the lab (preclinical), it becomes a clinical study for exploring on people. This could be called Phase 0, which is not a widely-used term. A single dose or even a microdose is given to a few people to see if it does anything, good or bad, or nothing at all.
Phase I is considered the first stage of human testing. The size of the study is up to 100 volunteers. The participants are usually watched full-time by medical staff as they receive several half-lives of the drug. Dosing is fine-tuned from this. It is based on the half-life of the drug: how long it takes for the body to get rid of 50% of the drug. This phase can be very risky, and is offered sometimes to people who are

healthy, but sometimes to people who have no other treatment choices, such as those with a metastatic cancer, considered terminal otherwise.
Phase II usually treats more people than Phase I, and studies the drug further. Dosing is figured out from this and how well the drug works (efficacy) is observed. This is when new drugs are noted for other effects, including toxic effects, and the drug may be scrapped.

Phase III is the most exciting. A new drug is given to several hundreds or even thousands of participants. If successful, the study will be written up and submitted for publication, and to regulatory agencies for their approval. Phase III trials are very expensive. If the drug proves to be working well, the study will continue while approval is sought.

Phase IV trials are ongoing, studying long term effects after the drug has been approved. As people who consume unknown mixtures of foods and medication take this new medication, the side-effects are noted. This is when Vioxx was found to have detrimental long term effects and pulled from the market. So be aware that even after a drug is released into general population usage, long term effects are not known.

Discuss your comfort level with your doctor and decide for yourself which phases you may be willing to try.
(*www.cancer.org/docroot/ETO/content/ETO_6_3_Clinical_Trials_-_Patient_Participation.asp#C4*)

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NOTE Please remember that the above is not medical advice. It is opinions, often from different members of the Hep C community. Always see your doctor, before trying anything unusual.

Go soothingly on the greasy mud, for therein lies the skid demon. - *Chinese Road Sign*