FORWARD

The management, care and treatment of hepatitis C (HCV) has come a long way since it was identified in 1989. While there are still many unanswered questions, we have a much better understanding of hepatitis C transmission, prevention, disease progression and treatment. This factsheet will focus on a brief review of the history of hepatitis C and the major strides made in treating HCV since the identification of the virus.

Ancient History

It is impossible to really know the origins of HCV since there are no stored blood samples to test for the virus that are older than 50 years. However, given the nature of the evolution of all viruses, hepatitis C has probably been around for hundreds of thousands of years or more before evolving into the current strains.

Some experts speculate that since HGV/GBV-C, a close relative of HCV, originated in Old and New World primates, the beginnings of HCV might be traced back to 35 million years ago. However, this is just speculation and it is impossible to corroborate these theories at the present time. On firmer ground is the prediction that the different subtypes of HCV originated approximately 500 years ago in West Africa. However, it has also been pointed out that it is difficult to limit the origin of HCV to such a short period of human history because the virus is found in remote areas all over the world. As well, the virus is mainly spread by direct blood-to-blood contact, making it difficult to spread and evolve rapidly – especially considering that the main transmission routes (blood product use and needle use) have only been in existence for a short period of time.

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There have been 7 genotypes discovered:

- **Genotype 1**: is the most common genotype worldwide—46.2% of the population of the world is infected with hepatitis C. The reason that genotype 1 is the most common worldwide is because of contaminated blood transfusions, blood products and organ transplantation and unsafe injection drug use.

- **Genotype 2**: accounts for about 9.1% of the cases of hepatitis C worldwide. Genotype 2 has always been one of the easiest genotypes to treat and remains so even with the newer HCV therapies.

- **Genotype 3**: is the second most prevalent genotype worldwide—about 30% of the population worldwide. At this time, genotype 3 is the most difficult to treat.

- **Genotype 4**: is mostly confined to Africa. It accounts for 90% of the genotypes in Egypt, which has the highest prevalence of HCV in the World. Many of the same medications to treat genotype 1 can be used to treat genotype 4 and generally the cure rates are somewhat higher.

- **Genotype 5**: has almost exclusively been found in South Africa and little is known about it—it accounts for .8% of the worldwide population of hepatitis C.

- **Genotype 6**: accounts for 5.4% of the worldwide population of hepatitis C and is mostly found in Southeast Asia.

- **Genotype 7**: There has only been a small number of people identified with genotype 7. They have all been from the Democratic Republic of the Congo.

1960-1970’s

Scientists developed blood tests to identify hepatitis B (1963) and hepatitis A (1973), but many of the blood samples taken for post-transfusion illness tested negative for hepatitis A and hepatitis B.

Given that the mode of transmission (blood transfusion) was the same, scientists classified the unidentified cases as non-A, non-B hepatitis. It is now believed that approximately 90-95% of cases previously classified as non-A, non-B (NA/NB) were actually HCV.

1980-1990’s

Investigators from the Centers for Disease Control (headed up by Daniel W. Bradley) and Chiron (Michael Houghton) identified the virus in 1989. In 1990, blood banks began screening blood donors for HCV, but it wasn’t until 1992 that a blood test was perfected that effectively eliminated HCV from the blood transfusion supply. Now, there is less than one per two million transfused units of blood estimated to be tainted with HCV. Prior to the screening of the blood supply for HCV, approximately 300,000 Americans contracted it through blood transfusions or blood products.

Treatment Timelines

- 1991—FDA approves first alfa interferon (Intron A) to treat hepatitis C.
- 1992—FDA approves first interferon (Intron A) to treat hepatitis B.
- 1996—FDA approves alfa interferon (Roferon A) to treat hepatitis C.
- 1997—FDA approves consensus interferon (Infergen) to treat hepatitis C.

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1957

Scientists discovered the antiviral properties of interferon, a naturally occurring substance in 1957. It was named interferon since it has the ability to ‘interfere’ with viral replication. Three different types of interferon were identified — alfa, beta and gamma. While it was found that there is only one form of beta and gamma interferon, it was discovered that there were many forms of alfa interferon. Interferon was approved to treat a variety of disorders including hairy cell leukemia, and Kaposi’s sarcoma.
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The general treatment protocol was to inject 3 million units of interferon, three times a week for 48 weeks. Sustained virological response rates (negative viral load 6 months post-treatment) were approximately 9% for genotype 1 and 30% for genotypes 2 and 3.

TREATMENT BREAKTHROUGH

1998
FDA approves Rebetron (Intron A plus ribavirin) for the treatment of HCV.

Ribavirin is a synthetic nucleoside analogue with a broad spectrum of antiviral activity that was initially developed as a possible treatment for HIV. As it turned out, ribavirin was not effective against HIV, but it was found that it did have antiviral activity against several flaviviruses (a family of viruses that includes HCV), and it was studied as a single agent for the treatment of HCV. In some small studies, ribavirin was found to reduce serum ALT levels, but also that it had no effect on HCV. The clinical findings that ribavirin reduced ALT levels led to the studies of combination ribavirin and interferon therapy. It was found that ribavirin when combined with interferon produced a synergy that proved to be a major breakthrough for treating HCV. Ribavirin (in a mist form) is also approved for the treatment of respiratory syncytial virus (RSV) infection in children.

The treatment with combination therapy consists of interferon (Intron A—3 million units thrice weekly) plus ribavirin (800-1200mg/day). The clinical trials conducted on combination therapy also determined the duration of treatment for genotype 1 as 48 weeks and 24 weeks for genotypes 2 and 3. Overall sustained virological response rates are genotype 1—29% (high viral load—27%); genotypes 2 and 3—62% (high viral load—60%).

Pegylated Interferon and Ribavirin Therapy

Synthetic interferon is a protein that is broken down rapidly by the body within 12 to 24 hours after injection. The standard protocol for interferon was to inject 3 times a week. But once the synthetic interferon is eliminated by the body, there is no further interferon available to suppress or kill the virus.

Pegylation is a process that attaches polyethylene glycol (a biologically inert compound) strands to the interferon molecule making it less likely to be cleared from the bloodstream. The benefit of increased concentrations of interferon levels over a prolonged period of time is constant suppression of the virus and increased likelihood of a sustained virological response.

2001

Peg-Intron Approved

Peg-Intron (pegylated interferon alpha-2b) was the first pegylated interferon FDA approved to treat hepatitis C. Peg-Intron is a powder that needs to be reconstituted (with a sterilized solution) before it can be injected. Peg-Intron also needs to be dosed by a person’s body weight. Peg-Intron is now available in a “Redipen” for dosing and reconstitution.

The sustained virological response rates for Peg-Intron monotherapy are 14% for genotype 1, and 47% for genotypes 2 and 3.

Peg-Intron plus Rebetol Approved

PEG-Intron plus Rebetol (ribavirin) was also approved in 2001 to treat HCV. Sustained virological response rates are 41% for genotype 1 and 75% for genotypes 2 through 6.

2002

Pegasys Approved

Pegasys (pegylated interferon alpha-2a) was approved to treat HCV in 2002. Pegasys comes in a ready made solution (does not need to be
reconstituted) and in a dose fixed at 180 micrograms regardless of a person’s weight. Pegasys is available in pre-filled syringes.

The sustained virological response (SVR) rate for Pegasys is 28% for genotype 1, and 56% for genotypes 2 and 3. People with advanced fibrosis or compensated cirrhosis (a group that is more difficult to treat) achieved an SVR of 20%. A clinical trial of cirrhotic patients also showed that Pegasys reduced liver inflammation and scarring in treatment responders and, to a lesser degree, in non-responders.

Pegasys plus Copegus Approved
In 2002 Pegasys plus Copegus (brand of ribavirin) was also approved for treatment of HCV. Sustained virological response rates are: 44 - 51% for genotype 1, and 82% for genotypes 2 and 3, while another study found 70% SVR for genotypes 2 through 6.

2003
Intron A (interferon) plus Rebetol (ribavirin—available in oral solution) approved for treating pediatric patients with chronic HCV.

2005
HCV Replicated in Test Tube
For the first time, scientists at the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) were able to replicate HCV (genotype 1) in a test tube. This system only represents the end of the viral life cycle, but is a very important advance. Another HCV model system is needed to show the beginning stages of the viral life cycle.

Saliva Antibody Test
Israeli scientists developed a saliva-based test for detecting HCV antibodies, which, if confirmed in larger studies, could lead to a new testing mechanism that would be less labor intensive, easier to administer and less expensive thereby making mass testing of HCV is a possibility.

2006
Mouse Model
Scientists made dramatic inroads into understanding the various mechanisms of action of HCV and replicated various HCV genotypes in a test tube. Importantly, scientists using an HCV cell culture were able to infect a mouse model. Creating a mouse model for HCV has the potential to dramatically increase our knowledge of the hepatitis C virus.

2007
Drugs in Development
In 2007, many new drugs were advanced into development. The leading compound is VX-950 (telaprevir) an HCV protease inhibitor that is being developed by Vertex to treat genotype 1. There are also many other drugs that are advancing through the clinical trial process and it now appears that a new drug will be added to pegylated interferon plus ribavirin therapy by 2011-2012.

HCV Rapid Test
An HCV rapid test (HCV anti-body test) clinical trial by OraSure was launched in 2007.

2008
OraSure Technologies completed their clinical studies of an HCV rapid test and submitted the data to the FDA for marketing approval.

Vertex initiated a phase III study of their HCV protease inhibitor, telaprevir, in combination with pegylated interferon plus ribavirin to treat HCV genotype 1. Merck/Schering also initiated
a phase III study of their HCV protease inhibitor, boceprevir, in combination with pegylated interferon plus ribavirin (FDA Approved May 2011) to treat HCV genotype 1.

The FDA approved the use of PegIntron plus Rebetol (ribavirin) for the treatment of pediatric patients with compensated chronic HCV. There were a total of 107 pediatric patients who received PegIntron dosed at 60 mcg/m once weekly plus ribavirin dosed at 1.5 mg/kg/day for 24 or 48 weeks based on genotype and baseline viral load. The SVR rates by genotype and treatment duration were 52.8% (all genotype 1—48 weeks duration); 93.3% (all genotype 2—24 weeks); 100% (genotype 3 low viral load (<600,000 IU/mL); 66.7% (genotype 3 high viral load); and 80% (all genotype 4—48 weeks).

2009
This is the year that the first interferon and ribavirin-free regime of an HCV protease inhibitor and a polymerase inhibitor was tested in people with HCV. The study results were encouraging, but it will be many years before a regime without interferon/ribavirin will be available.

2010
It was a remarkable year—scientists discovered the connection between HCV and the brain, how fat is involved in the replication process and many studies of experimental drugs were started and completed as well.

Boceprevir and telaprevir completed their phase III clinical studies and submitted applications to the FDA to market the drugs. In addition to the pegylated interferon plus ribavirin add-on therapy of HCV protease inhibitors, many new drugs were tested and showed tremendous potential for future treatments. These include direct-acting antivirals (DAAs) in combination with pegylated interferon plus ribavirin as well as combinations of various DAAs with and without interferon and ribavirin (FDA approved May 2011).

Also, Oraquick HCV Rapid Antibody test using whole blood samples was approved by the FDA and the finger prick was approved. OraSure has applied to the FDA for a CLIA waiver for their whole blood draw and finger prick testing devices. OraQuick HCV Antibody test—oral swab is waiting for FDA approval.

2011

2011 – HCV Protease Triple Therapy

The Food and Drug Administration (FDA) approved two HCV protease inhibitor (PI) combination therapies—boceprevir (Victrelis) and telaprevir (Incivek). The PI medications were approved for the treatment of people with HCV genotype 1 and are used in combination with pegylated interferon and ribavirin.

Boceprevir

In May 2011 boceprevir (band name Victrelis) was approved in combination with pegylated interferon plus ribavirin for the treatment of chronic HCV in people with genotype 1. Boceprevir is a pill taken every 7 to 9 hours. The rates of viral cure with the triple combination therapy are up to 66% in HCV genotype 1 treatment-naïve (never been treated) and up to 66% in people who are prior non-responders (depending on the type of prior non-response). In a sub-group analysis, treatment-naïve African American patients achieved a 53% viral cure. Treatment with boceprevir consists of a 4-week lead-in phase (pegylated

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interferon plus ribavirin only) followed by the triple combination of boceprevir, pegylated interferon and ribavirin. The length of treatment is guided by the type of on-treatment response for a total treatment duration of 28, 36 or 48 weeks.

**Telaprevir**

In May 2011 telaprevir (brand name Incivek) was approved in combination with pegylated interferon plus ribavirin for the treatment of chronic HCV in people with genotype 1. Telaprevir is a pill that is taken every 7 to 9 hours. The rates of viral cure with the triple combination therapy are up to 79% in HCV genotype 1 treatment-naïve and up to 86% in prior non-responders (depending on the type of prior non-response). In a sub-group analysis, treatment-naïve African Americans achieved a viral cure of up to 88% and treatment-naïve cirrhotic patients achieved an 84% viral cure. Treatment consists of the triple combination of telaprevir, pegylated interferon and ribavirin, and treatment duration is guided by the type of on-treatment response for a total treatment duration of 24 or 48 weeks.

**2012**

**DAAs**

This was the year of the Direct Acting Antiviral (DAA) medications. There were many clinical trial results with combination DAAs from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb and Gilead with cure rates approaching 90 to 100%. It was also the first year that an interferon-free Phase 3 study completed trials—GS-7977 in combination with ribavirin to treat HCV genotypes 2 and 3.

**HCV-Related Deaths**

A study released in 2012 reported on deaths from HIV, HCV and HBV and it was found that in 2007 deaths from hepatitis C (15,106) surpassed deaths from HIV (12,734). Deaths from HBV were 1,815 in the same year.

**Baby Boomer Testing**

The Centers for Disease Control and Prevention published their recommendation for a one-time HCV antibody test for everyone in the United States born between 1945 and 1965. It is hoped that, if implemented, it could identify 800,000 people with HCV and save 120,000 lives.

**HCV Testing Day**

May 18, 2012 was the first National Hepatitis Testing Day. Testing initiatives occurred in over 20 cities across the nation that will, hopefully, continue to grow every subsequent year. In addition to testing people it is an occasion to increase the level of awareness about hepatitis B and C in the general public.

**National Helpline (877.help.4.hep)**

Formed by Project Inform and various regional HCV organizations, the first national helpline was launched that provides much needed support, education and other services.

There were many important developments and ‘firsts’ for HCV that are too numerous to mention in this short fact sheet, but some outstanding milestones include the first use of direct acting antivirals to treat pre- and post-transplant patients, the establishment of new Canadian Management Guidelines and access to HCV protease inhibitors, and many new clinical trials using DAAs for HCV mono-infected and HIV/HCV coinfected among other important milestones.

**2013**

In 2013 the United States Preventive Services Task Force (USPSTF) endorsed the one-time test for everyone in the United States born between 1945 and 1965. It is estimated that that more than 800,000 people with HCV will be identified and will then be able to access management. This was a big win for the HCV advocacy community who responded to a

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draft of a lukewarm recommendation to move the USPSTF to upgrade to a strong recommendation.

In 2013 the Food and Drug Administration (FDA) approved new therapies to treat hepatitis C.

- Janssen's Olysio (simeprevir) plus pegylated interferon plus ribavirin to treat HCV genotype 1. The cure rates are up to 80% and most people were treated for 24 weeks.

- Gilead's Sovaldi (sofosbuvir) plus pegylated interferon plus ribavirin to treat HCV genotype 1 and 4. The cure rates are up to 90% in people with HCV genotype 1 and up to 96% in people with HCV genotype 4. The treatment duration is 12 weeks.

- Gilead's Sovaldi (sofosbuvir) plus ribavirin (without interferon) to treat HCV genotype 2 and 3. The cure rates are up to 93% in people with HCV genotype 2 who were treated for 12 weeks and 84% in people with HCV genotype 3 who were treated for 24 weeks.

Phase 3 studies for interferon-free therapies were begun in 2013. These include:

- Gilead's sofosbuvir, ledipasvir, ribavirin,
- AbbVie's combination of AFT-450/ritonavir, ABT-267, ABT-333, ribavirin,
- Bristol Myers Squibb's daclatasvir, asunaprevir, ribavirin (cancelled 2014),
- Boehringer Ingelheim's faldaprevir, deleobuvir, ribavirin (2014)

These interferon-free therapies are expected to be approved by the end of 2014 or the beginning of 2015.

2014
Phase 3 studies of interferon-free therapies of various drug combinations have been completed, submitted to the Food and Drug Administration (FDA) and approved: for marketing. The therapies cured up to 90 to 100% of patients with hepatitis C included:

- Genotype 1a & 1b: Gilead's HARVONI (sofosbuvir, ledipasvir), for a treatment duration of 8 to 24 weeks.
- Genotype 1a & 1b: VIEKIRA PAK AbbVie's 3D combination with and without ribavirin for a treatment duration of 12 to 24 weeks.

There are many drugs being developed to treat hepatitis C. Visit our drug pipeline to learn about the current drugs that are being developed to treat hepatitis C.

2015
The majority of 2015 was driven by the high cost of HCV medications and the restrictions placed on access to the drugs to treat hepatitis C. Harvoni was priced at $90,000 for a 12-week course of therapy—the standard course of treatment for people with HCV genotype 1. The $90,000 cost is before negotiated prices. Viekira Pak came in at $84,200 before negotiated prices.

Another disastrous issue for patients was the carry-over issue from 2013, the severe access restrictions put in place by Medicaid and insurance companies. The high cost of the medications was a substantial part of the problem along with the number of people who would have to be covered.

The high drug prices also led to exclusivity deals between pharmaceutical companies and insurance/payers to reduce the cost of the medications. The problem was that the medical decision-making process that should be made by a medical provider and a patient was now being made by a pharmaceutical company and an insurance company or pharmacy.

The high cost also led to the production of generic HCV drugs outside of the United States that a small number of patients were importing. Finally, lawsuits started popping up all over the country challenging Medicaid and insurance denials. Hopefully, these
lawsuits will lead to easing the restrictions and enabling more access to the medications for patients.

**Acute Outbreaks**
Large outbreaks of acute hepatitis C continued throughout the United States. The outbreaks were among urban and rural areas, equally divided between men and women, people aged 15 years old to 57 years old, but generally, the majority of cases were among people under 30 years old. The acute cases were among people who inject drugs (oxymorphone and heroin) who shared needles and works. Unfortunately, needle exchange was not available where the outbreaks occurred.

The Centers for Disease Control and Prevention listed acute cases as 29,700 cases for the last year that we have tabulated numbers—2013, but the range listed was 23,500 – 101,400. In a study “Underascertainment of Acute Hepatitis C Virus Infections in the U.S. Surveillance System: A Case Series and Chart Review,” by S Onofrey, MPH et. al, published in the Annals of Internal Medicine, estimated that only 1% of the real number was reported to the CDC. This would lead us to believe that the actual number of acute HCV cases annually is closer to the 100,000 range. The outbreaks that have occurred in the past few years suggest a second epidemic of hepatitis C.

**AASLD**
In 2015, the American Association for the Study of Liver Disease finally updated their Guidance to include the following language:

“evidence clearly supports treatment for all HCV-infected persons, except those with limited life expectancy (less than 12 months) due to non-liver-related comorbid conditions.”

**Daklinza & Technivie Approved**
2015 also saw the FDA approval of Daklinza (daclatasvir) in combination with sofosbuvir to treat HCV genotype 3. Both drugs are taken once-a-day for 12 weeks. In clinical trials, the cure rates were up to 98% but, unfortunately, for those with cirrhosis the cure rates were only 58% for treatment naïve and 69% for treatment-experienced patients. Technivie plus ribavirin was also approved to treat treatment naïve genotype 4 patients. The cure rates were up to 100%.

**Cell Culture**
A new cell culture was discovered. The discovery was led by scientists from the Rockefeller University who identified a human cell that can replicate the hepatitis C virus. This will help scientists understand the hepatitis C virus and optimize hepatitis C treatment including treatment of people who develop RAVs.

**RAVs**
An issue that is coming to the forefront is resistant-associated variants (RAVs) or drug resistance that can occur naturally, during treatment (viral breakthrough) and after treatment (relapse) with direct-acting antiviral mediations. Drug resistance may lead to direct-acting antiviral treatment failure. The addition of ribavirin and/or adding multiple classes of drugs (protease, NS5A, polymerase inhibitor) seems to be an effective strategy to overcome drug resistance so far.

**Pan-Genotypic Drugs**
2015 also saw a move to develop more pan-genotypic drugs. Pan-genotypic drugs work on all of the genotypes, but generally, these pan-genotypic drugs work more effectively on some genotypes more than others. In early 2016 Merck’s Zepatheir was approved to treat HCV genotype 1 and 4. Gilead’s pan-genotypic drug combination is expected to be approved on June 28, 2016.
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2016

2016 was another newsworthy year for hepatitis C. It was the year that even better HCV medications were approved to treat hepatitis C, some of the restrictions to treat people were lifted and many more items made 2016 another historic year in hepatitis C.

HCV Medications

The medications to treat and cure hepatitis C just keep getting better. Starting in 2016 Harvoni (Genotypes 1, 4, 5, and 6) and Viekira Pak (genotype 1) were the most likely prescribed HCV medications. In 2016 Zepatier (genotype 1 and 4), Viekira XR (genotype 1), and Technivie (genotype 4) were approved by the Food and Drug Administration (FDA) to treat hepatitis C.

Epclusa—A Pan-genotypic Drug

2016 was the first year that a pan-genotypic drug—Epclusa to treat genotypes 1 through 6—was approved by the FDA to treat hepatitis C. A major achievement! All of the medications listed above have very high cure rates (up to and over 90%).

Drugs in Development

Two new combinations of drugs were submitted to the Food and Drug Administration for marketing approval—Gilead’s combination of three drugs—sofosbuvir, velpatasvir and voxilaprevir—one pill once a day and AbbVie’s combination is glecaprevir plus pibrentasvir—one pill, once-a-day. Both drugs have been granted FDA’s Breakthrough Therapy Designation and are expected to be approved in 2017.

Merck’s combination of MK-3682B (MK-3682/grazoprevir/ruzasvir) in phase 2 clinical trials to treat genotypes 1, 2 and 3 in phase 2 clinical trial produced cure rates of 86 to 100%. Regulus Therapeutics Inc.’s RG-101 plus various HCV direct-antiviral medications, and Janssen’s odalasivr, AL-335, and simeprevir in phase 2 studies produced very high cure rates. RG-101 was put on clinical hold in 2016.

Veterans

Congress allocated money to the Department of Veterans Affairs to treat all eligible veterans infected with hepatitis C. It was estimated that all Vets could be cured within 3 years.

Hepatitis C Positive Organs

For the first time, hepatitis C-positive kidneys were transplanted into a person who was hepatitis C-negative. When the people were transplanted and stabilized they were treated with Zepatier and cured. The same approach was announced for hepatitis C-positive livers although transplants would not be conducted until 2017.

Needle Exchange

The federal ban on needle exchange funding was lifted. Needle exchange sites continue to expand around the country especially in and around the Appalachia where the largest outbreaks of acute hepatitis C continue to rise.

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Harm Reduction
For the first time, the Surgeon General has recommended harm reduction – an endorsement that will help bring about more support, services and better care to the many people who will benefit from it.

New HCV Infections
The highest rate of new infections of acute HCV continue in the Appalachia area of the country. It is important to know, however, that high rates of new infections are occurring all over the United States.

Lasker Awards
Three scientists received the distinguished Lasker award for their discoveries related to hepatitis C. Drs. Bartenschlager and Rice discovered how to grow the hepatitis C virus in a laboratory. Dr. Sofia and collaborators of Pharmasset developed sofosbuvir—the first effective direct-acting antiviral medication used to treat hepatitis C—the backbone of Gilead’s many HCV therapies. These discoveries led to many incredible breakthroughs in the field of hepatitis C including the treatments that can cure almost everyone infected with hepatitis C.

Related publications:

- Dispersing HCV Myths
  http://hcvadvocate.org/hepatitis/factsheets_pdf/Myths.pdf

- First Steps with HCV for the Newly Diagnosed
  http://hcvadvocate.org/hepatitis/First%20Steps/First_Steps_with_Hepatitis_C_for_the_Newly_Diagnosed.pdf


For more information:

- Americans with Disabilities Act
  www.ada.gov

- Centers for Disease Control and Prevention
  www.cdc.gov

- Mayo Clinic
  www.mayoclinic.org

- MedlinePlus
  www.nlm.nih.gov/medlineplus