Hepatitis C Virus (HCV) and HCV / HIV Co-infection Handbook

Version IV

National AIDS Treatment Advocacy Project
(NATAP)

Prepared by Jules Levin

National AIDS Treatment Advocacy Project

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Written by Jules Levin, Executive Director, NATAP
Contributions from Claire Wingfield.

Medical Editor:

Raymond T. Chung, M.D.
Medical Director, Liver Transplant Program GI Unit
Massachusetts General Hospital
Assistant Professor of Medicine
Harvard Medical School
Boston, MA

NATAP
580 Broadway, Suite 1010
NY, NY 10012
Tel. 212 219-0106
Fax: 212 219-8473
Email: info@natap.org

Free copies of this handbook are available from NATAP

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Brief Facts and Statistics about Hepatitis C (HCV)

What is Hepatitis C?

The hepatitis C virus (HCV) is a liver disease caused by infection with the hepatitis C virus (HCV). HCV is spread by contact with the blood of an infected person, and can cause liver inflammation and scarring (fibrosis). Disease progression can result in increasing inflammation and scarring.

The body's immune system is able to mount an effective response to most foreign invaders. But as with human immunodeficiency virus (HIV), a person's immune system is usually unable to adequately respond to HCV. It is not yet clear how HCV is able to evade the immune response. It is believed that certain types of CD4 and CD8 cells (called cytotoxic T-cells or CTLs), which usually play a role for humans in producing an immune response to foreign invaders like a virus, are unable to mount an adequate response. It is believed that HCV-specific CD4 and CD8 CTLs play a role for individuals able to clear HCV (about 15%) and for those whose disease progression is delayed over time, or for those individuals who are able to mount a good response to treatment. It is also believed that like HIV, HCV is able to mutate to avoid the immune response.

About 1 million individuals have HIV in the USA, but about 4 million individuals have HCV -- about 1.8% of the entire US population (CDC statistics). Of those 4 million about 2.7 million people have chronic HCV-infection.

The mechanisms by which HCV causes disease and damage remain poorly understood. The infected person's immune response to HCV may play a role in harming the liver by attacking HCV infected liver cells.

HIV may be a chronic manageable disease for many individuals, but end stage liver disease is an increasing concern for people coinfected with HIV and hepatitis. As people with HIV live longer, liver disease can progress, and HIV appears to accelerate HCV progression. You must pay attention to this. HCV-related liver failure can occur even if HIV is under control with low HIV viral load and good CD4 counts.

HCV was initially identified in the late 1980s. Interferon was the only treatment for HCV, starting around 1990. It was the only known treatment until 1998 when ribavirin and interferon were launched as combination therapy, doubling the response rates. The latest development in treating Hepatitis C is pegylated interferon (see page 17). And, additional drugs and therapies are being researched.

A person's HCV viral genotype and viral load are important to understanding the person's ability to respond well to HCV therapy and in designing treatment strategies. *(See Genotype Section on pg10 for better explanation).*

Facts on People with HCV Alone (monoinfected)

Eighty-five percent of individuals exposed to HCV develop chronic hepatitis C; only about 15% clear the virus spontaneously within a few months of infection. Once HCV becomes chronic it remains in the body unless successfully treated. It's been suggested that having HIV may impair clearance of HCV.

Not everyone with HCV monoinfection progresses to being sick. 20% of individuals chronically infected with HCV monoinfection develop cirrhosis, (widespread scarring & inflammation of the liver), which usually takes as long as 10-30 years to develop. Once cirrhosis develops, liver cancer can develop at a rate of 1-3% per year, so after 5 years there may be a 15% chance of developing liver cancer (hepatocellular carcinoma). 40% never progress and 40% progress over the course of 40-50 years if they live that long.

For many patients, serious complications of liver disease may not develop, and HCV may not affect their lifespan. Some HCV-infected persons are at greater risk for faster & more serious liver disease progression. Unfortunately, it is difficult to predict who will progress more quickly. You can monitor liver disease progression by performing a biopsy every 3-5 years. Other factors that may play a role in contributing to faster liver disease progression include alcohol, IV and illicit drug use, and poor diet.

How Can a Person Get Hepatitis C?

- Intravenous drug use (IVDU), even once (IVDU is the leading risk factor for HCV). If you use IV drugs even once with a needle containing microscopic amounts of infected blood transmittion is a risk.
- Sharing IVdrug paraphernalia: microscopic amounts of infected blood can be present in cookers, used water, cottons, and on tourniquets.
- Sexual intercourse with an infected person (low risk) see pg. 14
- Tattooing with unclean needles or ink; body piercing (unknown risk)
- Transmission from mother to child (low risk: but presence of HIV increases risk of transmission)
- Sharing a razor or toothbrush - blood exposure (low risk)
- Blood transfusion before July, 1992 (high risk)
- Needlestick accident with a patient with HCV
- Hemodialysis
- Other exposures to infected blood (moderate risk)

What is Co-Infection?

When a person has HIV and hepatitis C, it's referred to as **co-infection**.

The precise number of co-infected people in the United States has yet to be determined. However, various studies estimate that approximately. 300,000 people with HIV are co-infected with hepatitis C (30%).

Intravenous drug use seems to increase the risk of co-infection because both HIV and HCV are transmitted by dirty needles. It's estimated that 60%-90% of people who contracted HIV from IVDU also have HCV.

Hepatitis C progression appears to be more rapid in HIV-infected individuals compared to persons with HCV monoinfection. It is not yet clearly defined how much more quickly acceleration occurs, but several studies have found that progression could be as much as 2-5 times faster. The longer a person has had HCV/HIV the more likely it is that HCV has progressed. HCV is more easily transmissible than HIV. Seventy to eighty percent of HCV infections appears to occur within the first year of IV drug use, so one may have had HCV longer than they have had HIV. One small study suggests that intervention with HIV therapy (HAART) may slow or stop HCV progression for some individuals. This remains unproven. It is unknown if HAART slows or accelerates HCV progression, or if it has no effect on progression. However HCV treatment may be very helpful in stopping or slowing progression.

If a person has HIV, they should:

Be tested for HCV, hepatitis A and hepatitis B

If negative for A and B, they should talk to their doctor about getting vaccines for A and B.

Find a doctor(s) knowledgeable about both HIV and HCV, and start discussing treatment strategies for HIV and HCV. Show this handbook to your doctor and engage your doctor in conversations about issues raised in this handbook.

Discussions about treatment strategies should include consideration of the benefits and risks of immediate or deferred HCV treatment, and whether treating for HIV or HCV first is better on an individual basis.

Symptoms of Hepatitis C

When a person is first infected with HCV, they may experience flu-like symptoms such as malaise, fatigue, and weakness. But, often there are no symptoms. With chronic infection, HCV usually progresses slowly for years and there are few symptoms, until serious liver damage occurs. Some patients will develop non-specific symptoms including mild fatigue and malaise, itching, and nausea. These symptoms are called non-specific because they may appear to be caused by other factors. HIV itself and HIV medications can also be associated with fatigue, malaise and nausea.

Diagnosis and Testing

Key tests: ALT, genotype, HCV viral load, and biopsy

IF YOU HAVE HIV YOU SHOULD BE TESTED FOR HCV.

Despite having no symptoms, having HIV means a person is also in a high-risk group for having HCV, because both infections can be acquired in similar ways. People who contracted HIV through IVDU are at high risk for also having HCV.

Early detection means better options and outcomes.

Your lab tests for liver enzymes (ALT/AST) may be normal, but this does not mean you do not have HCV, or progressing HCV liver disease.

The **ELISA** (Enzyme-Linked Immunosorbent Assay) antibody test indicates past or present HCV infection. A false negative test result can occur, particularly if a person's CD4 count is <100. If you are in an obvious risk group (such as a former IVDU), you should re-test or consider performing a PCR viral load test, which tests directly for the presence of virus.

The **RIBA** (Recombinant Immunoblot Assay) test is used to confirm the presence of HCV infection.

When a person is at high risk for HCV (for example, an IVDU) it might be appropriate to only test using the HCV-PCR viral load test, skipping over using the ELISA or RIBA tests; or to use the HCV-PCR test to confirm a positive antibody test.

Liver Function Tests (LFT)

A key LFT is the ALT. ALT is a liver enzyme that is released by liver cells that are under pressure, sick or dying. Thus, its presence in the blood indicates that the individual is suffering from liver damage or inflammation. In general, an HCV-infected person with normal ALT is considered to have mild or little liver disease. However, ALT may not always accurately reflect the liver condition. A person with normal or relatively low ALT could have moderate fibrosis (in 10% of cases) or severe fibrosis (in 20% of cases). ALT levels should be monitored closely, as increasing levels suggest disease progression. High ALT levels in HCV-infected individuals suggest more advanced disease. HIV medications or other drugs can also cause elevations in ALT. A person with normal ALT and minimal/mild liver disease as determined by a biopsy may want to defer treatment. However, close monitoring is recommended because HCV may progress more quickly when HIV is present.

AST (aspartate aminotransferase; serum glutamic-oxaloacetic transaminase; SGOT): This enzyme is made in many places throughout the body (heart, intestines, muscle), so an elevated AST alone cannot determine liver damage. It is often used to monitor liver disease in combination with other tests. An individual may be asked to fast for 4 hours before the blood sample is taken.

ALT (alanine transaminase; serum glutamate pyruvate transaminase; SGPT): This enzyme is produced by the major cell found in the liver. Therefore, it is a good indication of liver damage or inflammation. Increased ALT levels may be caused by all types of hepatitis or shock or drug toxicities. Therefore, as with each of these tests it must be evaluated in relation to other information.

ALP (alkaline phosphatase): This enzyme is found in all tissues but is found in high concentrations in the liver, bile ducts and bone cells. There are different types of ALPs, therefore medical providers are able to distinguish ALPs from the liver and the bone cells. ALPs are used to determine the location of damaged or diseased tissues in the body. When assessing HCV, ALPs must be evaluated regularly to monitor liver damage or disease. The normal range is 44 to 147 IU/L. An elevated ALP or abnormal ALP may indicate damaged liver tissue due to HCV.

GGTP (gamma glutamyl transpeptidase; GGT): These enzymes are found in the bile ducts and may be elevated by any type of liver disease. GGTP levels may be elevated by heavy alcohol and drug use.

Bilirubin: Oxygen is carried through the blood by hemoglobin. Red blood cells carry oxygen to the tissues by binding oxygen to hemoglobin. When red blood cells die, the hemoglobin is broken down to bilirubin in the liver. It is then excreted into

the bile and leaves the body in the feces. However, when liver function is decreased, there is a backup of bile in the blood and an individual may become jaundiced. Jaundice is a yellowing of the eyes and the skin, also urine may be very dark. This does not happen to all persons with elevated bilirubin. Persons with chronic infection like HCV may maintain normal bilirubin levels until significant liver damage has occurred (i.e., cirrhosis). In persons with acute viral hepatitis (hepatitis A) the bilirubin level is increased relative to the severity of the infection. The normal range for bilirubin is 1.1 mg/dl (milligram per deciliter) or lower. Elevations in bilirubin can occur while taking Crixivan (indinavir), which is a protease inhibitor for treating HIV. Elevations due to Crixivan are usually transient.

Albumin: Albumin is a protein that is manufactured by the liver and has a variety of functions, including transporting small molecules such as bilirubin and drugs in the blood. Another one of its main functions is to maintain fluid levels within the body. A person whose body has not received adequate hydration (fluids) may have a low albumin level. As the person rehydrates, the level will return to normal. A person who has hepatitis C and a low albumin level may suffer from a variety of conditions, such as edema (swelling in the ankles) or ascites (fluid accumulation in the abdomen) and pulmonary edema (fluid in the lungs).

PT (prothrombin time; pro-time): PT is a test to determine the liver's ability to produce clotting factor. PT measures how long it takes blood to clot. When the liver is damaged, its ability to make clotting factors is impaired. Decreased clotting factor levels may increase the likelihood of bleeding. A prolonged PT indicates decreased liver function. A normal range is anywhere from 11 to 12.5 seconds, a PT of about 1.5 to 2 times the control value is considered abnormal (the control is usually about 11 seconds).

HCV Viral Load: The PCR test can detect the presence of virus (HCV or HIV) in the blood, and can measure the viral load. The Roche qualitative HCV-PCR test only tells you if a person has above or below 50 copies/ml of viral load in their blood. The quantitative HCV-PCR tells you how *much* virus is present in the blood. There are three PCR quantitative tests, none of which have been FDA-approved: the Amplicor HCV Monitor (Roche), HCV Superquant (National Genetics Institute), and the Quantiplex HCV RNA test (Chiron). NGI/LabCorp offers a very sensitive HCV viral load test measuring as low as 2-10 IU/ml and up to as high as 100 million IU/ml. The Roche and Bayer quantitative tests have a lower level of detection of 600 and 615 copies/ml, respectively.

The viral load is considered along with a person's genotype in determining how long treatment should be. In general persons with high HCV viral load (>2 million) do not respond as well to therapy as persons with low viral loads, so they may require longer treatment.

Genotype

It is important to do a genotype test because the HCV viral genotype can predict the patient's response to treatment and dictates the type and length of treatment. A person with genotype 1 or with > 2 million HCV viral load may need 12 months treatment rather than 6 months. In HIV-coinfected individuals, longer courses of treatment are in general likely to be required. Genotypes refer to the genetic make-up of the virus. There are 6 major genotypes throughout the world. In the USA, genotype 1 is the most common (73%), and genotype 2 or 3 are the next most common. In general, individuals with genotype 1 respond least well to therapy, while individuals with genotype 2 and 3 respond much better. Most individuals contracting HCV through IVDU have genotype 1. One large study showed over 90% of African-Americans had genotype 1. The genotype test is done from a blood sample.

The Biopsy

If you are co-infected with HCV and HIV, I suggest you speak with your doctor about having a liver biopsy. **Consult with a doctor knowledgeable and experienced in both HIV and hepatitis C.** A liver biopsy may not always be necessary, but it is usually very important. The biopsy is useful in deciding when to begin therapy, what type of treatment a person will receive, and in evaluating how much and what kind of damage has been done to the liver -- it reveals the degree of liver inflammation and fibrosis, which helps predict when cirrhosis may develop. Generally, the treatment response rates are lower in people with cirrhosis, and complications and symptoms can develop after cirrhosis develops. If advanced fibrosis is identified by biopsy, treatment intervention may prevent or delay progression to cirrhosis. Because hepatitis C may progress more quickly in persons infected with both HIV and HCV, the information from a biopsy may be of more significance for persons who are co-infected.

When should a person get a biopsy? Some doctors feel that liver damage is minimal if the ALT is normal or low. However in co-infected individuals with moderate or severe liver damage, ALT could be normal. A biopsy is the only way to truly assess the stage of liver disease. A person could have high CD4s and undetectable viral load but still have cirrhosis. I suggest considering a biopsy as soon as a person is diagnosed with HCV/HIV co-infection. The risk of complication from a biopsy is low (1-3%), and it should be a painless procedure. A well qualified doctor should be selected to perform the biopsy, as they will be better at minimizing discomfort and risk for complication. Working with a highly qualified Gastroenterology and Hepatology clinic can be helpful.

HIV and HCV Similarities and Differences

HIV and HCV Similarities:
Both viruses are transmitted through blood. Ie.) sharing IV drug paraphernalia--needles, cookers, used water, cottons, tourniquets with blood on it, etc. Any time there is blood to blood contact, HCV can be transmitted. Both viruses can evade the immune system, and both are resistant to eradication, but it appears as if HCV can be "cured" in some people. What is meant by "cure"? (See Treatment Section pg 15). Both viruses can mutate, although mutation rates appears greater for HCV because it replicates more quickly than HIV. The high mutation rates make eradication and vaccine development more difficult.

HIV and HCV Differences:
CONSIDER EARLY HCV TREATMENT: In HIV, response to treatment may be better if treatment is started early in the course of the disease. But early HIV treatment also has downsides: HIV treatment can be for a lifetime or at least many years. So toxicities and side effects associated with HIV medications, as well as the need to follow often complicated treatment schedules or regimens, may be problems for as long as you take the medications. HCV treatment may also be more successful if started earlier. But HCV treatment is different in that it may be for a defined relatively brief period of time that may be limited to 6 or 12 months. Maintenance HCV therapy (see treatment section for explanation) may be ongoing or intermittent. You and your doctor should weigh the risks and benefits of immediate or deferred therapy. See "When to Begin Therapy pg 25 " section of this handbook.

Viral load has a different significance with HIV than with HCV. You could have a low HCV viral load and have cirrhosis. HCV viral load does not appear to correlate with liver damage, but in HIV a higher viral load means worse disease progression. In HIV, lower CD4 counts place a person at risk for infections and disease progression. In HCV, a person's genotype affects the outcome of treatment.

HCV viral load can fluctuate more randomly and be less predictable than in HIV.

500,000 is high HIV RNA (viral load) but low HCV RNA (viral load).

In general individuals with >2 million HCV-RNA do not respond as well to HCV therapy, while those with <2 million respond better.

HIV is better understood than HCV. HCV research is nearly 10 years behind HIV research. There remain many unanswered questions about HCV; HIV has been researched much more.

The currently approved and recommended standard of care for HCV is pegylated interferon plus ribavirin, but there are 17 drugs approved to treat HIV.

Hepatitis Damages The Liver- Why is the liver so important?

Just as you cannot live without your heart or brain, you cannot live without your liver. Your liver performs many functions that are vital to survival. It transforms food into usable body chemicals. It filters waste, bacteria and poisons from your blood. The liver stores vitamins and sugars that your body uses for energy.

The liver is a wedge-shaped organ located underneath the rib cage. Weighing close to 3 pounds, the liver is the body's largest internal organ. It has four main functions in the body: purification, synthesis, storage and transformation.

Following is an overview of the liver's many roles:

Purification
Your liver changes toxic substances, including alcohol, into harmless substances. Inactivation of substances like alcohol and nicotine is good for the body as a whole, but liver cells can be damaged in the process. For example, detoxification of alcohol can lead to cirrhosis. Your liver also changes certain medicines into a form your body can use, and inactivates other medicines after they've worked, such as HIV drugs. If your liver enzymes are highly elevated, your liver may be having difficulty.

Synthesis
Your liver takes simple chemical building blocks and combines them to manufacture (synthesize) more complex substances. For example, the liver manufactures most of the proteins found in the blood, as well as those needed to clot blood, make new cells and cause chemical reactions inside of cells.

Storage
The liver is a warehouse for your body. Besides storing minerals and vitamins, the liver stores sugars that your body uses for energy. Your liver releases these sugars into the bloodstream between meals when other parts of your body, like muscles or the brain, need more energy.

Transformation
About 90 percent of the food you eat passes through your liver before it can be used. Your liver transforms food into vital body chemicals, including proteins, fats, and cholesterol. It also helps to digest fat and important vitamins carried in fats. When all of this is completed, your liver then sends this nourishment through the blood for cells to use.

When your liver is not well
The normal liver is smooth and firm to the touch. Progressive liver damage can lead

to fibrosis, shrinking and hardening, and formation of nodules. In cirrhosis, the liver may become small and hard, with extensive scarring and many nodules. Recent studies found that cirrhosis can be reversible with HCV therapy for a percent of patients.

As mentioned earlier, hepatitis is an inflammation of the liver. Elevations in liver enzymes (ALT) may indicate that the liver is not doing well. As hepatitis progresses, inflammation and scarring of the liver increase. As liver disease progresses, other changes occur and damage to the liver increases. For example:

Fibrosis
After becoming inflamed, the liver tries to repair itself by forming tiny scars. This scarring, called "fibrosis," makes it difficult for the liver to do its job. As damage continues, many scars form and begin to join together, leading to the next stage - cirrhosis. Certain HIV medications can be hard on the liver. It is possible that certain HIV medications may contribute to HCV progression or liver damage, but this remains unclear. The liver is good at repairing itself, but there is only so much damage it can tolerate.

Cirrhosis
With cirrhosis, large areas of the liver become permanently scarred from repeated damage. The liver begins to shrink and become hard. Chronic viral hepatitis is a common cause of cirrhosis, as is alcoholism. Scarring prevents blood from flowing freely through the liver, severely impairing liver function. When a person has cirrhosis, they are less likely to respond well to treatment.

Liver failure
As cirrhosis worsens, most liver function is lost. This means the liver is unable to filter wastes, toxins and drugs from the blood. It can no longer produce the clotting factors necessary to stop bleeding. Fluid builds up in the abdomen and legs, bleeding in the intestines is common, and eventually mental functioning is slowed. At this point, a liver transplant is the only option. Liver transplantation is a drastic last resort, and HIV+ persons have low priority to receive a liver.

Liver cancer
Sometimes damage to liver cells includes altering the genes inside cells in a way that causes them to become cancerous. Patients with chronic hepatitis B or C are at higher risk for this form of cancer.

Early detection and consultation with a good doctor may prevent a person from developing the serious liver damage described above.

Immuno-suppression associated with HIV appears to significantly alter the natural history and clinical course of HCV

HIV accelerates hepatitis C liver disease progression. HCV-induced liver failure may occur more quickly in HCV/HIV co-infection than in HCV alone. This accelerated progression may be caused by the effect of HIV on the immune system, which may effect or impair how the immune system responds to HCV or therapy for HCV. Perhaps lifestyle may play a role-- years of IVDU or alcohol use may have harmed the liver. The rate of HCV progression may vary from one person to another. We need more studies of HCV/HIV coinfected patients to better understand how and why HCV may progress more quickly in an individual, and to better understand the variables.

It is uncertain what the effect of HAART is on liver disease progression. The results from one small study suggested that a protease inhibitor containing HAART regimen can slow HCV progression. This remains unproven, and hasn't been confirmed by additional studies. A different preliminary study suggested the opposite, that a PI-regimen may harm the liver. It remains unclear whether HAART can slow or accelerate HCV progression, or whether HAART has no significant effect on liver disease.

Transmission of HCV

Potential routes for transmission of HCV are discussed on pg. 5. IVDU is the leading cause of transmission for HCV. The overall transmissibility of HCV appears to be higher in co-infected individuals than in those with HCV alone, perhaps due to HIV-induced immune suppression. Studies show that individuals with co-infection may have higher HCV viral loads, and this may be the cause for higher transmissibility of HCV. If a sex partner has HIV, this may increase risk of transmitting HCV. Does the presence of HCV increase the risk of HIV transmission? We do not have a clear answer to that question but it appears possible.

Vertical Transmission (Mother To Child Transmission - MTCT)
Some studies do not show an increased risk of HCV vertical transmission, but some studies do. There is a risk. One large study showed a 5% vertical transmission rate of HCV when only HCV was present in women, but 17% when the pregnant women were co-infected with HIV. Therefore, infection with HIV may increase the risk of HCV vertical transmission.

Heterosexual Transmission
The rate of heterosexual transmission has not been clearly determined. The risk appears low, but there are exceptions. Among long-term monogomous heterosexual partners of HCV-infected HIV-negative, several studies show a 0-3% risk of sex-

ual transmission of HCV. Having sex while a woman is menstruating may increase risk for transmission. Anal sex may increase risk of transmission.

When HIV co-infection is present, several studies show 9-13% risk of HCV transmission to sexual partners. So, the risk of sexual transmission of HCV appears to be increased when a person also has HIV.

This creates greater concern about HCV transmission rates in regions where HIV is spread primarily through heterosexual sex, such as in Africa.

High-risk sexual behavior also appears to play a role in sexual transmission of HCV. Any time blood is shared, there may be a risk of HCV transmission. Alcohol and drug use may encourage risky sex behavior resulting in HIV and HCV transmission.

Studies show that individuals with multiple sex partners are more likely to get HCV than those in monogamous relationships. Anal sex may damage the lining of the rectum, and potentially facilitate blood to blood transmission.

Men Who Have Sex with Men
Several studies show there can be a risk of HCV sexual transmission for men who have sex with men. Sexual behavior that may draw blood may increase risk. The presence of sores or ulcers may increase risk. Sexual practices such as fisting or rimming may increase risk.

Treatment for HCV and the Co-Infected Person

An HCV-infected person should ask his or her doctor the following question: what are my various **strategies** for when to begin HIV and/or HCV therapy, and what are my **options** for treatment? Each person's situation is different, and treatment decisions should consider the individual's situation, the potential outcome of treatment, and the disease stages of their HIV and HCV. In order to properly assess a person's HCV health status and potential outcome from treatment, certain lab tests need to be performed including: HCV viral load, genotype, liver function tests, and perhaps a biopsy.

What is the primary goal of HCV therapy?
To reduce HCV viral load to undetectable and normalize ALT/AST.

What is the secondary goal of HCV treatment?
The secondary goal of HCV treatment is to prevent progression of liver disease, and to improve the condition of the liver (improving inflammation and fibrosis (scarring). When the primary goal is not achievable the secondary goal becomes very important, and may be achieved without a reduced viral load.

What is the Best Treatment for HCV?

Combination therapy with interferon and ribavirin is considered the most effective in reducing HCV viral load and improving liver enzymes (ALT/AST). Before 2001, the FDA approved regimen was interferon at a dose of 3 Million International Units (3 MIU or MU) administered by subcutaneous injections three times per week, plus ribavirin pills taken twice per day (800, 1000 or 1200 mg per day). Ribavirin is a nucleoside analogue like AZT or d4T, but it does not have activity against HIV. In January 2001, a new form of interferon called pegylated interferon was approved by the FDA (see Treatment section). Pegylated interferon is the new form of interferon (see next page).

Some doctors have been prescribing interferon in dosing schedules different from the standard of 3 MIU 3 times per week. Many doctors felt interferon should be given more frequently, at least at the beginning of treatment, because interferon levels fall too low between dosing on the standard regimen. But study results with alternate dosing have been mixed. The introduction of pegylated interferon changes treatment options & strategies.

HCV therapy can be difficult to tolerate. Side effects can include: fatigue, irritability, depression, anemia, weight loss, loss of appetitie, reduced platelet count, low white blood cell count and neutrophil counts, flu-like symptoms (chills, low grade fevers, body aches, headaches), among others. For coinfected patients, weight loss may exacerbate lipoatrophy. Flu-like symptoms can improve by limited use of acetaminophen (Tylenol) or Advil, and drinking plenty of decaffeinated fluids. More than 2000 mg of Tylenol per day can cause liver toxicity. More serious toxicities from HCV therapy are possible. Ask your doctor about these. For people with HIV, the most common side effect seen with ribavirin can be anemia (reduced hemoglobin), which can be effectively treated with Procrit (EPO) therapy in many cases, while remaining on ribavirin. Hemoglobin should be monitored closely; weekly during the first month of treatment. Dose reduction of ribavirin for a brief period can also be considered for management of ribavirin-induced anemia. Anemia, and reduced platelets and blood cell counts can be reversed with treatment or by stopping therapy. Before starting treatment, make sure your doctor fully explains the potential side effects and toxicities (see page 18: how to manage side effects).

Ribavirin causes severe birth defects, therefore women who are pregnant should not take ribavirin. Women on HCV therapy who are considering pregnancy should wait atleast six months before conceiving. Those who become pregnant while taking ribavirin should discontinue therapy immediately. Women and/or their partners who are taking ribavirin should use effective contraception (two different and reliable forms) during treatment and during the 6 month post-treatment follow-up period.

Patients with psychiatric or mental illness may have problems tolerating or adhering to interferon. Depression can be a common side effect of interferon. Pre-existing mood disorders can be treated before starting HCV therapy. The use of anti-depressants can be used to treat depression before and during HCV therapy. Still, interferon may not be recommended for individuals with clinical depression or who are suicidal.

Can HCV be "Cured"?

HIV cannot be cured yet. But a number of doctors think HCV is "curable." What does "curable" mean? The goal of therapy is to reduce HCV viral load to undetectable and keep it there. Treatment for HCV may be time limited, unlike treatment for HIV. Standard HCV treatment is usually for 6 or 12 months. There are two types of treatment responses, End of Treatment Response (ETR) and Sustained Virologic Response (SVR). ETR is achieved when HCV viral load is undetectable (less than 100 copies per ml) at the end of treatment. SVR is achieved when the viral load remains undetectable at six months following treatment. A few small studies have shown that 3-11 years after achieving a SVR, HCV viral load is still undetectable in almost all the patients. They call this a "cure." Does this mean there is no HCV anywhere in the person's body? We do not know the answer to this. But a small study recently showed that if HCV was not found in the blood it could not be found in the liver either. One recent study showed that viral failure (relapse) appears to only occur within 2 years after stopping therapy.

What Treatment Responses Can Be Expected?

Results from the following studies were conducted in patients with HCV monoinfection (study patients did not have HCV/HIV co-infection). Two large studies from a few years ago found that about 40% of patients with HCV alone achieved an SVR using the standard interferon regimen of 3 million units 3 times per week plus ribavirin. In these studies, individuals with genotype 2 or 3 achieved an SVR 65% of the time, while individuals with genotype 1 had an SVR 29% of the time.

Pegylated Interferon. Pegylation is a new form of interferon that is injected subcutaneously but only once weekly. What is the process of pegylation? A chemical molecule (synthetic polyethylene glycol) is attached to interferon. This delays the clearance rate of interferon and achieves higher sustained interferon levels in the blood. In concept, pegylation is similar to sustained release vitamins or medications. There are 2 pegylated interferons. Pegasys (peginterferon alfa-2a) is made by Roche and was approved in late 2002 for use as monotherapy or in combination with ribavirin. Copegus is the Roche brand of ribavirin and was also approved in late 2002. PegIntron (peginterferon a-2b) is made by Schering-Plough. Rebetol is the Schering Plough brand of ribavirin. Study results of these two drugs are available from NATAP (see study results page 19).

Pegylated interferon is an advancement in treating HCV. Pegylated interferon is injected subcutaneously once per week. It is therefore more convenient & easier to take, and the pegylation process allows for higher and more sustained levels of interferon in the human body. The results from recently conducted studies show that pegylated interferon has superior response rates to standard interferon. Although, the response rates vary by the patient's genotype and viral load.

These studies found the overall SVR (sustained viral response [<100 copies/ml]) ranged from 53% to 61% for pegylated interferon plus ribavirin, compared to about 46% for standard interferon plus ribavirin. Individual response varies by genotype and usually viral load. Patients with genotype 2 or 3 respond well to therapy. For patients with genotype 2 or 3, 75%-90% of patients achieved an SVR.

For patients with genotype 1, the response rates in studies of pegylated interferon plus ribavirin were not as good: 53%-74% of patients with low viral load had an SVR. Patients with high viral load and genotype 1 do not generally respond as well: 30%-46% achieved an SVR. (see next page for study results). It appears adherence plays an important role in contributing to succeeding with HCV therapy, as it does in HIV therapy. Results from 2 preliminary studies found that patients with >80% adherence achieved higher response rates.

PegIntron is a powder that has to be reconstituted with purified water, both of which come in separate vials. Pegasys is a liquid that comes in 1 vial and is stored in the refrigerator. PegIntron is dosed by weight. Everyone receives the same dose of Pegasys regardless of weight.

How will coinfected patients respond to HCV therapy? The results of several small preliminary studies showed coinfected patients responded as well as HCV monoinfected patients. However, the interim results of several more recent larger studies suggest that coinfected patients may not respond quite as well. Some researchers suggest that on average the response rates for coinfected patients may be 20-30% less. Again, adherence appears to play an important role. The large studies in coinfected patients are ongoing and final results are expected.

In addition to full adherence, there are some things you can do to help improve response rates in coinfected patients: starting therapy early in HCV disease, when CD4 count is higher, and when HCV and HIV viral loads are lower. A healthy lifestyle may help: don't eat too much fat in your diet, as fat can get deposited in your liver, called fatty liver; exercise; relaxation, good diet (adequate protein; not too much fast food; eat fresh vegetables and fruit). Drinking alcohol can accelerate progression of HCV.

Study Results Based on 48 Weeks of Therapy & 24 Weeks Follow-up

PegIntronTreatment Response in Patients with Genotype 1		
	High Viral Load (>2million)	Low Viral Load (<2million)
Interferon + Ribavirin (1000-1200mg/day)	70/247 (28%)	42/96 (44%)
PegIntron 1.5μg/kg + Ribavirin(800mg/day)	75/256 (29%)	66/92 (72%)

PegIntronTreatment Response in Patients with Genotype 2-6		
	High Viral Load	Low Viral Load
Interferon + Ribavirin (1000-1200mg/day)	72/97 (74%)	47/65 (72%)
PegIntron 1.5μg/kg Ribavirin(800mg)	68/95 (72%)	55/68 (81%)

Pegasys Treatment Response in Patients with Genotype 1		
	High Viral Load	Low Viral Load
Interferon + Ribavirin (1000-1200mg/day)	33%	44%
Pegasys 180mcg + Ribavirin (1000-1200mg/day)	41%	56%

Pegasys Treatment Response in Patients with Genotype 2/3		
	High Viral Load	Low Viral Load
Interferon + Ribavirin (1000-1200mg)	59%	65%
Pegasys 180mcg + Ribavirin (1000-1200mg/day)	74%	81%

Results from a second large study of Pegasys + ribavirin in HCV monoinfected patients were reported in April 2002. The study compared 24 vs. 48 weeks of treatment, and also compared 800 mg of ribavirin vs. 1000/1200 mg of ribavirin. If patient weight was less than 165 lbs, they received 1000 mg per day. If patients were greater than 165 lbs they received 1200 mg of ribavirin per day. The study showed different and better results than those from the first Pegasys + ribavirin study: in particular, patients with genotype 1 and high viral load (> 2 million copies/ml) had better results. FDA approval for Pegasys is pending and is expected in Fall 2002.

2nd Pegasys + Ribavirin Study – Patients with Genotype 1

	High Viral Load	Low Viral Load
Pegasys 180 mcg + ribavirin 800 mg - 24 weeks treatment	16%	41%
Pegasys 180 mcg + ribavirin 1000/1200 mg - 24 weeks treatment	26%	51%
Pegasys 180 mcg + ribavirin 800 mg - 48 weeks treatment	35%	53%
Pegasys 180 mcg + ribavirin 1000/1200 mg - 48 weeks treatment	46%	61%

Patients with genotype 1 had better results with 48 weeks rather than 24 weeks of treatment. Patients with genotype 1 had better results with 1000/1200 mg per day of ribavirin than with 800 mg per day. Most patients in the USA have genotype 1 and high viral load.

2nd Pegasys + Ribavirin Study – Patients with Non-1 Genotype	
	High or Low Viral Load
Pegasys 180 mcg + ribavirin 800 mg - 24 weeks treatment	78%
Pegasys 180 mcg + ribavirin 1000/1200 mg - 24 weeks treatment	78%
Pegasys 180 mcg + ribavirin 800 mg - 48 weeks treatment	73%
Pegasys 180 mcg + ribavirin 1000/1200 mg - 48 weeks treatment	77%

Patients with non-1 genotype had the same results whether or not they had high or low viral load. Patients who received 24 weeks treatment did as well as patients receiving 48 weeks treatment. Patients without cirrhosis had an overall response rate of 65% in this study, while patients with cirrhosis had an overall response rate of 50%. The study authors reported that patients with greater than 80% adherence can improve upon these response rates, and higher ribavirin dosing may be associated with more side effects.

Initially after starting HCV therapy, interferon may reduce CD4 cell count, but CD4 percentage should not decrease. Usually CD4s bounce back after stopping HCV therapy. In a few small studies, interferon reduced HIV viral load but the studies were short term (six months).

It is unclear whether d4T and AZT interact with ribavirin in such a way as to reduce the effectiveness of these AIDS medications. Research in test tubes suggested that ribavirin may have this effect. Preliminary studies in HIV-infected individuals suggest this may not be an issue, but we do not have a definite answer to this question yet. More conclusive studies are ongoing. Test tube studies suggest ribavirin may increase the amount of ddI a person is exposed to, which could increase ddI toxicity. Several studies have found a few patients taking combination d4T/ddI who after adding ribavirin and interferon experienced symptoms related to elevated hyperlactatemia and mitochondrial toxicity. Patients should be monitored if they add ribavirin to d4T/ddI.

Predictors of the Response to HCV Therapy

- HCV viral load: persons with >2 million do not in general respond as well
- Genotype: persons with genotype 1 do not respond as well as individuals with genotype 2
- Persons with cirrhosis do not respond as well
- Women < 40 years of age tend to respond better than men
- Excessive alcohol intake worsens HCV progression
- Persons with lower weight tend to respond better to therapy
- Better adherence improves response
- Excess of fat in your diet can be harmful to the liver

Managing Side Effects of HCV Therapy

Therapy can be difficult to tolerate but there are things you can do to make side effects more tolerable. Tylenol or Advil can be helpful, but over 2000 mg per day of Tylenol can be toxic to the liver. Vioxx and non-steroidal anti-inflammatory drugs can reduce aches & pains. Make sure to discuss with your doctor which of these types of medications are appropriate for you, and how to dose them. Maintaining regular physical and mental activity can help cope with fatigue & depression. Light walking and physical activity may help. Do not overdo exercise. It's important to nap or rest when you feel tired, but remaining sedentary will not help with fatigue and depression.

If you are having trouble with depression, anxiety, and irritability, tell your doctor. Prescribing an anti-depressant can be helpful. Remain well hydrated by drinking and

plenty of fluids. Some individuals lose weight because they do not eat well. This could be due to loss of appetite while taking HCV therapy or to experiencing GI side effects (nausea, diarrhea). Eating small, frequent snacks or meals throughout the day rather than infrequent large meals may be easier to tolerate and may sustain you better. Not eating properly can increase fatigue and this can increase depression. HCV therapy can reduce your ability to think clearly and may impair your motor skills. Adequate rest and relaxation may help. Remember HCV therapy is only for up to 12 months. By reminding yourself it will end in one year and is time-limited, this may help you stick it out. It may be helpful to share with people close to you or people you live with information about these potential side effects. Ask them to read about it in this handbook.

When to Begin HCV and HIV Therapy: HAART and HCV

Consult with a knowledgeable doctor about whether or not you should begin HCV or HIV therapy first. You should weigh the pros and cons about which treatment to begin first. It may be appropriate for you to treat HCV first. There is no consensus on when to begin therapy, but there is information that can help you decide whether to start HCV treatment early or to delay it

HIV medications can be burdensome to the liver: Opinions are mixed about whether HIV medications have a negative impact on HCV disease.

- Use of some HIV drugs can result in elevated liver enzymes, which are often just mild elevations. Liver enzymes should be closely monitored, particularly after starting HAART. Persons co-infected with HIV and hepatitis C or B are more likely to have elevated liver enzymes. The significance of elevated liver enzymes are not understood yet.
- Elevated levels of fats (cholesterol, tryglicerides) can result from HIV drugs and may be unhealthy to the liver.
- Certain NRTIs (for example, AZT, d4T) can cause mitochondrial toxicity to cells, and this may be harmful to cells in the liver.
- HCV infected patients may develop elevated glucose and reduced bone mineral density.
- HCV coinfected patients may be more likely to develop lipodystrophy (body changes) elevated cholesterol, triglycerides, and glucose or insulin resistance, perhaps due to liver impairment.haps due to liver impairment.
- There is little research into the question of the effect of HIV medications on a person's HCV disease.

- There is little research into the question of the effect of HIV medications on a person's HCV disease.

- Treating HCV before treating HIV may be beneficial because it might help the liver tolerate the HIV drugs better.

- If liver toxicity occurs after starting HAART, options include continuing current regimen with close monitoring, changing HIV drugs, and treating HCV.

Bear in mind that not treating HIV can have severe consequences. Since HIV can progress more rapidly than HCV, it may be preferable to treat HIV first. HIV therapy improves the immune system, which can result in a temporary flare up of ALT (liver enzymes) within the first 5 months after starting HIV therapy. These flare-ups usually settle down on their own, but can also be controlled by changing or interrupting therapy.

Each individual is different and treatment decisions should be determined on an individual basis. A comprehensive and informed discussion with a specialist about the concerns listed here is recommended.

Starting HCV therapy early in the disease stage may present a better opportunity to achieve undetectable HCV viral load or a Sustained Virologic Response. Response to HCV treatment may be better in early disease, due in part to perhaps less mutations and damage to the liver having occurred, and because the person's immune system may be able to be more responsive to the virus and to treatment.

Once a person has cirrhosis, they may be less likely to achieve a Sustained Virologic Response to therapy. When CD4s are high, such as over 500, this may be the best opportunity to achieve undetectable HCV viral load and a Sustained Virologic Response (SVR). If CD4s decline too low, the ability to achieve undetectable HCV viral load may be lessened. We do not know what is too low of a CD4 count, but possibly 200 CD4s.

Given an individual's personal situation, it may be more important to get HIV under control, and therefore, to treat HIV first. This may be based on the person's HIV viral load, CD4 count, and health status. Some doctors will decide that if HIV viral load is greater than 40,000 copies/ml, treatment for HIV should start first. But, opinions by doctors may be mixed. A CD4 count of 500 or more before declining may be more helpful in response to HCV therapy and the immune response to HCV than an increase in CD4 count to 500 after starting HIV therapy. But this is not established.

Additional factors to consider in deciding whether to defer HCV treatment include: readiness to begin and complete therapy, difficulty in tolerating interferon and ribavirin, low response rates, more tolerable and effective treatments may be available in several years. Bear in mind that HIV may accelerate HCV progression. Therefore, if treatment is deferred, close monitoring of the liver condition may be crucial.

Among people with HCV alone, some individuals may not get sick from HCV, but we do not know if this is also true for persons with co-infection.

What is Maintenance Therapy?

If a patient does not achieve a Sustained Virologic Response (SVR) and has advanced liver disease, continuing on interferon rather than stopping therapy is called Maintenance Therapy. Frequently, the maintenance therapy regimen will consist only of a reduced dose of interferon (for example, half-dose of pegylated interferon). At times, they may use a full dose of interferon. Some doctors add ribavirin to a reduced interferon dose. Maintenance therapy may be an important alternative if a person cannot achieve an SVR and may have advanced liver disease. Reasons for maintenance therapy follow:

A number of studies suggest that interferon can improve the condition of the liver (fibrosis and inflammation) even when it has no effect on HCV viral load. Continuing on a maintenance therapy regimen of interferon may be able to maintain that improvement.

Results from several studies suggest that interferon may reduce the risk of progression to liver cancer and severe liver disease (decompensated cirrhosis), even when there is no sustained reduction in viral load and no normalization of ALT. Also, interferon may reduce ALT without a virologic response.

It is believed that interferon may have a preventive effect that is not related to an anti-viral effect. It may have an anti-fibrotic effect and effect the immune response, which could slow or stop progression of fibrosis & inflammation.

The decision to continue or maintain therapy should take into consideration the person's ability to tolerate treatment and the risk of HCV progression (if the patient has a high degree of inflammation and fibrosis, maintenance therapy may be more important to slowing their disease progression, so they do not progress to a serious condition).

Treatment Effect of Maintenance Therapy

As discussed earlier, the response rate is lower for people with genotype 1, and in general with viral loads above 2 million, or with early cirrhosis. Response rates are higher for individuals with genotype 2 or 3. Unfortunately, most co-infected persons and most people in the US have genotype 1. If a person has had HCV for many years they may have advanced liver disease. Achieving an SVR is less likely in the circumstances described above.

As mentioned above, studies show that even if a person cannot achieve a SVR, the condition of the liver may have improved and progression of fibrosis may be slowed or stopped. If such an individual stops therapy, the improved liver condition (referred to as improved histology) may fade over time. Research studies suggest that keeping a person on maintenance therapy may sustain that improvement. Bear in mind, there is no consensus that maintenance therapy will be successful in slowing or stopping progression. Two large studies are ongoing to look at this, but study results may not be available for several years. Maintenance therapy may be the only option for some persons with advanced liver disease.

New Goal for HCV Treatment

In many ways, HCV is at the same point as HIV was 10 years ago. There is currently only one treatment for HCV: interferon and ribavirin. Ten years ago only AZT was available to treat HIV. So, the goal ten years ago was to stay alive long enough and remain relatively healthy until new treatments could be developed. This applies to HCV now. If a person cannot reduce their HCV viral load to undetectable or achieve a Sustained Virologic Response, a secondary goal is to improve the condition (inflammation and fibrosis) of the liver enough so that a person can be alive and healthy enough for treatments now in development. As discussed above, that is the goal of maintenance therapy -- to delay or prevent HCV progression.

New HCV Drug Research

Research into new drugs for HCV is receiving much attention. Many new potential treatment directions and drug candidates are being explored. Various types of antiviral and immune therapies are in early research. A few new potential treatments have just started in human studies. It is expected that a number of new treatments will be developed and available, but not for several years. Promising potential drug developments include protease inhibitors for HCV, helicase inhibitors, polymerase inhibitors, maximine (immune-based therapy), ribozymes, and antisense molecules. Drugs that slow or stop fibrosis are being researched. In November 2002, initial results were reported from a small study of the first HCV protease inhibitor. Patients with chronic HCV received the drug for 48 hours and saw potent 2-3 log reductions in HCV viral load, and so far there were no safety concerns observed. Follow-up studies are expected to begin in early 2003.

Vaccine Development
There are a number of research efforts in trying to find a vaccine--both for prevention and therapeutic. But the possibility of finding a vaccine for HCV has similar difficulties to the problem of finding a vaccine for HIV. The high mutation rates and the genetic diversity of these viruses, make it difficult to find a vaccine to conquer them.

Diet, Herbs and Vitamins

If a person has cirrhosis they should avoid raw clams, mussels and oysters, and iron and vitamin A supplements (which can accumulate in the liver).

Some doctors or nutritionists may suggest unusual diets for people with HCV, such as a meat-free diet. Many doctors do not feel there is evidence that such a diet is helpful unless a person has serious complications of liver disease. It is generally accepted that a diet with adequate amounts of fresh vegetables and fruits should be followed. Try to eat an overall healthy and balanced diet. Moderate exercise should be helpful. For the person with HIV, a meat free diet may be harmful.

Herbs:
There are several concerns about using herbs. There is little evidence that herbs can help with HCV. In fact, some herbs have been identified as being harmful to the liver. Herbal products are not regulated by the FDA. There is no inspection or monitoring for safety of ingredients and the uniformity of the amount of active ingredients. This means that one capsule or a portion of raw herbs could have more active ingredients than another could. Another concern is that an herbal product can have an interaction with HIV drugs. For example, one herb has been studied by the National Institutes of Health -- St. John's Wort. NIH researchers found that this herb severely reduced blood levels of the HIV protease inhibitor Crixivan. As a result, the FDA has issued a recommendation to doctors that St. John's Wort should not be used with protease inhibitors or NNRTIs, also used to treat HIV. Preliminary research at the NIH found that Milk Thistle did not appear to affect indinavir levels. Further research is expected to confirm this.

Vitamins:
It is generally accepted that if a person with HCV takes a multiple vitamin, it should be iron-free. You can see iron-free on the front of the bottle.

Additional Alternative Approaches:
Stress reduction may be helpful. Various techniques which can be used include: yoga, exercise, meditation and relaxation techniques, massage therapy, and acupuncture. Before starting an exercise regimen, please consult with your doctor.

National AIDS Treatment Advocacy Project

NATAP Programs:

-- NATAP Reports newsletter
-- NATAP Web Site www.natap.org
-- Community Treatment Education Program: on site at over 100 AIDS Service Organizations
-- HIV and Hepatitis Treatment Education Series Forums at NYU Medical Center
-- Email Treatment & Conference Updates
-- All programs and materials available in English and Spanish

NATAP National Hepatitis C and HCV/HIV Co-infection Training Institute

This program provides treatment education on HCV and HIV to organizations and community in any city throughout the USA. If you would like NATAP to visit your site or provide educational programs in your city, please call 1-888-26-NATAP.

NATAP
580 Broadway, Suite 1010
New York, NY 10012
Tel: (212) 219-0106
Fax: (212) 219-8473
Email: info@natap.org

Free copies of this handbook are available from NATAP.

National AIDS Treatment Advocacy Project
(NATAP)
580 Broadway, Suite 1010
New York, NY 10012
Tel: (212) 219-0106
Fax: (212) 219-8473
Email: info@natap.org
Treatment Website: www.natap.org

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