

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

Version V

National AIDS Treatment Advocacy Project  
(NATAP)

*Prepared by Jules Levin*

## **National AIDS Treatment Advocacy Project**

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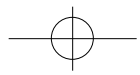
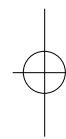
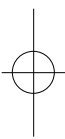
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Free copies of this handbook are available from NATAP



<b>Table of Contents</b>	<b>Page Number</b>
Introduction: by Jules Levin .....	5
Brief Facts and Statistics About Hepatitis C .....	6
--What is Hepatitis C? .....	6
Facts on People with HCV Alone (monoinfected) .....	7
How Can A Person Get HCV? .....	7
--Hetrosexual Transmission .....	8
--Men who have Sex with Men .....	9
What is Co-Infection? .....	9
Symptoms of HCV .....	10
Diagnosis and Testing .....	10
--Key tests: ALT, genotype, HCV viral load, biopsy .....	10
Liver Function Tests .....	11-13
Genotype .....	13
The Biopsy and Non-invasive Evaluation .....	13
--When to get a biopsy .....	14
HIV and HCV Similarities and Differences .....	15
Liver Functions - Why is the liver so important? .....	16
-- Purification, Synthesis, Storage .....	16
-- Transformation, When Your Liver is Not Well .....	17
-- Fibrosis .....	17
-- Cirrhosis, Liver Failure, Liver Cancer .....	18
Treatment for HCV and the Co-Infected Person .....	18
-- Primary Goal of Therapy .....	18
-- Secondary Goal of Therapy .....	19
-- What is the Best Treatment for HCV .....	19
-- Managing Therapy Side Effects .....	19
-- Can HCV be "cured"? .....	21
-- What Treatment Responses Can Be Expected .....	22
-- Pegylated Interferon .....	22
-- Predicting SVR 12 Week Early Viral Response .....	23
-- How to Improve Treatment Response .....	23
-- Study Results Tables .....	24 - 26



- Treatment of Non-Responders ..... 27
- Predictors of the Response to HCV Therapy .....27
- Response to Therapy for HCV/HIV Coinfection .....27

Three Coinfection Studies

- RIBAVIC, APRICOT, ACTG 5071 .....28
  - Comparison of Baseline Characteristics Between Studies .....28
  - Response ACTG 5071, APRICOT, RIBAVIC .....29
  - PEG-IFN Virologic Response Rates Across 3 Studies .....29
  - APRICOT: SVR Rates .....30
  - A5071: SVR Rates .....30
  - RIBAVIC: SVR Rates .....31
  - Early Virologic Response 100% Negative Predictive Value .....31

Special Coinfection Issues

- Fatty Liver .....32
- Drug Interactions .....32
- Adverse Effects of Therapy .....32

ART Hepatotoxicity .....33

Things to Consider Before HCV or HIV Therapy .....38

- What is Maintenance Therapy .....40
- Secondary Goal for HCV Treatment .....41

Update on New HCV Drug Research .....41

HCV Protease Inhibitors: VX-950 .....42

HCV Polymerase Inhibitors: NM283 .....42

Viramidine: a potential substitute for ribavirin .....42

Vaccine Development .....43

Diet, Herbs and Vitamins .....43

- Herbs .....43
- Vitamins .....43
- Additional Alternative Approaches .....44



## INTRODUCTION

By Jules Levin

This is the 5th version of the Hepatitis C Virus and HIV/HCV Coinfection Handbook. Since the first edition of this Handbook, there have been numerous advancements in the treatment of hepatitis C. It is my commitment to update and revise this handbook as new developments arise. Updates in this edition include the latest new drug developments, and the latest information regarding HCV/HIV coinfection as of the summer of 2005. I have also included data results from three key studies in the treatment of HCV/HIV coinfection.

It should be noted that Hepatitis has become a leading cause of death, perhaps the # 1 cause of death, in HIV today. Since HIV can accelerate the progression of HCV, it is important not to delay the diagnosis of HCV and the assessment of the stage of liver disease. Determining when to begin treatment for HCV is based on the stage of liver disease an individual may be in. Therefore due consideration for when to begin therapy is crucial. Undue delay in therapy can result in serious liver damage.

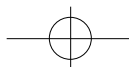
Research in discovering new drugs to treat HCV is receiving much attention. I am convinced new and more effective treatments will become available, but this process will take time. Two potential new HCV drugs are currently being studied in patients. The present developmental status of these new drugs are reviewed in this Handbook.

This Handbook also provides important treatment information regarding the slowing of HCV disease progression until new drugs are made available. This brings hope for those individuals who are not able to achieve the desired response from current HCV therapy, or what is also know as, a Sustained Viral Response.

This booklet was published during the Summer of 2005. For more late-breaking and up-to-date developments read the NATAP website (<http://www.natap.org>). You can also read the NATAP Hepatitis C Review Newsletter, which can be ordered from NATAP (888 26-NATAP) and is available on the NATAP website.

May health and happiness be with you, and always remember to keep fighting.

Sincerely,  
Jules Levin  
Executive Director, NATAP



## 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.

One million individuals have HIV in the USA, but about five million individuals have chronic HCV-infection -- about 2% of the entire US population (CDC statistics).

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 serious concern for people coinfecting with HIV and hepatitis. As people with HIV live longer, liver disease can progress, and HIV can accelerate HCV progression. It is important to pay attention to the risk that HCV disease can accelerate in a person with HIV and to therefore screen for and monitor liver disease if you are infected, so that one can avoid waking up one day with advanced liver disease. 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 22). Researchers are in the process of developing new drugs, and several of

them are in the very early stages of study in patients.

A person's HCV viral genotype and viral load are important to understanding the infected person's ability to respond well to HCV therapy, and in designing treatment strategies. (also see Genotype Section on pg10).

### **Facts on People with HCV Alone (mono-infected)**

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 sickness. 20% of individuals chronically infected with HCV monoinfection develop serious complications or cirrhosis, (widespread scarring & inflammation of the liver), and this usually takes as long as 20-30 years to develop, meaning 40% never progress and 40% progress over the course of 40-50 years if they live that long. 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).

For most HCV monoinfected individuals, serious complications of liver disease is not expected to develop, and HCV may not affect their lifespan. Some HCV-infected persons are at greater risk for faster and 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, though this may not be feasible for HIV/HCV coinfecting individuals.

### **How Can a Person Get Hepatitis C?**

- ◆ Intravenous drug use (IVDU). IVDU is the leading risk factor for HCV. If you use IV drugs even once with a needle containing microscopic amounts of infected blood, transmission is a risk.
- ◆ Sharing IV drug paraphernalia: microscopic amounts of infected blood can be present in cookers, used water, cottons, and in blood on tourniquets.
- ◆ Sexual intercourse with an infected person (low risk)
- ◆ Tattooing with unclean needles or used 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 that may have microscopic amount of infected blood (low risk)
- ◆ Blood transfusion before July 1992 (high risk)

- ◆Needlestick accident with a patient with HCV
- ◆Hemodialysis
- ◆Sharing straws to snort drugs (low risk)
- ◆Other exposures to infected blood (moderate risk)

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 a risk for transmission of HCV from mother-to-child, 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 monogamous heterosexual partners of HCV-infected HIV-negative individuals, several studies show a 0-3% risk of sexual transmission of HCV. Having sex while a woman is menstruating may increase risk for transmission. Anal sex may increase risk of transmission. Anal sex may damage the lining of the rectum, and potentially facilitate blood-to-blood 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. The presence of STDs, herpes, and open sores may increase risk.

These concerns suggest HCV transmission rates in regions where HIV is spread primarily through heterosexual sex, such as in Africa, may be greater than we realize.

High-risk sexual behavior also appears to play a role in sexual transmission of HCV. Any time there is blood-to-blood contact, 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.

### **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. In the past year a number of new studies from several hospitals have highlighted these concerns by reporting that they noticed a recent influx of acute HCV-infection among men who have sex with men who also have HIV. Sexual behavior that may draw blood may increase risk for HCV transmission. The presence of sores or ulcers may increase risk. Sexual practices such as fisting or rimming may increase risk. The presence of STDs and HIV may increase risk as well.

### **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%). It's estimated that 5-8% of people HIV-infected also have the hepatitis B virus.

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 through 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 disease has progressed. HCV is more easily transmissible than HIV. Seventy to eighty percent of HCV infections appear to occur within the first few years of IV drug use, so one may have had HCV longer than they have had HIV. Findings from several studies suggest that intervention with HIV therapy (HAART) may slow or stop HCV progression for some individuals, but the impact of antiretroviral drugs on the progression of HCV-related liver fibrosis is not clear. And about 8-10% of coinfecting patients on HAART experience severe hepatotoxicity (elevated liver enzymes), and the effect of this remains uncertain. It is uncertain if HAART slows or accelerates HCV progression, or if it has no effect on progression. As well, research has yet to examine the effect of fatty liver and insulin resistance on coinfecting individuals. In HCV monoinfected individuals, these conditions have been found to contribute to liver disease. However, HCV therapy may be very helpful in stopping or slowing liver disease progression.

**If a person has HIV, they should:**

- ◆Be tested for hepatitis A, B, and C. If negative for A and B, they should talk to their doctor about getting vaccines for A and B.
  
- ◆Try to find a doctor(s) knowledgeable and experienced in treating about both HIV and HCV, and start discussing treatment strategies for HIV and HCV. Show this handbook to the doctor and engage the 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. One ought to consider on an individual basis whether treating for HIV or HCV first is better. Treating HCV first may improve liver inflammation and virus activity and prevent HAART-related hepatotoxicity. As well, response rates to HCV therapy are better when HCV is treated in the early stages of HCV disease.

**Symptoms of Hepatitis C**

When a person is first infected with HCV, they may or may not experience flu-like symptoms such as malaise, fatigue, and weakness. With chronic infection, HCV usually progresses slowly for years and there are few or most often no 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. Because it is common to be symptom-free if you have HCV, it is important to be tested for the presence of hepatitis C if you are in a risk group. HIV+ individuals should be tested for HCV. Equally important, if a person is HCV+ they should be in care and be monitored for hepatitis progression.

**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 HCV-related 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 of HCV 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 HCV 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-RNA viral load test (see next section), skipping over using the ELISA or RIBA tests or to use the HCV-RNA test to confirm a positive antibody test.

### **Liver Function Tests (LFT)**

**ALT** (alanine transaminase; serum glutamate pyruvate transaminase; SGPT): A key LFT is the ALT. This enzyme is produced by the major cell found in the liver. Therefore, ALT elevation 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.

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.

**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. It can cause the urine to be very dark. Jaundice 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.

**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-RNA** (viral load): The HCV-RNA test can detect the presence of virus (HCV) in the blood, and can measure the viral load. There are 2 types of viral load tests: qualitative and quantitative tests. The Roche qualitative HCV-RNA version

2.0 test is FDA-approved and tells you if a person has above or below 50 international units (IU)/milliliter (ml) of HCV viral load. The Bayer TMA qualitative test is FDA-approved and also tells you if a person has above or below 10 IU/ml of HCV viral load. The quantitative HCV-RNA test tells you how much virus is present in the blood. The Bayer Versant HCV-RNA quantitative test version 3.0 is FDA-approved and has a lower limit of detection of 615 IU/ml, and has an upper limit of detection of 7.7 million IU/ml of HCV viral load. The Roche Amplicor HCV Monitor version 2.0 has a lower limit of detection of 600 IU/ml, and an upper limit of detection of 500,000 IU/ml of HCV viral load.

The HCV viral load is considered along with a person's genotype in determining the duration of treatment. In general, persons with high viral load (>800,000 IU), particularly with genotype 1, do not respond as well to therapy compared to persons with a low viral load (<800,000 IU), and so may require longer duration of treatment.

### **Genotype**

It is important to do a genotype test because the HCV viral genotype dictates the type and length of treatment. In general, response rates to HCV therapy for patients with genotype 1 are significantly lower than for individuals with genotype 2 or 3. A person with genotype 1 or with > 800,000 IU HCV viral load usually receives 12 months treatment rather than 6 months, which may be adequate for HCV monoinfected individuals with genotype 2 or 3 and low viral load. In HIV-coinfected individuals, longer courses of treatment of at least 12 months are in general likely to be required regardless of genotype. 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. Most individuals contracting HCV through IVDU have genotype 1. One large study showed over 90% of HCV-infected African-Americans had genotype 1. The genotype test is done from a blood sample.

### **The Biopsy and Non-invasive Evaluation**

If a person is co-infected with HCV and HIV, they should speak with a 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 important to assess disease in the liver. 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. The biopsy reveals the degree of liver inflammation and fibrosis, which helps predict when cirrhosis may develop. A biopsy has been considered the "gold standard" for evaluating liver disease. Recently, non-invasive markers of liver disease (fibrosis) have been evaluated. Some of them, such as the aspartate aminotransferase

(AST)/alanine aminotransferase (ALT) ratio, the platelet count and the prothrombin index represent measurements routinely obtained in the clinical evaluation of patients. Their combination into multi-component indices generally improve their diagnostic accuracy. Recent studies evaluating combinations of these markers suggest they are useful in evaluating the stage of liver disease (fibrosis), but it remains controversial whether they are ready for "prime-time" (that is, to be a reliable substitute for a liver biopsy).

Generally, HCV treatment response rates are lower in people with cirrhosis. As well, complications and symptoms can develop after cirrhosis develops. By assessing the stage of liver disease in a timely fashion with a liver biopsy you can identify liver disease before cirrhosis develops, and timely treatment intervention can 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. Liver biopsy can also find the presence of fatty liver, which is associated with liver disease and reduced response to interferon therapy. Results from studies of treatment intervention with diet and pioglitazone, an anti-diabetes oral drug, have demonstrated improvement of fatty liver and improved fibrosis.

#### **When should a person get a biopsy?**

Some doctors feel that liver damage is minimal if the ALT is normal or low. ALT, liver function tests, are not reliable in assessing the stage of liver disease or if it is time to begin HCV therapy. Of note, ALT has been found to be normal in up to 40% of HCV-infected individuals with moderate or severe liver damage. In addition, a coinfecting person could have high CD4s and undetectable viral load but still have cirrhosis. One should consider performing a liver biopsy as soon as being 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 with extensive experience in performing liver biopsy 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. Any time there is blood-to-blood contact, HCV can be transmitted, including sexually. Both viruses can evade the immune system, and both are resistant to eradication. Both viruses can mutate, although mutation rates appear 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 usually is limited to 6 or 12 months. Maintenance HCV therapy (pg 42) may be ongoing or intermittent. You and your doctor should weigh the risks and benefits of immediate or deferred therapy.

◆ With current therapies HIV cannot be eradicated, treatment is continuous. But, treatment for HCV is time limited, for 6 or 12 months or perhaps 18 months.

◆ Viral load has a different significance in 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, while 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. There are no reasons in general to perform serial HCV viral load tests. HCV viral load tests should be performed when they are useful: after diagnosing HCV, before starting therapy to get a baseline to evaluate response to therapy; and to evaluate the response to therapy at these timepoints: after 12 weeks on HCV therapy; after 24 weeks; at the end of treatment; 6 months after treatment has ended; and periodically for several years to confirm sustained response.

◆ 500,000 is an example of a high HIV RNA (viral load) but low HCV RNA (viral load).

◆ In general individuals with >800,000 IU HCV-RNA do not respond as well to HCV therapy, while those with <800,000 IU respond better.

◆ HIV is better understood than HCV or HBV. Hepatitis research is nearly 10 years behind HIV research. There remain many unanswered questions about HCV and HBV. HIV has been researched much more.

◆ There is currently one standard of care therapy for HCV, pegylated interferon plus ribavirin combination, but there are about 20 different drugs to treat HIV.

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

Numerous studies show that HIV accelerates hepatitis C liver disease progression. Therefore, there is a serious risk that 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. We need more studies of HCV/HIV coinfecting patients to better understand how and why HCV may progress more quickly in an individual, and to better understand the variables. In HCV mono-infected individuals fatty liver and insulin resistance or diabetes can lead to fibrosis, which can contribute to liver disease, and these factors have been found to reduce response rates to HCV therapy (interferon/rinavirin). Although this has not been studied in coinfection, perhaps these are factors in reduced response rates to HCV therapy in coinfection.

The effect of HAART on liver disease remains unclear. HAART may have a dual effect by improving the immune system, which might reduce rates of HCV-associated liver disease progression or it might accelerate progression due to hepatotoxicity or other yet unknown effects. Several recent studies suggest that a good response to HAART with good CD4 count and low or undetectable HIV RNA may slow HCV disease progression to a rate on par with HCV mono-infected individuals. However, elevations in ALT can occur, the effect of which has not been well evaluated. ALT elevations, also called hepatotoxicity, are crude measures of liver disease. Although, up to 40% of individuals with normal ALT have advanced liver disease, high ALT can be a sign of advanced liver disease. Performing liver biopsies before starting HAART and after a period of time on HAART may be the best way to evaluate HAART's effect on the liver.

### **Liver Functions- 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 these four 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).

### **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, including those needed to clot blood and makes new cells and causes 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.

### **Hepatitis Damages The Liver: 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 significant percentage 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.

### **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.

### **Treatment for the HCV Mono-infected and the Co-Infected Person**

An HCV-infected person should ask his or her doctor the following question: what are the various strategies available to me 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 and the timing of when to begin therapy should consider the situation (including readiness for therapy), 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 and ultrasound.

### **What is the primary goal of HCV therapy?**

To reduce and sustain HCV viral load to undetectable (SVR), which results in normalization of ALT/AST, and improves the condition (inflammation, fibrosis) of the liver. Studies show that achieving and maintaining a Sustained Viral Response stops fibrosis progression and can prevent liver cancer. Study results suggest that

even a partial response to HCV therapy, reduction in viral load, may slow fibrosis for a period of time.

### **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 (reducing inflammation and fibrosis [scarring]). When the primary goal (SVR) is not achievable the secondary goal becomes very important, and may be achieved without a sustained viral response through the anti-fibrotic effects of interferon.

### **What is the Best Treatment for HCV?**

Combination therapy with pegylated interferon and ribavirin is the current standard of care for HCV and is 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.

Some doctors had 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 using the old interferon regimen. But study results with alternate dosing have been mixed. The introduction of pegylated interferon changed treatment options & strategies.

### **Managing Therapy Side Effects**

HCV therapy can be difficult to tolerate. Side effects can include: fatigue, irritability, depression, anemia, weight loss, loss of appetite, reduced platelet count, low white blood cell count and neutrophil counts, flu-like symptoms (chills, low grade fevers, body aches, headaches), among others. For coinfecting patients, weight loss may exacerbate lipoatrophy, and anemia may be more of a concern, particularly if taking AZT.

Flu-like symptoms can improve by limited use of NSAIDs (non-steroidal anti-inflammatory drugs), acetaminophen (Tylenol) or Advil, and drinking plenty of decaffeinated fluids. More than 2000 mg of Tylenol per day can cause liver toxicity. Make sure to discuss with a 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 and depression. Light walking and physical activity is helpful, but don't overdo exercise. It's important to nap or rest when

you feel tired, but remaining sedentary will not help with fatigue and depression.

More serious toxicities from HCV therapy are possible, one should consult with their doctor about these. For people with HIV, the most common side effect associated with ribavirin can be anemia (reduced hemoglobin), which can be effectively treated with Procrit (EPO) therapy in many cases, while remaining on ribavirin. Studies show that EPO can increase hemoglobin, and improve fatigue.

Sometimes doctors reduce ribavirin dosing to prevent anemia, but studies showed that EPO allows patients to tolerate higher ribavirin doses. This is important because reducing ribavirin dosing can reduce response rates to HCV therapy. Hemoglobin should be monitored closely: weekly during the first month of treatment. Although dose reduction of ribavirin for a brief period can also be considered for management of ribavirin-induced anemia it may not be optimal. Anemia, and reduced platelets and blood cell counts can be reversed with interventional treatment or by stopping therapy. Before starting HCV treatment, make sure your doctor fully explains the potential side effects and toxicities.

**Ribavirin causes severe birth defects, therefore women who are pregnant should not take ribavirin.** Women on HCV therapy who are considering pregnancy should wait at least six months after stopping ribavirin therapy before conceiving. Ribavirin remains in the body for six months after stopping the drug. 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 depression or psychiatric or mental illness may have problems tolerating or adhering to interferon. Depression can be a common side effect of interferon, and is associated with anemia caused fatigue. 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. Remain well hydrated by drinking 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 due to experiencing gastrointestinal 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 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 your concerns about these potential side effects with people close to you or people you live with. Ask them to read about it in this handbook. Joining a support group can also be helpful. The potential reward of eliminating HCV is worth the effort.

### **Can HCV be "Cured"?**

HIV cannot be cured yet. But it appears that HCV may be "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 by the viral load blood test your doctor uses at the end of treatment. SVR is achieved when the viral load remains undetectable at six months following treatment. Achieving an SVR is the primary goal of therapy. A few small studies have shown that 3-11 years after achieving an SVR, HCV viral load is still undetectable in almost all the patients (over 95%). 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 showed that if HCV was not found in the blood it could not be found in the liver either. Another recent study showed that viral failure (relapse) appears to only occur within 2 years after stopping therapy.

Two recent studies using sensitive PCR testing found HCV in certain cells in patients who achieved a Sustained Viral Response. The common wisdom is that once HCV is gone, it is gone; and there is a substantial body of work countering these recent findings that HCV can be found in cells of patients who have achieved a Sustained Viral Response.

There may be traces of the virus left behind that do not cause any disease or are not clinically relevant. The common wisdom is that the findings of HCV after a Sustained Viral Response will not impact clinical practice, and patients with a Sustained Virologic Response will have sufficient clinical benefit.

The larger question comes back to what is the goal of therapy. These studies suggest the goal of therapy may not be to eradicate every trace of the virus but to decrease the risk for liver disease, liver failure, and liver cancer, and perhaps to eliminate active virus replication. These studies reinforce the need to continue following patients who achieve a Sustained Viral Response (SVR).

## What Treatment Responses Can Be Expected? Results to therapy for HCV mono-infection

Results from the following studies were conducted in patients with HCV mono-infection (study patients did not have HCV/HIV co-infection). Two large studies from 7 years ago found that about 40% of patients with HCV alone achieved an SVR using the old standard interferon regimen of 3 million units injected subcutaneously (under the skin) 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 FDA approved 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. More recently, Pegasys plus Copegus therapy was approved for treatment of HCV in HIV/HCV coinfection and Pegasys was approved for treatment of HBV. 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. PegIntron plus Rebetol combination is approved for treatment of HCV mono-infection. Study results of these two drugs in HCV mono-infection and HCV/HIV coinfection are provided in this booklet.

Pegylated interferon is an advancement in treating HCV because Pegylated interferon is injected subcutaneously only 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.

The studies in HCV mono-infection found the overall SVR rates 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. 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.

### **Predicting SVR: 12 Week Early Viral Response**

After 12 weeks on therapy, a number of studies found that the viral load response at week 12 can predict response to the full course of treatment. In HCV mono-infected, 65% of patients with a reduction in HCV viral load of 2 logs or more achieve a Sustained Viral Response, and in HCV/HIV coinfecting patients a study found 56% achieve an SVR. Over 95% of patients who don't achieve a 2-log reduction in viral load by week 12 do not achieve an SVR. So, after 12 weeks of therapy you can consider discontinuing therapy if it has not achieved the desired response.

### **How To Improve Treatment Response**

There are some things that improve response rates to therapy. Full adherence substantially improves response rates (100% is better than 80%). Of note, studies show missing ribavirin doses has a more detrimental effect than missing peginterferon doses, particularly in the early stages after beginning therapy. There are some additional things you can do to help improve response rates. Starting therapy early in HCV disease is associated with better response rates. For coinfecting patients, starting HCV therapy when HIV is well under control (high CD4 count and low HIV viral load) can improve response to HCV therapy. A healthy lifestyle may help improve response rates: don't eat too much fat in your diet, as fat can get deposited in your liver, a condition called fatty liver. Exercise, relaxation, and good diet (adequate protein; not too much fast food; eat fresh vegetables and fruit) can also be helpful in improving response rates. **Drinking alcohol can accelerate progression of HCV.**

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

<b>PegIntron Treatment Response in Patients with Genotype 1</b>		
	High Viral Load (>800,000 IU/ml)	Low Viral Load (<800,000 IU/ml)
Interferon + Ribavirin (1000-1200mg/day)	70/247 (28%)	42/96 (44%)
PegIntron 1.5µg/kg + Ribavirin(800mg/day)	75/256 (29%)	66/92 (72%)

<b>PegIntron Treatment Response in Patients with Genotype 2-6</b>		
	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%)

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

<b>Pegasys Treatment Response in Patients with Genotype 2/3</b>		
	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 (> 800,000 IU) had better results.

<b>2nd Pegasys + Ribavirin Study – Patients with Genotype 1</b>		
	High Viral Load	Low Viral Load
Pegasys 180 mcg + ribavirin 800 mg - 24 weeks treatment	<b>16%</b>	<b>41%</b>
Pegasys 180 mcg + ribavirin 1000/1200 mg - 24 weeks treatment	<b>26%</b>	<b>51%</b>
Pegasys 180 mcg + ribavirin 800 mg - 48 weeks treatment	<b>35%</b>	<b>53%</b>
Pegasys 180 mcg + ribavirin 1000/1200 mg - 48 weeks treatment	<b>46%</b>	<b>61%</b>

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	<b>78%</b>
Pegasys 180 mcg + ribavirin 1000/1200 mg - 24 weeks treatment	<b>78%</b>
Pegasys 180 mcg + ribavirin 800 mg - 48 weeks treatment	<b>73%</b>
Pegasys 180 mcg + ribavirin 1000/1200 mg - 48 weeks treatment	<b>77%</b>

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.

### **Treatment for Non-Responders**

Results from several studies suggest treatment strategies for patients who have failed standard peginterferon plus ribavirin therapy. Using double the dose of peginterferon in combination with ribavirin is being studied. Preliminary findings suggest that some patients can achieve a Sustained Viral Response, but the higher dosing may be associated with additional side effects. A second approach is using daily high dosing of Consensus Interferon. Results from several preliminary studies found some patients who failed peginterferon plus ribavirin achieved an SVR with high dose Consensus Interferon plus ribavirin. Phase III study is ongoing.

### **Predictors of the Response to HCV Therapy**

- ◆Caucasians respond better than African Americans
- ◆HCV viral load: persons with >800,000 IU 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 may respond better
- ◆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 and reduce response to therapy; Fatty Liver (accumulation of fat in the liver; also referred to as non-alcoholic steatohepatitis or NASH) can reduce response to therapy. Risk factors associated with the development of fatty liver include obesity, hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and hypertension.

### **Response to Therapy for HCV/HIV Coinfection**

Recently, the results of three large randomized controlled trials of peginterferon versus standard interferon in coinfecting subjects have been reported.

There is a decreased response to HCV therapies in HIV positive patients compared to those without HIV, perhaps due in part to a compromised immune system. Recent data from three key studies in HIV-HCV coinfecting patients showed response rates of 14% to 29% in genotype 1 and 43% to 62% in genotypes 2 and 3 (see slides of study results in the next section). It is important to bear in mind that the average overall results from 800 study participants do not predict an individual's response. There is no way to predict in advance how an individual will respond to therapy. The only way to see if an individual will respond is to try therapy, and use the 12 week Early Viral Response rule.

Each of the three studies in HIV-HCV coinfecting patients had patients with different baseline characteristics, different dosages of HCV medications used and dif-

ferent discontinuation rates. These issues complicate comparison of response rates between studies. Although the response rates may be lower in the coinfecting patient, there is still the keen possibility of 'cure'. Combination pegylated interferon and ribavirin was shown in these studies to be more effective than pegylated interferon alone or non-pegylated interferon with ribavirin.

### Comparison of Baseline Characteristics Between Studies

It is important to bear in mind that ribavirin dosing was lower in these three coinfection studies than in the studies in HCV monoinfected described above. This was done out of concern that ribavirin-associated anemia would be worse in coinfecting individuals. In the APRICOT and RIBAVIC studies the ribavirin dose was 800mg daily. But, in ACTG 5071 patients started ribavirin dosing at 600mg daily and escalated to 1000mg daily over the first eight weeks. This was likely to have a negative effect on the ability to achieve a Sustained Viral Response. Both ACTG 5071 and APRICOT used Pegasys, the Roche peginterferon, and RIBAVIC used PegIntron, the Schering-Plough peginterferon. The number of patients in the 3 studies were: 133 in ACTG 5071; 860 in APRICOT; 412 in RIBAVIC. It's worth repeating: study results can provide guidance on overall response rates, but they cannot be used to predict how any one individual will respond. Although, response rates for genotype 1 are relatively low, you could be the person who responds.

**Three Coinfection Studies:  
RIBAVIC (PegIntron+ribavirin, n=418);  
APRICOT (Pegasys+ribavirin, n=868);  
ACTG 5071 (Pegasys+ribavirin, n=133)**

Results of these 3 studies were presented at the 2004 Retrovirus Conference. Ribavirin dosing was 800 mg a day in both APRICOT & RIBAVIC.

### Comparison of Baseline Characteristics Between Studies

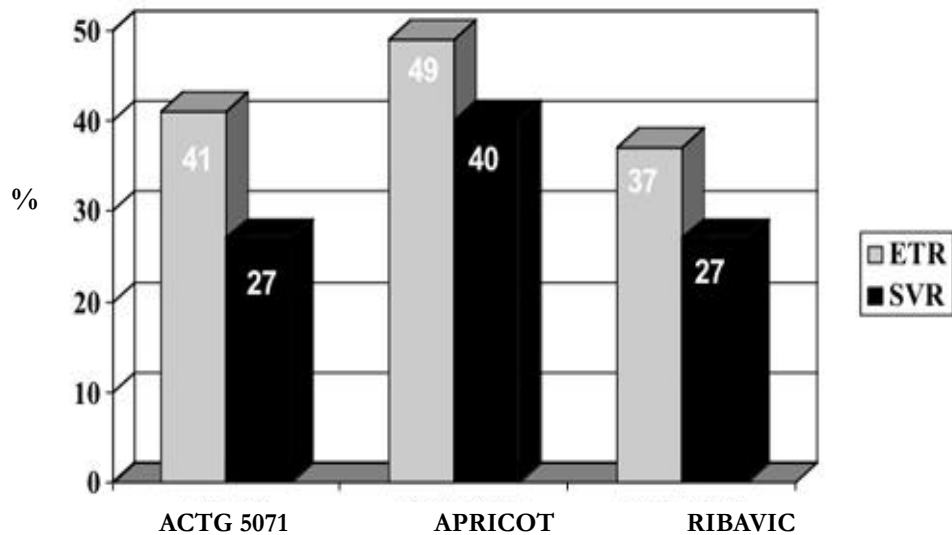
	<b>A5071</b>	<b>APRICOT</b>	<b>RIBAVIC</b>
<b>Ethnic: C/AA</b>	48% / 33%	78% / 10%	NR
<b>Genotype 1-4 / 2-3</b>	78% / 22%	61% / 39%	58% / 42%
<b>Log HCV RNA</b>	6.2	6.7	5.9
<b>Bridging or cirrhosis</b>	44%	15%	40%
<b>CD4 Count</b>	444-492	520-542	514
<b>%Taking HAART</b>	86 %	84 %	82 %

Response	ACTG 5071 Pegasys		APRICOT Pegasys			RIBAVIC PegIntron	
	Peg RBV	IFN RBV	Peg RBV	IFN RBV	Peg RBV	IFN RBV	IFN RBV
SVR							
Overall	27%	12%	40%	12%	20%	27%	19%
Genotype 1	14%	6%	29%	7%	14%	15%	5%
Non-1 Genotype	73%	33%	62%	20%	36%	43%	41%

Discontinuation rates were 25% in APRICOT from Pegasys/RBV and 39% in RIBAVIC from PegIntron/RBV. And 12% in ACTG 5071.

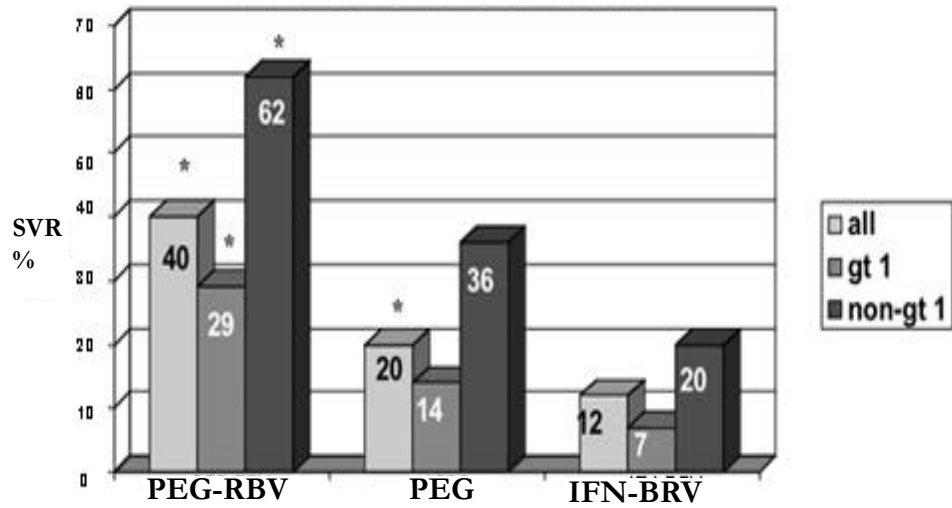
**Summary of all 3 studies:  
End of Treatment Response (ETR) & SVR**

**PEG-IFN Virologic Response Rates Across Studies**



**Apricot SVRs: for Pegasys+ribavirin- overall 40%; 29% for genotype 1; 62% for genotype 2/3**

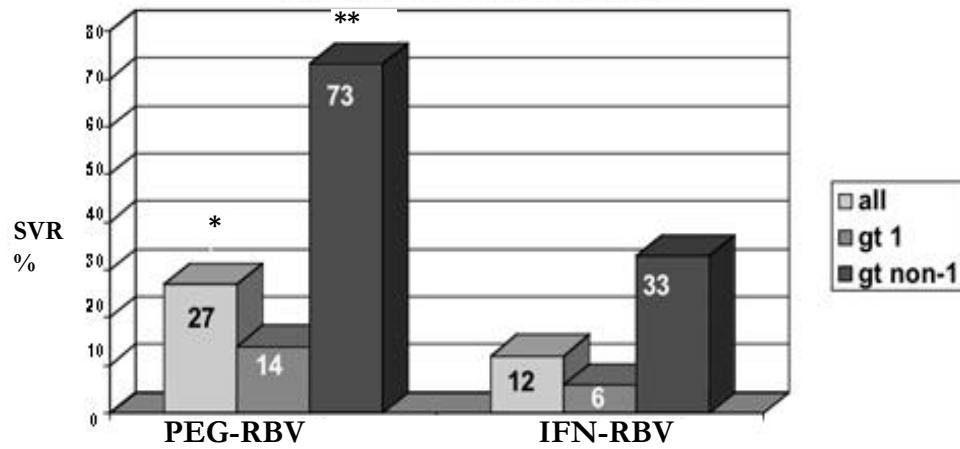
**APRICOT: SVR Rates**



\*p<0.05 compared to IFN/RBV

**Sustained Viral Response (SVR) in ACTG 5071: Overall 27%; 73% for genotype 2/3; 14% for genotype 1.**

**A5071: SVR Rates**

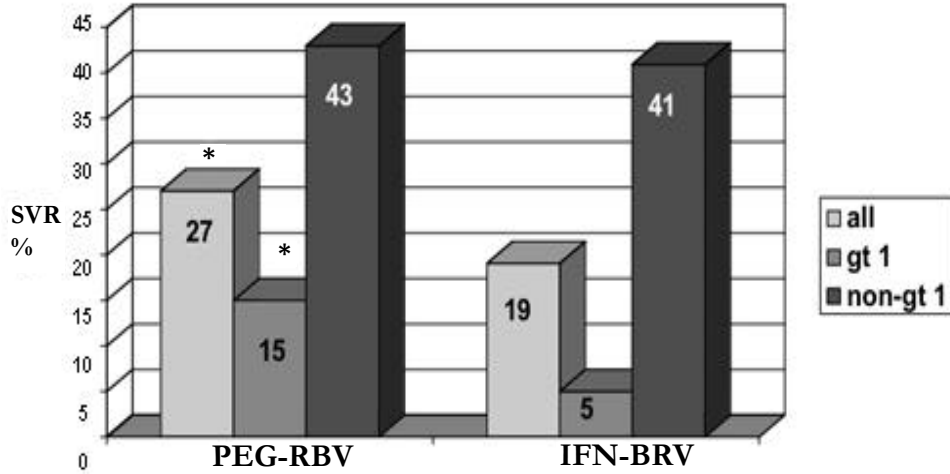


\*p=0.03 compared to IFN/RBV

\*\*p<0.001 compared to gt 1

**Ribavirin SVRs: for PegIntron+ribavirin- overall 27%; genotype 1- 15%; genotype 2/3- 43%.**

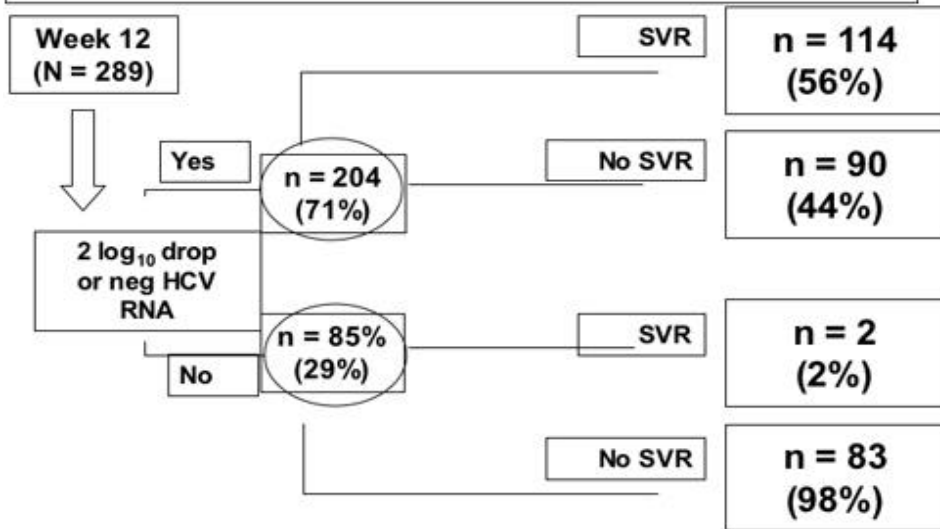
**RIBAVIC: SVR Rates**



\*p=0.05 compared to IFN/RBV

**Early Viral Response (EVR) by Week 12 in Apricot. 98% of patients without EVR by week 12 did not achieve SVR; 56% who had EVR had SVR.**

**Early Viral Response has 100% Negative Predictive Value**



### **Special Coinfection Issues**

HCV/HIV coinfecting individuals are at greater risk than HIV-infected individuals for lipodystrophy (body changes), and for abnormalities in cholesterol, triglycerides, and glucose.

#### **Fatty Liver**

This is a condition where fat is accumulated in the liver and occurs in association with hepatitis C. Risk factors include elevations in cholesterol, triglycerides, and glucose abnormalities. The presence of fatty liver can increase risk for fibrosis, and in studies has been found to reduce response rates to HCV therapy.

Studies find that insulin resistance and diabetes can cause fibrosis, and studies find that intervention with diet or pioglitazone (anti-diabetes drug) can improve fatty liver and reduce fibrosis.

#### **Drug Interactions**

Studies find that ribavirin may increase the amount of ddI (an HIV drug) a person is exposed to, which could increase ddI toxicity. Importantly, ddI has been clinically associated in combination with interferon and ribavirin with fatal cases of lactic acidosis. Therefore, it is strongly recommended that practitioners switch to an alternative non-ddI-containing regimen prior to the initiation of interferon and ribavirin-based therapy. The FDA recommends NOT to use ddI with ribavirin due to these potential serious toxicities.

Several studies have found a few patients taking combination d4T/ddI after adding ribavirin and interferon experienced symptoms related to elevated hyperlactatemia, and mitochondrial toxicity. Patients should be monitored if they add ribavirin to ddI or d4T/ddI.

Early research in test tubes (in vitro) suggested possible interaction between d4T and AZT with ribavirin in such a way as to reduce the effectiveness of these AIDS medications. Recently reported results from APRICOT study of Pegasys suggests there is NOT a relevant drug-drug interaction between NRTIs, besides ddI, and ribavirin. In this study 800mg of ribavirin was used.

#### **Adverse Effects of Therapy**

Anemia, which causes fatigue, can result from using ribavirin, EPO (PROCRIT) use can improve anemia. Anemia is defined as a reduction in hemoglobin to <10 mg/dl. Anemia can occur within weeks after starting HCV therapy.

White blood cell counts can be reduced on HCV therapy. Thus far studies suggest that this does not appear to be associated with an increase in opportunistic infec-



tions but adjunctive therapy is available.

Absolute CD4 count is often reduced after starting HCV therapy, but the CD4 percent usually remains the same. After stopping HCV therapy CD4 count is expected to return to levels prior to HCV therapy.

### **ART Hepatotoxicity**

Hepatotoxicity generally refers to more than moderate elevations in liver enzyme tests-- LFTs -- (ALT & AST). After starting HAART, studies show about 8-12% of HCV+ patients experience >5 times the upper limit of normal LFTs, and this is called severe hepatotoxicity. HCV & HBV coinfecting individuals have a greater risk for experiencing elevated liver enzymes compared to individuals with HIV who do not have HCV or HBV. The risk of harm to the liver when LFTs are so elevated has not been well studied. But liver enzyme levels are a crude assessment of damage to the liver. Sequential liver biopsies, although poorly tolerated by patients, may be required to truly assess changes in liver fibrosis accurately. Up to 40% of hepatitis infected individuals can have normal ALT/AST, but have advanced liver disease (fibrosis). Research suggests that 'persistent' elevations of ALT 150 IU/L or more may be related to progression of liver disease. One study found that persistent elevations of liver enzymes 5 times above the upper limit of normal appeared to affect liver disease progression. These situations may suggest that treatment for hepatitis may be in order. Our understanding of the effect of ART on the liver is limited, better designed studies might provide more insight.

All HIV ART drugs appear to be associated with the possibility of elevations in ALT/AST, but usually elevations are moderate. NNRTIs and PIs can lead to elevations in liver enzymes. As well, d4T can be associated with elevations in liver enzymes. In the past, the use of full dose ritonavir—600 mg twice daily or 400 mg twice daily—has been associated with higher rates of hepatotoxicity, but today no one uses full dose ritonavir. Nevirapine (Viramune), an NNRTI, has been associated with liver toxicity, but on average efavirenz (NNRTI) does not appear to be associated with a greater risk for hepatotoxicity compared to protease inhibitors that are not associated with higher risk. Low-dose ritonavir —100 mg once or twice daily—is now commonly used in combination with other protease inhibitors to boost their drug levels, such as Kaletra (LPV/r), indinavir/r, fosamprenavir/r (Lexiva), saquinavir/r (1000/100 twice daily), and Reyataz/r. But data from several studies show that low-dose ritonavir used to boost other PIs do not have any additional affect on ALT elevation. Overall studies do not show an inordinate risk for ALT elevations associated with tenofovir, 3TC, or abacavir,

Most coinfecting individuals do not experience hepatotoxicity on HAART, about 85%, so therefore, the increased risk of this toxicity in HCV-positive patients

should not by itself represent a reason to withhold anti-HIV therapy. After beginning HAART liver enzymes should be monitored because an ALT flare may occur within the first 6 months, but usually the flares subside. Continuing monitoring of ALT/AST is recommended for HCV and HBV coinfecting individuals.

A number of studies find that HIV accelerates HCV and HBV progression to a swifter pace than for individuals who have HCV or HBV without HIV. Recent results from a few studies suggest that reducing HIV viral load to undetectable and increasing CD4 count may have a beneficial effect on HCV disease progression, but this finding needs further study. At the EASL meeting (Spring 2004) Norbert Brau reported on a study in the Veterans Administration finding that patients with undetectable HIV RNA who also were coinfecting with HCV did not experience faster HCV progression than HCV mono-infected who did not have HIV. These findings suggest that full suppression of HIV may assist in slowing liver disease progression. Since Brau's presentation several additional published studies have observed similar findings. HAART may have a dual effect on the progression of chronic hepatitis C-associated liver fibrosis by reducing immunosuppression, but also association with hepatotoxicity. Further studies are in order to better understand these dynamics.

The FDA issued a report in July 2004 regarding Nevirapine and hepatotoxicity. The FDA said-- Severe and life-threatening hepatotoxicity, and fatal fulminant hepatitis have been reported in patients treated with Viramune (nevirapine). Hepatic adverse events have been reported to occur more frequently during the first 18 weeks of treatment, but such events may occur at any time during treatment.

In controlled clinical trials, clinical hepatic events regardless of severity occurred in 4.0% (range 2.5% to 11.0%) of patients who received the NNRTI Viramune (nevirapine) and 1.2% of patients in control groups. Transaminase elevations (ALT or AST > 5X ULN) were observed in 8.8% of patients receiving Viramune and 6.2% of patients in control groups in clinical trials.

Higher CD4 counts, increased AST/ALT levels, and co-infection with hepatitis B or C at the start of antiretroviral therapy are associated with a greater risk of hepatic adverse events. Patients with higher CD4 counts before starting HAART (>250 cells in women and >400 cells in men) appear to be at higher risk for rash-associated hepatic events with Viramune. Women appear to have a three fold higher risk than men for rash-associated hepatic events (4.6% versus 1.5%). In a retrospective study review, women with CD4 counts >250 cells before starting HAART had a 9 fold higher risk of rash-associated hepatic adverse events compared to women with CD4 counts <250 cells (8.4% versus 0.9%). An increased risk was observed in men with CD4 counts >400 cells before starting HAART (4.5% versus 0.7%

for men with CD4 counts <400 cells).

If patients present with a suspected Viramune-associated rash, liver function tests should be performed. Patients with rash-associated AST or ALT elevations should be permanently discontinued from Viramune.

Mark Sulkowski (Johns Hopkins Medical School), wrote in an article published in *Clinical Infectious Diseases* (March 2004; 38:S90-S97), "**Drug-Induced Liver Injury Associated with Antiretroviral Therapy that Includes HIV-1 Protease Inhibitors**":

...in the study by Wit et al., the use of low-dose ritonavir based ART (i.e., 200 mg/day) was not associated with any cases of grade 4 hepatotoxicity. Furthermore, in a randomized controlled trial that compared lopinavir therapy boosted with low-dose ritonavir and nelfinavir, only 4.5% of lopinavir/ritonavir recipients developed an AST or ALT level >5 times the ULN, which was similar to the incidence observed in nelfinavir recipients (5.2%). Similarly, Vora et al. reported that the addition of low-dose ritonavir to indinavir therapy for 19 patients coinfecting with HBV or HCV was not associated with significant increases in serum ALT or AST levels....emerging data indicates that the use of low-dose ritonavir to "boost" the levels of other PIs (e.g., lopinavir or indinavir) is not associated with significantly higher incidence of severe hepatotoxicity than is observed with most other PIs, such as nelfinavir.

Sulkowski reported in this study at the AASLD liver conference in November 2003 (published in *AIDS* November 2004): "**Hepatotoxicity and Protease Inhibitors: nelfinavir, Kaletra, indinavir/r, saquinavir/ritonavir**":

This study evaluated the incidence of severe hepatotoxicity, defined as a grade 3 or 4 change in ALT/AST levels, following initiation of ART-containing PIs with or without low-dose ritonavir at Johns Hopkins urban HIV clinic. 77% of patients were African-American; 46% HCV+; 10% HBsAg+ (infected with chronic hepatitis B); median ALT was 30 IU/L; median CD4 count 166; patients were followed for median 224-365 days.

This study looked at 1061 patients starting a PI regimen: nelfinavir (605 patients, no ritonavir); Kaletra (89 patients, 200mg of ritonavir per day), indinavir/ritonavir (94 patients, 200-400mg ritonavir per day), and SQV/ritonavir (800mg ritonavir per day) for the purpose of evaluating the rates for developing severe hepatotoxicity.

The study authors found that the rates of severe hepatotoxicity occurred in patients receiving nelfinavir regimen at 11%, Kaletra (LPV/rtv 200 mg) 9%, IDV/RTV (200-400mg ritonavir/day) 12.8%, SQV/RTV (800mg ritonavir/day) 17.2%. Overall 12% of patients experienced hepatotoxicity when on a PI regimen in this study. Having HCV was associated with experiencing severe hepatotoxicity. Hepatotoxicity was defined as grade 3 or 4 changes in ALT/AST. For patients with normal ALT/AST at baseline grade 3 was 5 x the upper limit of normal and grade 4 was 10 x the upper limit of normal. For patients with elevated ALT/AST before the study, grade 3 was defined as 3.6-5 x baseline and grade 4 as >5 x baseline.

HCV+ patients had a 2-fold higher risk for hepatotoxicity, but 83% of HCV+ patients did not experience hepatotoxicity. Overall, the incidence of grade 3/4 hepatotoxicity was higher in HCV+ subjects (8.7%) compared to HCV negative subjects (4%). In multivariate Cox proportional hazard analysis, grade 3/4 hepatotoxicity was independently associated with use of IDV/rtv (Relative Risk 2.97), SQV/rtv (RR 2.41), being HCV+ (RR 1.82), baseline CD4 count <200, and baseline HIV RNA level >10,000 copies/ml (RR 4.77).

The authors concluded the highest risk for grade 3/4 hepatotoxicity was observed in patients receiving SQV/rtv (800mg/day) and IDV/rtv (200-400mg/day). However, no increased risk of hepatotoxicity was detected in patients receiving NFV or LPV/rtv (Kaletra). In addition, while HCV+ pts had a 2-fold higher risk of hepatotoxicity, 83% of such patients did not experience toxicity, suggesting PIs should not be withheld.

Following initiation of PI-containing HAART, serum ALT levels remained less than 1.25 times the ULN of their pretreatment levels in 54% of LPV/rtv users, 62% of IDV/rtv users, and 54% of NFV users compared to only 42% of RTV/SQV users ( $p < .0001$  for comparison of RTV/SQV to other PI regimens). Overall, severe (grade 3 or 4) hepatotoxicity was observed in 135 of 1061 (12.1%) of patients prescribed PIs.

Hepatotoxicity (any grade) was observed in 58% of HCV-infected persons compared to 41% of HCV-uninfected than ( $p < .0001$ ). The detection of severe hepatotoxicity was more rapid among HCV-infected than HCV-uninfected pts. While 62% (84 of 135) of severe hepatotoxicity cases were observed in HCV-infected pts, 82.6% (400 of 484) of HCV-infected patients did not experience severe hepatotoxicity.

Tipranavir is a new protease inhibitor approved in June 2005 by the FDA for HIV-positive individuals who are highly treatment-experienced or with extensive resistance to multiple protease inhibitors. Tipranavir is taken twice daily and boosted by

200 mg of ritonavir taken twice daily. Tipranavir is associated with hepatotoxicity and clinical hepatitis, which generally occurred in patients with advanced HIV disease taking multiple medications at the same time. Extra vigilance is needed for patients with chronic hepatitis B or C co-infection, as these patients have an increased risk of hepatotoxicity.

The FDA Package Insert for tipranavir says:

Liver function tests should be performed at initiation of therapy with APTIVUS/ritonavir (tipranavir/ritonavir) and monitored frequently throughout the duration of treatment. Use caution when prescribing APTIVUS/ritonavir to patients with elevated transaminases, hepatitis B or C co-infection or other underlying hepatic impairment. APTIVUS is contraindicated in patients with moderate and severe (Child-Pugh Class B and C, respectively) hepatic insufficiency. APTIVUS should not be given to patients with moderate to severe liver disease.

Patients with chronic hepatitis B or hepatitis C co-infection or elevations in transaminases (liver function tests, ALT/AST) are at approximately 2.5-fold risk for developing further transaminase elevations or hepatic decompensation. Additionally, Grade 3 and 4 increases in hepatic transaminases were observed in 6% of healthy volunteers in Phase 1 studies and 6% of subjects receiving APTIVUS/ritonavir in Phase 3 studies.

Tipranavir is principally metabolized by the liver. Therefore caution should be exercised when administering APTIVUS/ritonavir to patients with hepatic impairment because tipranavir concentrations may be increased.

Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. Patients with signs or symptoms of clinical hepatitis should discontinue APTIVUS/ritonavir treatment and seek medical evaluation.

Atazanavir (Reyataz) is a relatively new protease inhibitor prescribed at a dose of 400 mg per day or boosted by low-dose ritonavir and prescribed as 300mg Reyataz plus 100 mg ritonavir. Reyataz has been FDA approved and available in the pharmacy for about 2 years. At the 3rd International AIDS Society Conference in Rio de Janeiro (July 2005), Perez-Elias and co-authors reported on a study examining the incidence of hepatotoxicity for treatment-experienced patients receiving ritonavir boosted Reyataz (300/100) in the Spanish Reyataz Early Access Program (EAP), followup was 6 months. Data from HBV/HIV and HCV/HIV co-infected patients were prospectively recorded and evaluated to determine the impact of coinfection. Median ALT was 106 UI/L for coinfecting patients at baseline, and 31

UI/L for non co-infected patients. Incidence of grade 3-4 hepatotoxicity through month 6 was low in co-infected patients (1.9%). Only 3 co-infected (1.7%) discontinued treatment because of elevated liver enzymes.

### **Things To Consider Before Beginning HCV or HIV Therapy**

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 understand the effects of having both HIV and HCV, and in deciding whether to start HCV treatment early or to delay it, or to treat HCV before treating HIV with HAART.

HIV medications can be burdensome to the liver, but having hepatitis C should not be a contraindication to taking HAART. 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 well understood yet.

- ◆Elevated levels of fats (cholesterol, triglycerides) can result from HIV drugs and may cause 'fatty liver' and can be unhealthy to the liver. Diabetes can cause fatty liver.

- ◆Certain NRTIs can cause mitochondrial toxicity to cells, and this may be harmful to cells in the liver.

- ◆Studies have found that HCV-infection can be associated with elevated glucose and reduced bone mineral density; HAART may also be associated with elevated glucose and HIV with reduced bone mineral density.

- ◆HCV coinfecting patients may be more likely than HIV-positive individuals to develop lipodystrophy (body changes), elevated cholesterol, triglycerides, and glucose, reduced bone density, and insulin resistance, all perhaps due to liver impairment.

- ◆Although there is some information about how HIV medications (HAART) effect a person's HCV disease, the information is limited

- ◆Treating HCV before treating HIV may be beneficial because it might help the liver tolerate the HIV drugs better. As well, treating HCV during early stage of HCV or HIV disease can improve response rates.

◆After HAART is started and the patient is stable on HAART, HCV therapy can be initiated. Patients usually are treated for both HIV and HCV at the same time.

◆If liver toxicity occurs after starting HAART, options include continuing current regimen with close monitoring, changing HIV drugs, and initiating HCV therapy. Often, HCV therapy will reduce HCV associated inflammation and ALT elevations.

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 often settle down on their own, but can also be controlled by changing or interrupting HAART therapy, or by starting HCV therapy. Treating with HCV therapy before HAART may prevent these flare-ups.

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 hepatitis 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 HCV 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.

Treating HCV during early HIV disease also can be more successful in achieving an SVR. 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.

Depending on 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. 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; the difficulty in tolerating interferon and ribavirin
- ◆response rates observed in studies
- ◆more tolerable and effective treatments may be available in several years
- ◆but peginterferon will still be needed to be used along with new therapies for the foreseeable future.

Bear in mind that HIV may accelerate HCV progression. Therefore, if treatment is deferred, close monitoring of the liver condition may be crucial. The problem is that close monitoring of liver disease progression in coinfecting individuals is complicated because HCV may progress much more quickly in HIV and frequent liver biopsies, such as every year or two, are difficult to perform. Because it is difficult to accurately monitor liver disease progression in coinfection, HCV therapy is often recommended in early stages of liver disease such as at stage 2 fibrosis or even stage one. Close monitoring of liver disease progression is easier and less complicated in HCV monoinfection, because liver disease progression is slower and more predictable. So, the standard of care has developed in HCV monoinfection to perform a liver biopsy every 3-5 years for purposes of monitoring.

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 since HIV can accelerate HCV disease progression.

#### **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. Typically, 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. 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. That is, 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 for slowing their disease progression, so they do not progress to a serious condition).
- ◆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 current option for some persons with advanced liver disease.

### **Secondary Goal for HCV Treatment: slowing HCV disease progression**

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. The main goal of HCV therapy is to achieve and sustain undetectable HCV viral load, called a Sustained Viral Response (SVR). If this goal cannot be attained the secondary goal of HCV therapy is to slow down disease progression in order to be healthy for the new drugs in development. Maintenance Therapy may slow disease progression by improving the condition (inflammation and fibrosis) of the liver. As discussed above, that is the goal of Maintenance Therapy -- to delay or prevent HCV progression.

### **Update on New HCV Drug Research**

Research into new drugs for HCV is receiving much attention. Many new potentially rewarding treatment directions and drug candidates are being explored. Promising drug developments include protease inhibitors for HCV, helicase inhibitors, polymerase inhibitors, and perhaps antisense molecules. Drugs that slow or stop fibrosis, called anti-fibrotic agents, are being researched. Currently, protease inhibitors and polymerase inhibitors are the most advanced in development and being studied in patients. The most advanced in development and interesting new drugs at the time of this publication (Summer 2005) are the HCV protease

inhibitor VX-950, the polymerase inhibitor NM283, and a potential substitute for ribavirin called Viramidine. Results from phase I study of VX-950 and phase II study of NM283 in HCV+ patients demonstrated antiviral efficacy and safety. Further studies are planned. Phase II study of Viramidine demonstrates it is associated with a much lower incidence of anemia compared to ribavirin. Phase II studies suggest similar viral response when using Viramidine or ribavirin in combination with peginterferon, but we await results from ongoing phase III studies. Bear in mind safety issues can emerge at any time and halt any drug development. If development of these drugs are successful it may take several years from now to become available in the pharmacy. Peginterferon will still have to be used in combination with these drugs for the foreseeable future.

Various types of additional anti-viral and immune therapies are in early research. It is expected that a number of these new potential treatments will be developed, but not for at least 5 years.

#### **HCV Protease Inhibitors: VX-950: 14 day phase I study**

In Spring 2005, promising study results were reported for the first time at a major hepatitis conference from an initial study in patients of the HCV protease inhibitor VX-950. 36 patients with genotype 1 received one of three doses of VX-950 for 14 days. Full analysis of safety was still pending at the time, but preliminary reporting said VX-950 was well tolerated in healthy subjects and in patients with HCV: no serious adverse events; there were no discontinuations; no elevations in ALT/AST, or other clinical chemistry findings. The median reduction in HCV RNA (viral load) was an impressive -4 logs, ranging between 3 and 6 logs. 7 patients achieved undetectable HCV RNA by day 14: 5 <30 IU/mL; 2 <10 IU/mL. Further study is planned.

#### **HCV Polymerase Inhibitors: NM283**

In Spring 2005 promising phase II study results were reported for the HCV polymerase inhibitor NM283. 30 treatment-naïve HCV+ genotype 1 patients received NM283 monotherapy or NM283 plus peginterferon (Peginterferon a-2b 1.0 ug/kg). Study investigators reported NM283 appears safe. There were no serious adverse events or dose limiting toxicities. Gastrointestinal side effects were associated with NM283. Other side effects reported included headache, dyspepsia, and arthralgia.

Mean HCV viral load reductions by week 24 were -1.9 log IU/mL for 1 patient still receiving NM283 monotherapy, and -4.5 log IU/mL for patients receiving combination therapy with NM283 plus peginterferon. At week 24, 8/9 patients had <600 IU/mL, 7/9 had <50 IU/mL, and 6 of 9 patients had <10 IU/mL using the sensitive TaqMan assay.

### **Viramidine: a potential substitute for ribavirin**

Viramidine results in significantly less anemia than ribavirin and if it proves to be as effective in terms of viral response compared to ribavirin Viramidine may be a safer and more tolerable alternative to ribavirin. Global Phase III studies are ongoing.

### **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. There is little evidence that such diets are 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. Although one study did not find Milk Thistle harmful, studies have shown mixed results on whether it is in fact helpful.

### **Vitamins**

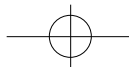
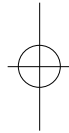
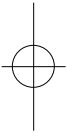
It is generally accepted that if a person with HCV takes a multiple vitamin, it



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](http://www.natap.org)
- Email Treatment & Conference Updates
- Community Treatment Education Program
- HIV and Hepatitis Treatment Education Series Forums at NYU Medical Center in NYC
- Spanish HIV / Hepatitis National Treatment Education Program
- 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.

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Free copies of this handbook are available from NATAP.

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