



Hepatitis

Hepatitis

Liver problems are a frequent cause of disease and sometimes death in people with HIV. Technically, any significant irritation or inflammation of the liver is called “hepatitis”, but the term is more commonly used to refer to several infections of the liver. The majority of such liver diseases in people with HIV are caused by viruses, especially hepatitis B virus (HBV) and hepatitis C virus (HCV). Other organisms that may cause liver disease include cytomegalovirus (CMV), Epstein-Barr virus (EBV), mycobacterium avium complex (MAC), toxoplasmosis and histoplasmosis. Studies have shown that almost a quarter of people with HIV are also co-infected with HBV. Additionally, many drugs used in the treatment of HIV disease can also cause forms of liver disease or hepatitis as a side effect.

The liver is the largest organ in the body. Its primary functions include eliminating toxins from the body, manufacturing cholesterol, making clotting factors as well as heparin (an anti-clotting factor), secreting bile (a digestive juice which helps in the food digestion process), manufacturing new proteins which are needed for body growth and general well being, regulates blood volume and is one of the main sources of body heat. Additionally, the liver converts sugars into stored energy and in between meals converts the stored energy back into blood sugars to meet the body’s energy needs. The liver also stores the body’s iron reserves, vitamins A, B₁₂, D, E and K and other minerals.

This publication focuses on the most common forms of viral hepatitis—those that are caused by an infectious agent. While more than five types of hepatitis (A-E and G) have been identified, this article will deal primarily with hepatitis A, B and C. Hepatitis A and E are mainly transmitted through sexual contact while hepatitis B, C and D are primarily spread through blood or other body fluids.

In addition to specific symptoms described below, the symptoms of the various hepatitis viruses are quite similar, with all causing elevated levels of liver enzymes.

Diagnosis of viral hepatitis is usually done by a blood test. It is important to get an accurate diagnosis so that sex partners and people living in the same household can take appropriate preventive measures. Recent advances have led to the development of more sophisticated and sensitive technologies to monitor hepatitis levels in blood (these include the PCR tests and bDNA test). These are the same technologies currently used to measure HIV levels (viral load). Currently, these tests are available for investigational use to measure HBV and HCV levels and have not yet been approved by the FDA.

Hepatitis A

Travelers who visit countries where HAV is common and sexually active gay men are particularly at risk for becoming infected with hepatitis A. The virus can be contracted through contact with infected people, by drinking contaminated water or by eating contaminated food. Additionally, gay men are most often infected through sexual contact, especially through oral-anal contact with infected persons. A person is most infectious about 2 weeks before the onset of jaundice (yellowing of the skin and eyes). Although HAV can be found in saliva, it is very unlikely that it can be transmitted by saliva. HAV very rarely results in chronic liver disease.

Symptoms

Hepatitis A most commonly causes high fevers, jaundice, nausea, diarrhea, fatigue, abdominal pain, dark urine, vomiting and loss of appetite.

Table of Contents

Hepatitis A	1
Symptoms	1
Prevention	2
Post Exposure Prevention	2
Treatment	2
Hepatitis B	2
Symptoms	2
Prevention	2
Post Exposure Prevention	3
Treatment	3
Hepatitis C	3
Symptoms	4
Prevention	4
Treatment	4
New Drugs in Development	5
Considerations for Therapy	5
Side Effects	6
Summary	6
Supplemental: Hepatitis A	6
Supplemental: Hepatitis B	6
Supplemental: Hepatitis C	7
Supplemental: New Drugs	7
Supplemental: Peg-Intron	7-8





Hepatitis

Prevention

Hepatitis A can be easily prevented. Maintaining good personal hygiene, such as routinely washing hands, is successful in interrupting outbreaks when the mode of transmission is from person to person. Vaccination is the most effective method of preventing HAV infections. Hepatitis A vaccines (Havrix and VAQTA) are 94%-100% effective in preventing HAV infection. An initial injection with the vaccine protects adults for up to a year and a second booster shot is given 6 to 12 months later. The second dose provides long-term protection against the virus. Immune globulins (IG) are also sometimes used to prevent hepatitis A. IG is over 85% effective in preventing HAV infection, however, the period of protection is relatively short (usually between 3 and 6 months depending on the dose of IG used).

Hepatitis A vaccination (VAQTA) is shown to be safe and effective in people living with HIV. For more information see page 7.

Post Exposure Prevention

People recently been exposed to HAV (household or sexual contact with someone who has hepatitis A) should consider post exposure prevention. People who have not been vaccinated against HAV should receive IG within 2 weeks of exposure. People who were vaccinated at least a month before exposure do not need IG.

Treatment

There are no treatments for hepatitis A. Most people clear the infection on their own (without medication) and usually people will only develop hepatitis A once. Therapies that may cause liver damage or which are metabolized (broken down) in the liver should be used with caution.

Hepatitis B

Almost everybody is at risk for developing hepatitis B. This includes health care workers, people who are sexually active, injection drug users, people who require blood or blood products, prisoners, infants born to mothers who are infected with HBV and people who have intimate contacts or live with people with chronic HBV. Most cases of HBV (30–60%) are believed to be sexually transmitted.

Initial infection with HBV often results in a flu-like syndrome when a person feels seriously ill with fevers, liver pain and swelling and severe fatigue. This period usually lasts from as little as one week to as long as a month, after which a person will generally feel better, though the virus will remain “quiet” (called *latent infection*). However, some people with HIV may suffer from reactivation of previously latent HBV despite taking anti-HBV therapy. This is rarely seen among people who are not HIV-infected.

Some people go on to develop a chronic (ongoing) form of HBV infection, which means that the virus and sometimes the symptoms of hepatitis remain “active”. Chronic HBV infection develops in up to 10% of people infected with HBV as adults, which increases their risk of developing chronic liver disease as well as transmitting HBV to others. Additionally, people who are co-infected with HIV and HBV are more likely to develop chronic HBV infection. People with lower CD4+ cell counts appear to be more likely to develop chronic HBV infection.

Chronic HBV infection can take two general forms. In most people who develop chronic HBV, the disease is largely harmless and with-

out significant symptoms. Its presence is detected only through blood tests. In a small percentage of people, chronic HBV is aggressive, producing bouts of illness. Over time, this aggressive form of chronic HBV can lead to liver failure and liver cancer. Regardless of which form chronic HBV takes, chronic carriers are believed capable of transmitting the disease to others.

Symptoms

Hepatitis B most commonly causes fatigue, jaundice, vomiting, abdominal pain, nausea and anorexia.

Prevention

Vaccination is the most effective method of preventing hepatitis B infection. However, most researchers recommend that gay men and injection drug users be screened for hepatitis B antibodies (evidence of previous HBV infection) before being given the vaccine. Approximately 95% of people with HIV have previously been infected with HBV.

Hepatitis B vaccine (Engerix-B and Recombivax HB) is usually given in a three-dose cycle. The first dose is about 50% protective, the second dose 85% protective and the third dose is typically 90% protective. The second dose of the vaccine should be given at least one month after the first and the third dose should be given at least 4 months after the second dose. It is important to complete the entire regimen, as the third dose is required to provide long-term protection.

Hepatitis



Some studies suggest that people with HIV may not get the same response to the vaccine as someone who is not infected with HIV. Therefore, it is currently recommended that people with HIV who are vaccinated check for hepatitis B surface antibody levels (an indicator of how protective the vaccine might be) 1–2 months after the third vaccine dose. People should consider revaccination with three more doses if no or very low levels of antibodies are detected.

Post Exposure Prevention

A person who has sexual contacts with someone who has recently been infected with hepatitis B, or someone with symptoms of hepatitis B disease, should receive hepatitis B immune globulin (HBIG) and hepatitis B vaccine within 14 days after the most recent sexual contact. Adults who live in the same household as someone with acute hepatitis B are generally not at risk for infection. However, it is recommended that children and adolescents be vaccinated against HBV. Furthermore, if the person still has detectable hepatitis B surface antigen (a marker of hepatitis B infection), then everyone in the household should be vaccinated. Hepatitis B vaccine is currently recommended to prevent HBV transmission for people with casual/household and sexual contact with people who have chronic HBV infection.

Treatment

No treatment is approved for people with acute HBV infection and only two drugs are approved for the treatment of chronic hepatitis B, Interferon alfa-2b (Intron A) and lamivudine (3TC, Epivir, Epivir-HBV). Interferon alfa-2b is about 40-50% effective in eliminating chronic HBV infection after 24 weeks of therapy, with people who infected during adulthood being more likely to respond to this treatment. Some studies suggest that people with HIV have a lower response rate to interferon therapy than people who are not HIV-infected.

Interferon alfa-2b is usually given at a dose of five million international units (MIU) daily or ten MIU three times a week for 16 weeks or longer, under the skin (subcutaneously) or into the muscle (intramuscularly). A significant number of people develop side effects while on this therapy, with fevers, depression, fatigue and headaches being the most commonly reported.

Studies have shown that lamivudine is about 15-17% effective in eliminating chronic HBV infection after 52 weeks of therapy. The majority of people have an initial decrease in HBV levels following lamivudine therapy, but HBV levels returned to detectable levels over time in many people. This suggests that lamivudine is not potent enough to be used alone and should be used in combination with other anti-HBV therapies. The recommended dose of lamivudine for treating HBV is 100mg tablet once a day. This dose is lower than the

dose used to treat HIV, so people who are infected with HIV and HBV should use the 150mg twice a day dose to avoid developing lamivudine resistant HIV. HBV can become resistant to lamivudine when a dose below 100 mg/day is used. The most commonly observed side effects reported in the studies include fatigue, sore throat and headaches.

Most people with HIV who are using anti-HIV medications have been or are currently taking lamivudine-containing regimens. Even if lamivudine has failed to be effective in treating HIV, it still might be useful for treating HBV in people living with both viruses. Results from a small study of lamivudine in people with both HIV and HBV suggest it is useful in treating HBV in co-infected people. HBV resistant to lamivudine appeared most common in people with lower CD4+ cell counts (below 50). For more information about this study, see page 7.

Several therapies are currently being studied for the treatment of HBV, including interferon alfa-2a (Roferon-A), interferon alfa n3 (Alferon N), thymosin alpha, adefovir dipivoxil and emtricitabine (FTC, Coviracil). Preliminary results have shown that adefovir dipivoxil and emtricitabine are all effective in reducing hepatitis B levels with some normalization in measures of liver function.

Hepatitis C

Hepatitis C is mainly contracted through body fluids, primarily blood or blood products, sharing needles, mother-to-child transmission and to a lesser degree through sexual contact. Only about 25% of people infected with HCV develop symptoms after the initial infection. These symptoms, usually flu-like such as fever, fatigue, muscle and joint pain, nausea and vomiting, appear within 2–6 weeks after initial infection. Because the symptoms of initial HCV infection are usually milder than those of HAV and HBV, they often go unrecognized by people and their doctors. Furthermore, because most people infected with HCV do not have symptoms, they are more likely to unknowingly infect others. Chronic HCV develops in up to 85% of HCV infected people and about 70% develop some form of liver disease as a consequence. While overall there are fewer cases of HCV compared to HBV, HCV is spreading more rapidly and the severity of the disease is far worse. End-stage HCV disease is now the leading cause for liver transplantation in the United States and chronic HCV increases the risk of liver cancer.

There are several different types of HCV (how the virus is made up, called *genotypes*). Most people in the US and Western Europe are infected with type 1, which is also the most difficult type to treat. After initial infection with HCV, people experience increases in liver enzymes (specifically ALTs or alanine aminotransferases). With the help of the immune system, the level of liver enzymes decreases, but gradually increases again over time. Immune responses against HCV



Hepatitis

(called *HCV antibodies*) take a while to develop, rendering HCV antibody testing after initial infection unreliable. In most people with HCV, their HCV levels, without treatment, are in the 100,000 to 10,000,000 copies HCV RNA range. (Note: *These numbers should not be compared to the viral load numbers we are accustomed to seeing from HIV.*)

Recent studies suggest that HCV levels are higher and the course of HCV-related liver disease is accelerated among people who are co-infected with HIV and HCV. There are conflicting reports, however, as to whether HCV impacts HIV disease progression. The use of anti-HIV therapies has no activity against HCV itself and as a result controlling HIV replication to below 400 copies does not result in lowering of HCV levels.

Another study found that people who are co-infected with HIV and HCV are significantly more likely to die from sudden liver failure.

Mother to child transmission of HCV is much higher among women who are co-infected with HIV.

Often times, by the time HCV is diagnosed, the liver is already damaged. The use of alcohol considerably increases the risk of progression of liver disease. HCV, like HIV, is a very difficult virus to treat because it can mutate quickly and escape the natural immune response.

Symptoms

Hepatitis C most commonly causes fever, appetite loss, jaundice, nausea, diarrhea and vomiting.

Prevention

There is no vaccine against HCV. Because of the numerous types of HCV, the development of an effective vaccine is especially difficult. Currently, the only method to prevent transmission of HCV is to practice safer sex and to make sure that needles are sterilized (this includes needles and ink used for tattooing, body piercing and acupuncture).

Pregnant women who are also HIV-positive are more likely to transmit HCV to their newborns than women who are only HCV-positive. Most researchers recommend that to reduce the risk of HCV transmission, pregnant women should consider using anti-HIV therapies to reduce HIV levels as low as possible.

Treatment

The only approved treatments for hepatitis C is interferon alfa-2a, interferon alfa-2b and consensus interferon (Infergen). Interferon alfa-2b is also approved in combination with ribavirin (Rebetol) and sold as a bundled product under the name Rebetron. The combination of interferon alfa-2b with ribavirin is shown to be more effective

than interferon-alfa alone. People who are co-infected with HIV and HCV should be aware that use of this new recommended treatment for HCV infection can cause some interactions with anti-HIV therapies. In particular, the use of ribavirin tends to increase the potency of ddI several fold, which could increase side effects associated with ddI. In laboratory studies ribavirin interacts with AZT (and probably d4T), which results in decreased anti-HIV activity of AZT. This laboratory observation has not been confirmed in human studies.

Currently, there is little or no information about how HCV levels relate to illness, and therefore, treatment decisions should not be made based on viral levels alone. Because of the rapid rate of mutation seen with HCV, it seems logical to expect that combination therapy may be more effective and more durable than single-agent anti-HCV therapy.

Studies show that people who are most likely to respond to interferon-alfa therapy are likely to be younger, have low HCV levels (under two million copies), have CD4+ cells above 200, drink less than 50grams (about two ounces or two drinks or two beers) of alcohol per day, have HCV genotypes 2 or 3 and do not have cirrhosis. Cirrhosis is a permanent scarring of the liver and indicates a decrease in the amount of functioning liver tissue. Furthermore, the scarring interferes with the normal flow of blood through the liver and results in poor liver function.

The current recommendation is to use a combination of interferon alfa three times a week and ribavirin daily for at least a year. Most researchers believe that there is little difference in effectiveness between the three different versions of interferon-alfa, however, there may be slight differences in side effects. There is also preliminary evidence that treating immediately, after initial hepatitis C infection may reduce the risk of developing chronic disease.

The safety and effectiveness of interferon-alfa and ribavirin is not known in people under 18 years of age.

One disturbing observation reported in some HCV studies involving people who were HCV- but not HIV-infected show that African Americans appear less likely to respond to interferon-alpha therapy, with or without ribavirin, compared to white people. Preliminary results suggest that about 30% of white people respond to interferon-alfa therapy compared to only about 5% of African-Americans. Conversely, women and Asians seem to have better responses.

The reason why African-Americans do not have as good a response is not known, although this is not the first disease therapy responses vary by race. For instance, many studies have shown that African-

Hepatitis



Americans do not respond as well to approved therapies for treating hypertension compared to other races. Interestingly, at least one study suggests that African-Americans and Latino/as were more likely to benefit from anti-HIV therapy compared to white people. More research needs to be focused in this area so that effective therapy against HCV can be given to everyone.

Confusion remains regarding the use of protease inhibitors in people co-infected with HIV and hepatitis C virus (HCV). This concern arises because most of the protease inhibitors place some degree of strain on the liver, which is already greatly stressed by HCV. There have been conflicting reports, however, about the risks and benefits of protease inhibitor use in people with HIV and HCV. Many researchers monitor HCV levels carefully prior to and following the initiation of anti-HIV medications. There have been a few reported cases of reactivation of HCV (e.g. symptoms of HCV disease) after initiation of anti-HIV therapy.

The non-nucleoside reverse transcriptase inhibitors can also increase liver enzymes. Most researchers believe that nevirapine (Viramune) is the most likely to increase liver enzymes followed by delavirdine (Rescriptor) and efavirenz (Sustiva).

On a positive note, a treatment study found that people co-infected with HCV and HIV responded equally well to interferon-alfa, a treatment for hepatitis C, compared to HCV infected individuals who are not HIV-infected. This is contrary to the experience of people co-infected with HIV and hepatitis B virus who usually do not respond well to interferon treatment. It should be noted, however, that treatment with interferon-alfa alone is no longer considered state of the art treatment for hepatitis C. The combination of interferon-alfa with ribavirin is considered optimal therapy. For more information on Hepatitis C treatment, see page 7.

New Drugs in Development

Results from a small study of peg-interferon (Pegasys, a new formulation of interferon-alfa) suggest that it's far more effective in treating HCV than the current formulation of interferon-alfa.

Another version of peg-interferon (PEG-Intron) also shows better activity than the current version of the drug.

PEG-Intron, likely to be used in combination with ribavirin, might be approved by the Food and Drug Administration as early as spring 2001 and should be available by prescription shortly thereafter.

Several other therapies are being studied for the treatment of hepatitis C including thymosin alpha, interferon beta, mycophenolate, VX-497, oral alpha interferon, milk thistle, coenzyme Q10, vitamin B12 and amantadine (a common flu drug).

Considerations for Therapy

The current guidelines recommend that people with HCV with increased liver enzyme levels, a liver biopsy showing some degree of fibrosis (scarring of the liver) and at least a moderate degree of inflammation and necrosis (death of areas of tissue) consider starting anti-HCV therapy. People with persistent increases in liver enzymes but no other changes based on a liver biopsy, or people with cirrhosis, are encouraged to discuss the risks and benefits of starting anti-HCV therapy.

The standard dose of interferon-alfa is three million units three times a week and the standard dose of ribavirin is 1,000 to 1,200mg per day

based on body weight. For people who weigh under 75kg (about 165 pounds) the dose of ribavirin is two 200mg capsules in the morning and three 200mg capsules in the evening, for a total daily dose of 1,000mg. For people over 75kg, the dose of ribavirin is three 200mg capsules in the morning and three 200mg capsules in the evening, for a total daily dose of 1,200mg. The dose of ribavirin is usually reduced to 600mg per day (one 200mg capsule in the morning and two 200mg capsules in the evening) if red blood cells (hemoglobin) levels are below 10g/dL.

Most researchers now believe that it's beneficial for people to be on anti-HCV therapy for at least a year if not longer to increase the likelihood of achieving long-term benefits. Additionally, higher doses of interferon-alfa and dosing the drug every day are being studied to determine if this will result in even greater anti-HCV activity.

The current guidelines also recommend that people stop anti-HCV therapy if their liver enzymes continue to be elevated or if they have detectable HCV levels after receiving therapy for at least three months. Studies have shown that the likelihood of achieving long-term response is very low.

Most researchers believe it's wise for people who are co-infected with HIV and HCV to treat their HIV infection first. However, if the liver disease is severe, then it may be appropriate to treat the HCV first. Starting therapies for HIV and HCV at the same time is discouraged as this dramatically increases the likelihood of side effects. In general, at least a one to two month gap between starting anti-HIV and anti-HCV therapies is encouraged.



Hepatitis

Discuss the possibility of side effects from the therapies with your healthcare provider and try to come up with a plan on how to manage these side effects if they should arise.

Side Effects

Interferon-alfa and ribavirin can cause a lot of side effects. The most common side effects of interferon-alfa include: flu-like symptoms, fevers, muscle ache, depression (taking an anti-depressant before starting interferon-alfa may help), fatigue and headaches. The most common side effects of ribavirin include: anemia (decrease in red blood cells), coughing, difficulty in breathing, rash, insomnia and anorexia (loss of appetite).

Studies with ribavirin show that the drug causes birth defects in the offspring of laboratory animals, including malformations of the skull, eye, jaw, skeleton and gut (gastrointestinal tract). The severity and likelihood of developing these effects increased with higher doses of the drug. Additionally, in animal studies, there was reduced survival of the fetus and newborns.

Because of these studies, sexually active women and men, where the risk of pregnancy is of concern, are strongly encouraged to use effective birth control (two reliable forms, such a hormonal pill and a barrier method, like a condom) while they are taking interferon-alfa and ribavirin and for six months after stopping the drugs.

If a woman becomes pregnant or a partner of someone taking interferon-alfa and ribavirin becomes pregnant while taking the combination or within six months of stopping the drugs, they should call (800) 727-7064 to report the pregnancy.

Summary

A vaccine and treatments for hepatitis C are desperately needed. An effective public health campaign needs to be implemented to alert the public about the dangers of hepatitis, especially hepatitis C. Since the route of transmission for HAV, HBV and HCV is similar to that of HIV, many people are co-infected with these viruses. It is important for people to find out whether they are co-infected so that an appropriate treatment strategy can be put together. People co-infected with HIV and HBV are encouraged to talk to their doctors about the various treatments for HBV and HIV. Some therapies are active against both viruses. Combination therapy will likely result in better activity against hepatitis B and hepatitis C. However, some therapies may be broken down in the liver and may cause liver enzymes to increase, potentially aggravating the hepatitis. On the other hand, for someone who is HIV infected but not infected with HAV or HBV, vaccination should be considered.

Animal studies with ribavirin showed that the drug causes teratogenic effects resulting in malformations of the skull, eye, jaw, skeleton

and gastrointestinal tract. The severity and likelihood of developing these effects increased with higher doses of ribavirin. Additionally there was reduced survival of the fetus and newborns.

Women should use effective contraception (two reliable forms) when they are on interferon-alfa and ribavirin and for a further six months after the drugs are stopped. Additionally, men and their female partners should use effective contraception (two reliable forms) when they are on this combination therapy and for a further six months after therapy is stopped.

If a woman becomes pregnant or a partner of someone taking interferon-alfa and ribavirin becomes pregnant while taking the combination or within six months of stopping the drugs, they should call (800) 727-7064.

Supplemental: Hep A Prevention

Results from a new study suggest that almost all people with HIV who are given the hepatitis A vaccine (VAQTA) achieve responses that are believed to be protective against hepatitis A virus. Everybody with CD4+ cell counts above 300 showed antibody titer levels that should be protective against hepatitis A compared to 88% of people with CD4+ cell counts below 300. This study suggests that hepatitis A vaccines can be safely administered to people with HIV.

Supplemental: Hep B Treatment

A study in France followed 19 people co-infected with HBV and HIV who started 3TC (150mg twice a day, total 300mg) as part of their anti-HIV regimen. Volunteers also used another NARTI, and most also took a protease inhibitor or a NNRTI. About a third had failed interferon-alfa for treating their HBV infection. All the participants were men with a mean CD4+ cell count around 200 and HIV levels of 50,000 copies HIV RNA. Almost all had good anti-HIV and anti-HBV responses with 14 people having HBV levels below the limits of detection with currently available HBV tests. However, four developed 3TC-resistant HBV even with the higher dose. People who developed 3TC-resistant HBV generally had lower CD4+ cell counts (about 30) and have been on anti-HIV therapies longer. Interestingly, HBV levels were not predictive of HBV resistance to 3TC. There were

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Hepatitis



cases of increases in HBV levels when 3TC was stopped in people whose HBV was still sensitive to the drug. People co-infected with HIV and HBV may want to consider continuing on 3TC even if their HIV is resistant to the drug, as it may still be active against HBV.

Supplemental: Hep C Treatment

One small study also showed that hepatitis C levels temporarily increased significantly after starting highly active antiretroviral therapies (HAART). However, HCV levels returned to pre-HAART levels after 17–32 weeks while continuing on HAART. The researchers speculated that HAART results in a better immune response, destroying more HCV infected liver cells, which could result in the release of HCV particles. Many researchers are now measuring HCV levels before starting HAART and closely monitoring that level thereafter. There have been a few reports of reactivation of hepatitis C (e.g. symptoms of HCV disease) after starting potent anti-HIV therapy.

One study suggests that people co-infected with HIV and HCV who start on a protease inhibitor-containing regimen may be at greater risk of developing cirrhosis. This study also found that people generally had higher HCV levels after starting a protease inhibitor and these levels remained elevated throughout the duration of therapy. There was no apparent correlation between pre-therapy HCV levels and the impact of protease inhibitor therapy on liver disease. This means that people with low HCV levels prior to starting anti-HIV therapy were just as likely to develop active symptoms of liver disease as people with high pre-therapy HCV levels. Thus, people with low pre-therapy levels could not be assured that they could safely use protease inhibitor therapy. However, another study contradicts these findings. This second study found that although protease inhibitors appeared to increase HCV levels and liver enzymes, this was transient and lasted only a few weeks. In longer-term follow-up (over 2 years), people were able to use the protease inhibitors safely with no effect on HCV levels or liver enzymes. A third study suggests that people taking the protease inhibitor ritonavir (Norvir) are far more likely to have elevated liver enzymes than those on other protease inhibitors, though it's unclear if these elevations result in poorer outcomes of either HIV or HCV disease.

A treatment study found that people co-infected with HCV and HIV responded equally well to interferon-alfa, a treatment for hepatitis C, compared to HCV-positive individuals who are not HIV-positive. This is contrary to the experience of people co-infected with HIV and HBV who usually don't respond well to interferon treatment. Volunteers received three weekly injections of interferon-alfa (3 million units) for three months. Those who responded to therapy continued for another nine months. This study found that both HIV-positive and HIV-negative individuals had similar decreases in HCV RNA levels and normalization in liver enzyme tests, with about 25% of both

groups having a sustained response past one year of therapy. However, people who were co-infected and had HCV levels over 10,000,000 copies or a CD4+ cells below 500 were less likely to have a response. It should be noted, however, that treatment with interferon-alfa alone is no longer considered state of the art treatment for hepatitis C.

Supplemental Information: New Drugs in Development

PEG-Intron was compared to standard interferon-alfa in 1,219 people with HCV and abnormal liver enzymes (an indicator of liver injury). This study did not involve people co-infected with HIV and HCV. People took the drug for 48 weeks followed by a 24-week follow-up period with no therapy. They either used 0.5mcg/kg, 1mcg/kg or 1.5mcg/kg of peg-interferon or three million international units of interferon-alfa. Both formulas require injections under the skin.

Almost 70% of the participants had genotype 1 HCV (the most difficult type to treat), and about 75% had HCV levels of over 2 million copies. Results were as follows:

People taking the 1.0 and 1.5mcg/kg doses of peg-interferon experienced slightly more side effects than those on the other two doses. The most common side effects included headaches, fatigue, flu-like symptoms, depression, and decreases in white blood cell counts, platelets (cells needed for blood-clotting) and neutrophils (a type of white blood cell that helps control bacterial and other infections).

Results After 48 and 72 Weeks

Treatment	% <100 HCV RNA @ 48 weeks	% <100 HCV RNA @ 72 weeks
0.5mcg/kg peg	33	18
1.0mcg/kg peg	41	25
1.5mcg/kg peg	49	23
3MIU interferon-alfa	24	12

Although its success rate is superior to the current interferon-alfa, PEG-Intron is still not overly impressive. It's likely peg-interferon will have to be combined with ribavirin or other anti-HCV therapies in development. Ongoing studies now use peg-interferon with ribavirin to determine whether this will be more effective than peg-interferon alone.

Supplemental Information: Peg-Intron Approved for Hep C

The Food and Drug Administration (FDA) recently approved peg-interferon-alfa (Peg-Intron) for treating hepatitis C virus (HCV). This new formulation is bound to a chemical called polyethylene glycol,



Hepatitis

which makes the drug stay in the blood stream for longer periods than standard interferon-alfa.

The FDA approved using peg-interferon alone and not in combination with ribavirin (Rebetol). One large study showed that the new formulation was about twice as effective in controlling HCV replication compared to the standard formulation (24% vs. 12% of the participants had HCV RNA levels below 100 copies after 72 weeks). However, more people taking peg-interferon developed mild bone marrow suppression.

The results of using peg-interferon alone are comparable to those seen with standard HCV therapy, which is a combination of standard interferon-alfa and ribavirin (bundled as Rebetron). However, more recent results suggest that combining peg-interferon with ribavirin will be more effective. Through injection under the skin, peg-interferon-alfa is dosed only once a week while standard interferon-alfa is dosed three times a week.

Schering-Plough, the developers of Peg-Intron, recently *unbundled* ribavirin from regular interferon, something the activist community has demanded for the past two years. So it is now possible for people to buy ribavirin separately and use it together with other interferon-alfa products or anti-HCV therapies. The cost of peg-interferon will be about twice that of standard interferon (\$1,200 vs. \$600 per month).

Other PI Publications

Opportunistic Infections Chart
Coping with Nausea

Drug Interactions
Drug Side Effects

This list is updated as new information develops, but it does not include all the materials available. Please call the Project Inform Hotline, or check out the website below for even more information.



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New Peg-interferon Results

Encouraging results were recently presented of the pegylated interferon products used in the treatment of hepatitis C (HCV). Pegylated interferon is a form of interferon to which polyethylene glycol (PEG) has been added. Adding PEG stabilizes interferon in the body and helps sustain a more even and long lasting level of the drug. The studies show that this new formulation, when used in combination with ribavirin (Rebetol) is more effective in treating HCV than the standard regimen of regular interferon-alfa combined with ribavirin (Rebetron).

One study showed that about 35% of people who did not benefit from standard Rebetron as first line therapy achieved a virologic response (a reduction in HCV RNA levels) with the combination of peg-interferon alfa-2b (peg-Intron, developed by Schering Plough) and ribavirin after 24 weeks of therapy. Although the preliminary results are encouraging, the usefulness of this combination as second line therapy will not be known until the study is completed.

Another study showed that 61% of the participants, who had not previously received anti-HCV therapy, had a sustained virologic response after 72 weeks of the peg Intron/ribavirin study. More specifically, 48% of people with genotype 1 (the most difficult type of HCV to treat) and 88% of people with genotypes 2 or 3 had a sustained response. The dose of peg-Intron used was 1.5mcg/kg once a week in combination with at least 10.6 mg/kg of ribavirin daily. This represents a very significant improvement in therapy for almost all HCV-infected people.

Peg-Intron is approved by the FDA (Food and Drug Administration) to treat HCV when used alone, but not in combination with ribavirin. It is only modestly effective when used alone. However, the result from the second study supports the use of the combination, for which it is likely to be approved soon.

Results from a study of a different pegylated interferon (Pegasys, developed by Hoffman-La Roche) are also encouraging. This study included 1,121 people who had not previously taken anti-HCV therapies and received the standard interferon/ribavirin combination (Rebetron), Pegasys alone or Pegasys in combination with ribavirin. The dose of Pegasys in this study was 180mcg once a week and the dose of ribavirin was 1,000-1,200mg daily. At the end of the 72-week study the percentage of people with HCV levels below 50 copies/mL were:

	Pegasys alone	Rebetron	Pegasys + ribavirin
Overall Response	30%	45%	56%
Response for genotype 1	21%	37%	46%
Response for genotype 2 or 3	45%	61%	76%

Further analysis of this study found that people who did not have a response by week 12 were highly unlikely to achieve undetectable HCV levels by the end of the study. Additionally, people who were over 80% adherent to their medications were significantly more likely to achieve undetectable HCV levels at study end. Side effects overall were similar between the three groups, although there appeared to be less severe flu-like symptoms and depression among people receiving Pegasys and ribavirin than those on Rebetron.