

Hepatitis C



Hepatitis C

Liver problems are common in people with HIV. Technically, any significant irritation or inflammation of the liver is called *hepatitis*, but the term is most commonly used to refer to several viral infections of the liver. The majority of liver disease in people with HIV is caused by viruses, especially hepatitis B virus (HBV) and hepatitis C virus (HCV). Studies have shown that almost a quarter of people with HIV are co-infected with HBV. Other causes of liver disease include cytomegalovirus (CMV), Epstein-Barr virus (EBV), mycobacterium avium complex (MAC), histoplasmosis, toxoplasmosis and alcoholism. 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. It has many functions including:

- Eliminating toxins from the body,
- Making cholesterol, blood clotting factors that help wounds heal and heparin (an anti-clotting factor),
- Secreting bile (a digestive juice which helps in the food digestion process),
- Converting sugars into stored energy and in between meals converts the stored energy back into blood sugars to meet the body's energy needs,
- Storing the body's iron reserves, vitamins A, B12, D, E and K and other minerals, and
- It is one of the main sources of body heat.

Hepatitis C can cause a permanent scarring of the liver, called *cirrhosis*. (This leads to the liver shrinking in size and impaired liver function. It can also cause liver failure and liver cancer.

This publication will only focus on hepatitis C. For more information on other forms of hepatitis, call Project Inform's Hotline and ask for the publication, *Hepatitis*. The symptoms of the hepatitis caused by viruses are quite similar and include elevated blood levels of liver enzymes.

HIV/HCV Co-infection

Since HIV and hepatitis C virus (HCV) share many of the same routes of transmission, as many as 40% of people who are HIV-positive may also be co-infected with HCV. Upwards of 70% of people living with HCV develop associated symptoms of liver disease. This rate may be higher in people co-infected with HIV and HCV. Recent studies suggest that HCV levels are higher and the course of HCV-related liver disease, such as HCV-related cirrhosis, is accelerated among people who are co-infected with HIV and HCV. One study showed that people who are co-infected with HIV and HCV are significantly more likely to die from sudden liver failure.

It was commonly believed that HCV does not accelerate the progression of HIV infection although there are now emerging data suggesting that this may not be the case.

Several groups have now shown that co-infected individuals have an accelerated course of HIV disease progression. Some researchers believe that co-infected people have an increased risk of trans-

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mitting the HCV because their HCV levels are generally higher than those only living with HCV.

The use of anti-HIV therapies has no activity against HCV and as a result controlling HIV replication does not result in lowered HCV levels. Furthermore, some people taking a protease inhibitor-based regimen experience a temporary increase in liver enzymes and HCV viral load. The increase in liver enzymes is thought to be related to an enhanced immune response against HCV, causing inflammation in the liver. Others contend it may be the result of protease inhibitor-related liver toxicity enhanced because of underlying HCV infection. Results from a French study suggest that people receiving protease inhibitors had a delay in progression of HCV-related scarring of the liver (*fibrosis*) and cirrhosis.

Prevention

There is no vaccine against HCV. 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).

Transmission

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. There is also a risk of transmission due to body piercing, tattooing and acupuncture. Other activities that are associated with a lower risk of transmission include: salon manicures, breast feeding, sharing a toothbrush and sharing a straw to snort cocaine.

Studies have shown that HCV is much more easily transmitted than HIV via contaminated blood whereas HIV is more easily transmitted by sexual and mother-to-child transmission routes.

Pregnant women who are also HIV-positive are more likely to transmit HCV to their newborns than women who are only HCV-positive. Furthermore, co-infected women are also more likely to transmit HIV to their newborns. 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. Similar to HIV, some studies have shown that women with high HCV levels are more likely to transmit HCV to their infants than women with low HCV levels. Some data suggest that an elective cesarean section before the rupture of membranes may decrease the risk of mother-to-child HCV transmission.

Symptoms

Only about 25% of people infected with HCV develop immediate symptoms after becoming infected with the virus. These can begin suddenly or gradually within 2-8 weeks after infection and are usually flu-like symptoms such as fever, fatigue, muscle and joint pain. Some people also experience nausea and vomiting. Most people have no signs of yellowing of the skin or the whites of the eyes, a condition called *jaundice* that is associated with other kinds of hepatitis infections.

Because the symptoms of initial HCV infection are non-existent or milder than those of hepatitis A and hepatitis B, 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.

In about 15% of people, the immune system is able to tackle and eliminate HCV infection. HCV develops into an established *chronic* infection in up to 85% of HCV infected people. 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, which is often untreatable.

Symptoms of chronic hepatitis C are usually very subtle and intermittent even though there may be may be slow progressive damage to the liver. Some people develop joint pain, fatigue, nausea and loss of appetite but for many others, they experience no symptoms until they develop very serious end-stage liver disease or liver failure.

Symptoms of severe liver damage include: fatigue, muscle weakness, nausea, weight loss, dark urine, fluid retention and loss of appetite. Furthermore, the liver and/or spleen may be enlarged and a person may experience yellowing of the skin and eyes (*jaundice*), muscle wasting, swelling of the ankles and an accumulation of fluid in the stomach area, called *ascites*.

Diagnosis

Diagnosis of HCV is done by a blood test called an ELISA (*enzyme-linked immunosorbent assay*), similar to the test used to determine HIV infection. As with HIV, antibodies to HCV may not appear for three to six months after initial infection. Recent advances have led to the development of more sophisticated and sensitive technologies to monitor hepatitis levels in blood. These

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are the same technologies currently used to measure HIV levels (viral load). These tests are more sensitive than the ELISA tests and can be used to test for HCV infection prior to the appearance of antibodies against HCV or for co-infected individuals who may not produce enough antibodies to be detected by ELISA due to immune suppression.

In most people with HCV, 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*). The Food and Drug Administration (FDA) has not approved these tests for monitoring changes in HCV levels during treatment but are approved for the diagnosis of HCV.

Considerations for Therapy

Current guidelines recommend that people with HCV with increased liver enzyme levels (ALTs or alanine aminotransferases), a liver biopsy showing some degree of liver scarring (*fibrosis*) or at least a moderate to severe degree of inflammation and death of areas of liver tissue (*necrosis*) consider starting anti-HCV therapy. People with persistent increases in liver enzymes but no other changes based on a liver biopsy, or people with permanent scarring of the liver (*cirrhosis*), are encouraged to discuss the risks and benefits of starting anti-HCV therapy with their doctor. Currently, there is little or no information about how HCV levels relate to illness, and therefore, treatment decisions should not be made based on HCV levels alone.

People with permanent scarring of the liver (*cirrhosis*) are encouraged to consider therapy if they have no signs of fluid retention in their stomach area (*ascites*) or persistent yellowing of their skin and whites of their eyes (*jaundice*).

Most researchers now believe that it's beneficial for people with co-infection to be on anti-HCV therapy for at least a year if not longer to increase the likelihood of achieving long-term benefits.

The guidelines 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 to six months. Studies have shown that the likelihood of achieving long-term response is very low. Some researchers argue, however, that there are potential benefits of continuing treatment even in the presence of detectable HCV levels because treatment can decrease liver scarring (*fibrosis*), increase the immune systems ability to combat HCV and decrease the incidence of liver cancer. Additionally, although still detectable, there may be a lowering of HCV levels that may allow a person to better tolerate anti-HIV therapies.

There is no consensus on how to best treat co-infected people. Most researchers believe it's wise for co-infected people 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. However, other researchers argue that the recent changes in the guidelines on when to start treatment of HIV-positive people means that it may be more appropriate to treat the HCV first. They also point out that by treating HCV first and lowering HCV levels, people will more likely tolerate anti-HIV drugs and as a result experience a good anti-HIV response. In general, at least a one to two month gap is encouraged between starting therapy for HIV and HCV.

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

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. One study showed that co-infected people with HCV genotype 1 had a more rapid progression to AIDS and death than co-infected people with other HCV genotypes.

Treatment for HCV

HCV, like HIV, is a very difficult virus to treat because it can quickly mutate and escape immune response and become resistant to therapies. The only approved treatments for hepatitis C are listed in the chart below:

Drug	Standard Dose
interferon alfa-2a (Roferon)	Three million units 3 times a week
interferon alfa-2b (Intron)	Three million units 3 times a week
consensus interferon (Infergen)	9mcg 3 times a week
peg-interferon alfa-2b (Peg-Intron)	1.5mcg/kg once a week
Interferon alfa-2b is also approved in combination with ribavirin and (sold as a bundled product under the name Rebetron).	
Additionally ribavirin (Rebetol) is approved (not part of a bundled product,) for use in combination with interferon alfa-2b and peg-interferon alfa-2b.	1,000 to 1,200mg per day based on body weight



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Ribavirin on its own is not effective in treating HCV and should not be used alone. Although ribavirin is only approved for use in combination with interferon alfa-2b and peg-interferon alfa-2b, there has been a lot of experience of using the drug in combination with the other interferon alfa drugs with good success. Peg-interferon alfa-2a (Pegasys) is expected to be approved soon.

Peg-interferon is a new version of interferon alfa that is bound to a chemical called *polyethylene glycol*. This helps the interferon to remain stable and active in the blood for longer periods than standard interferon, allowing for less frequent dosing and consequently less frequent side effects.

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. A combination of interferon alfa three times a week and ribavirin daily for at least a year is currently recommended for treating HCV. Most researchers believe that there is little difference in effectiveness between the three different versions of interferon alfa, although 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 an established HCV infection.

There is likely to be a change in the standard of care for treating HCV. It is likely that peg-interferon in combination with ribavirin will become the treatment of choice for treating hepatitis C in the near future. Studies are suggesting that this combination may be superior to other HCV regimens.

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

Dosing Considerations

All of the interferon alfa drugs, regardless of formulation, is given via an injection under the skin (subcutaneous). 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. Some researchers believe that it may be possible to use a lower dose of ribavirin, which will result in the drug being better tolerated, but studies have not been conducted to determine if this strategy is safe and effective.

Treatment for HIV

Confusion remains regarding the use of protease inhibitors in people co-infected with HIV 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. One study showed that people taking ritonavir (Norvir) were 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. 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 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).

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, nausea, vomiting, weight loss, hair loss, bone marrow suppression and headaches. Some people have noted that side effects are less troubling if interferon alfa is taken at night.

The most common side effects of ribavirin include: anemia (decrease in red blood cells), coughing, difficulty in breathing, rash, fatigue, itching, insomnia and anorexia (loss of appetite).

Studies with ribavirin show that the drug causes birth defects in the offspring of laboratory animals. 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 their doctor immediately and seek guidance and call (800) 727-7064 to report the pregnancy.

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What Does the Research Show?

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 (zidovudine, Retrovir), which results in decreased anti-HIV activity of AZT. There may also be a similar interaction with d4T (stavudine, Zerit). This laboratory observation has not been confirmed in human studies. Additionally, a few studies have shown that some people experience a dramatic decrease in CD4+ cell counts after starting interferon alfa therapy. In some, but not all, people there is a rebound in CD4+ counts while continuing on interferon alfa therapy or after discontinuing the drug.

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 permanent liver scarring (cirrhosis).

Results from a small study of peg-interferon alfa-2a (Pegasys) suggest that it's far more effective in treating HCV than standard interferon alfa. The new formulation was compared to standard interferon alfa in 271 people with permanent liver scarring (cirrhosis) due to HCV. This study did not involve people co-infected with HIV and HCV.

In the study, people took 48 weeks of anti-HCV therapy with a follow-up period of 24 weeks when they received no therapy. They took either 90 micrograms (mcg) or 180mcg of peg-interferon alfa-2a once a week or three million international units of interferon alfa three times a week. Both formulas required injections under the skin.

Results showed that at 72 weeks, 29% of the people receiving peg-interferon alfa-2a had undetectable blood levels of HCV compared to only 6% using standard interferon alfa. Side effects were similar between the two formulas and included headaches, fatigue, flu-like symptoms, nausea, vomiting, depression, fever and chills.

A different study compared peg-interferon alfa-2b (PEG-intron) to standard interferon alfa in 1,219 people with HCV and abnormal liver enzymes. 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 alfa-2b or three million international units of interferon alfa. Both formulas required 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:

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

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).

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

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Another study showed that 61% of the participants, who had not taken anti-HCV therapy before, had a sustained virologic response after 72 weeks of the peginterferon alfa-2b/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 peginterferon alfa-2b 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.

Results from a study of a different peginterferon alfa-2a (Pegasys) 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), peginterferon alfa-2a alone or peginterferon alfa-2a in combination with ribavirin. The dose of peginterferon alfa-2a in this study was 180mcg once a week and the dose of ribavirin was 1000-1200mg daily. At the end of the 72 week study the percentage of people with HCV levels below 50 copies/mL were:

	peg-interferon alone	Rebetron	peg-interferon + ribavirin
Overall Response	30%	45%	56%
Response for people with genotype 1	21%	37%	46%
Response for people with 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 by the end of the study. Side effects overall were similar between the three groups, although there appeared to be less severe flu-like symptoms and depression among people receiving the combination of peginterferon alfa-2a and ribavirin than those on Rebetron.

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 alfa 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 all African Americans. Conversely, women (including African American 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 where therapy response varies by race. For instance, many studies have shown that African 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.

Another disturbing observation reported in several co-infection studies is that co-infected individuals appear to have a blunted increase in CD4+ cells after starting potent anti-HIV therapy compared to people who are not HCV-infected. It is unclear whether this will result in a higher risk for HIV disease progression.

New Drugs in Development

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

The Bottom Line

HIV appears to accelerate the course of HCV-related liver disease and genotype 1 of HCV may accelerate the course of HIV progression.

Combination therapy has been shown to be more effective in treating HCV. However, some commonly used anti-HIV therapies are broken down in the liver and may cause liver enzymes to increase, potentially aggravating the hepatitis. Women should use effective contraception (two reliable forms) if they are taking 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.

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