

HCV / HIV COINFECTION

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SECTION

2

WESTERN (ALLOPATHIC) TREATMENT OPTIONS

Introduction

The management and treatment of coinfection with the *human immunodeficiency virus (HIV)* and the hepatitis C virus (HCV) are complex and challenging. Much progress has been made in recent years, but many unknowns remain. Some of the many questions about HCV/HIV coinfection include:

- Should the infections be treated simultaneously or individually? If the infections are treated individually, which virus should be treated first? If treated simultaneously, what are the best approaches?
- Should all coinfecting people be treated for HCV? If not, what subgroup of people should be treated?
- Do the choice of medicines used and their dosages need to be adjusted if both infections are treated simultaneously?
- How can the complications of coinfection be minimized?
- How should liver transplant be managed in the setting of coinfection?

Concerns about treating both HIV and HCV at the same time center on the risk of liver *toxicity (hepatotoxicity)* and interactions between *antiviral* drugs. The effects of each virus on the natural disease progression of the other infection are also important issues in treatment decisions.

This section discusses western medicine's current knowledge and approach to HCV/HIV coinfection. Keep in mind, this is a rapidly changing field of study, and all treatment decisions must take into account your unique circumstances and disease status.

Identification of Coinfection

The first issue of coinfection management is accurate diagnosis. Because of the high incidence of HCV/HIV coinfection,¹⁻⁸ experts agree that all people with HIV should be screened for coinfection with HCV. HCV screening is accomplished by testing the blood for *anti-HCV antibodies*. While the presence of HCV without detectable anti-HCV antibodies is quite rare in people with normal *immune systems*, it appears to occur in 5% to 19% of people coinfecting with HIV.^{9,10} Scientists believe this is probably due to the immunosuppressive effects of HIV and the loss of *CD4 cells*, the immune cells infected by HIV that are also necessary for *antibody* production. Thus, in HIV-infected persons with persistently elevated *liver enzymes (ALT and AST)* but a negative HCV screening test, most experts recommend testing for the hepatitis C virus (*HCV RNA*).¹¹

The Decision to Treat HIV, HCV, or Both

As discussed in *Chapter 20 Section 1, Overview of HCV/HIV Coinfection*, it is clear that HIV infection accelerates HCV disease progression.¹²⁻¹⁸ Decompensated cirrhosis is one of the leading causes of death in the coinfecting population.¹⁹⁻²¹ Further, coinfection appears to increase the risk of liver cancer (*hepatocellular carcinoma*).^{16, 22} Thus, the health risks of untreated HCV infection are higher among coinfecting persons than in those with HCV alone.

The effects of HCV on HIV disease progression are unclear. Most clinical studies evaluating this topic have failed to show a significant effect of HCV on the progression of HIV disease. However, this was not true in every study.^{2, 6, 8, 23-27} While the possibility still exists that HCV may negatively affect the natural history of HIV, it current appears that this is unlikely.

Both HIV and HCV are potentially life-threatening infections. The stakes involved in treatment decisions are very high and the issues are complex. Therefore, we urge all coinfecting persons to consult with healthcare providers who have experience managing coinfection.

The decision to treat HIV, HCV, or both infections simultaneous depends on many factors, including:

- **the timing of diagnosis**
Were the infections diagnosed at the same time or was one of the infections acquired after the other?
- **immune status**
What is the CD4 count? What is the HIV *viral load*? Is the client HIV-positive only or has there been disease progression to AIDS? Is the client already on anti-HIV medications? What medications have been prescribed?
- **HCV-related factors**
Is there evidence of *fibrosis* and/or *cirrhosis*? Is there evidence of liver failure (*decompensation*)? What are the liver enzyme levels? What is the HCV viral load? What is the *genotype*? Has the client received previous treatment for HCV?
- **mental health issues**
Does the client currently have or have a history of depression or other major mental illness? Is there active substance abuse (drugs or *alcohol*)?
- **overall health status**
Are there other active illnesses? Are they well controlled?

Depending on the specific circumstances, one of the following choices may be made:

- **Treat the HIV infection first until it can be controlled, then consider treatment for HCV.**
Low CD4 count has been identified as a factor that may decrease the probability of response to interferon-based therapy for HCV.²⁸ For this reason, and to prevent the progression of HIV disease to AIDS, many doctors believe treating HIV and gaining control of that infection is the first priority in patients who are coinfecting at diagnosis. The partial restoration of immune function that often occurs after beginning highly active antiretroviral therapy (HAART)²⁹ for HIV may increase the likelihood of response to *interferon-based therapy* for HCV. Further, one preliminary study suggests HAART may actually slow the accelerated HCV disease progression usually observed with coinfection.³⁰ However, as discussed in *Section 1* of this chapter, liver enzyme levels and HCV viral loads often increase when HAART is initiated.³¹⁻⁴³ The long-term effects of these spikes in liver enzymes and HCV viral loads are unclear.
- **Treat HCV first, and then begin HIV treatment.**
In theory, this approach has two potential advantages. It may eliminate the immediate threat of HCV-related liver disease by halting disease progression and allowing for at least partial restoration of liver health. A liver that has been partially or completely restored to normal function is better able to process antiviral drugs when

HIV treatment is initiated. This approach is usually reserved for people who have not received previous therapy for either infection and whose CD4 counts are greater than 350 cells/mm³.¹¹

- **Treat both infections simultaneously.**

This approach addresses both infections at the same time. Caution is required due to potential interactions between anti-HCV and anti-HIV medications.

The decision about which option is most appropriate for your specific circumstances is one that can be made only after a thorough medical evaluation by a healthcare provider experienced in the treatment of coinfection.

Interferon-Based Therapy for HCV in People with HCV/HIV Coinfection

Combination therapy with pegylated interferon plus ribavirin is the treatment of choice for chronic hepatitis C (See *Chapter 8, Sections 1 and 2* for additional information about pegylated interferon plus ribavirin therapy). Pegylated interferon alfa-2a (Pegasys®) in combination with ribavirin was approved by the Food and Drug Administration (FDA) in 2005 for the treatment of chronic hepatitis C in patients with HCV/HIV coinfection. While the manufacturer of pegylated interferon alfa-2b has not sought FDA approval of its drug for this indication (as of this writing), it is also used to treat hepatitis C in coinfecting patients.

While overall *sustained response* rates with peginterferon plus ribavirin therapy have been reported to be approximately 50% to 60% in people with HCV only, response rates are lower in coinfecting persons. Overall sustained response rates in coinfecting persons have been reported to be anywhere from 20% to 44%.⁴⁴⁻⁵³ Recent data indicate that optimal exposure to ribavirin is particularly important for coinfecting patients.⁵⁴⁻⁶³ Therefore, the HCV-HIV International Panel issued the following recommendation in 2007:

The current treatment of chronic HCV infection in HIV-positive persons should be pegylated interferon at standard doses plus weight-based ribavirin (1,000mg/day if <75 kg and 1,200 mg/day if > 75 kg).⁶⁴

Although research is accumulating that suggests duration of therapy may be safely reduced for rapid viral responders (by week 4 of treatment) among mono-infected patients, reduced duration of therapy remains largely unproven for those with HCV-HIV coinfection. There are some data that support the notion that the duration of therapy can be reduced to 24 weeks without significant risk of relapse if the following conditions are met.^{65, 66}

- low pretreatment viral load
- HCV genotype 2 or 3
- undetectable HCV viral load by week 4 of treatment
- fibrosis is not advanced
- patient adherence to therapy is good
- weight-based ribavirin dosing is used

Relapses are more frequently observed in the HCV/HIV coinfecting population than in those with HCV alone.^{45, 50}

Researchers speculate the increased relapse rate may be due to the reduced immune function of HIV-infected persons and/or the higher HCV viral loads commonly seen in coinfection. In addition, research suggests that the clearance of HCV after beginning pegylated interferon plus ribavirin therapy is slower in coinfecting patients than in those with HCV alone.⁶⁷ Recent studies have shown that extending treatment duration (60 to 72 weeks) may be of benefit to coinfecting patients with HCV genotype 1 or 4 who have also shown a slow response to treatment (early viral response but not rapid viral response).^{68, 69} It is important to note that despite the somewhat slower response seen in HCV/HIV coinfection, early viral response (at least a 100-fold drop in HCV viral load by week 12 of treatment) is predictive of sustained viral response just as it is in patients with HCV alone.^{70, 71}

Candidates for Interferon-Based Therapy

All people living with HCV/HIV coinfection should be evaluated for anti-HCV treatment. As noted in *Section 1* of this chapter, response to therapy is partially dependent on the CD4 cell count.^{72,73} Therefore, some doctors prefer treating only patients with CD4 cell counts greater than 350 cells/mm³.¹¹ The decision to treat people who have CD4 cell counts between 200 and 350 cells/mm³ is made on a case-by-case basis. Anti-HCV therapy is uncommon among people with CD4 counts less than 200 cell/mm³ because of the low response rate.^{72,73}

All factors that may affect response to therapy should be considered before making the decision to begin anti-HCV treatment such as:

- the HCV genotype
- the presence of fibrosis and/or cirrhosis
- current alcohol consumption or drug use
- mental health status

As with people with HCV only, coinfecting persons with liver failure are not candidates for interferon-based therapy. Anyone with liver failure should be referred for a liver transplant evaluation. Other relative contraindications to interferon-based therapy are the same in the coinfecting population as they are in those with HCV only. They include:

- active substance abuse (alcohol or illicit drugs)
- active mental illness or a history of serious mental illness
- uncontrolled heart disease
- uncontrolled diabetes
- uncontrolled *anemia*

The use of liver biopsy in making treatment decisions in the HCV/HIV coinfecting population has become less common in recent years. Many experts share the same opinion expressed in the 2007 updated recommendations of the HCV-HIV International Panel, and that is:

The higher response to pegylated interferon plus ribavirin compared with that to standard interferon, the faster progression of HCV-related liver disease in the HIV setting, and the chance to assess the virological response at earlier timepoints to identify who will and who will not respond to therapy are all factors that allow the opportunity to prescribe HCV therapy to most patients while avoiding a liver biopsy.^{64,74}

Those experts who believe liver biopsy is unnecessary for most coinfecting patients will still generally recommend other noninvasive testing to try to determine the level of liver fibrosis. There are now several noninvasive tests for liver fibrosis available. In general, tests that assess the elasticity of the liver tend to be more accurate in the HCV/HIV coinfecting population than those that rely on serum markers.⁷⁵⁻⁷⁹ It is important to note that among patients with inconclusive or inconsistent results from noninvasive tests for fibrosis, liver biopsy may be necessary.⁶⁴

There are experts who believe anti-HCV therapy should only be initiated in coinfecting persons who have evidence of significant fibrosis on liver biopsy. Those who take this approach believe the risk of serious side effects associated with treatment in the coinfecting population justifies the requirement for liver biopsy.

Side Effects of HCV Therapy in Coinfected Persons

People with coinfection are subject to the same side effects from combined pegylated interferon plus ribavirin therapy as those with HCV alone (see *Chapter 8, Section 2* for additional information about the side effects of interferon and ribavirin). However, since coinfecting people may already have HIV-related symptoms or HAART-related side effects, additional side effects may prove more difficult to tolerate. The high rate of discontinuation of therapy 47-50 in coinfecting people may be related to this phenomenon.

White blood cell counts may drop as a side effect of pegylated interferon. In coinfecting persons with already reduced CD4 counts, further decreases can be particularly troublesome.^{72, 80, 81}

Depression is one of the most common side effects of interferon-based therapy. It is important to report any symptoms of depression to your healthcare provider to prevent this side effect from interfering with completion of therapy.

Common symptoms of depression include:

- sleep disturbances – either poor sleep or sleeping too much
- appetite disturbances – eating more or less than usual
- loss of interest in things that used to give you pleasure
- withdrawal from loved ones
- feelings of hopelessness or helplessness
- loss of interest in sex
- suicidal thoughts

Toxic Interactions Between Anti-HIV and Anti-HCV Therapies

Anemia

Anemia is a frequent side effect of ribavirin. Interferon adds to this problem by decreasing the production of both red and *white blood cells*. Overall, significant anemia occurs in approximately 7% to 9% of HCV-infected people treated with combination therapy.⁸² A recent study suggests this side effect of pegylated interferon plus ribavirin is more frequent in coinfecting persons than in those infected with HCV alone.⁸³ The anti-HIV drug zidovudine (AZT, ZDV, Retrovir[®]) is also known to cause anemia.⁸⁴ Therefore, most doctors discontinue zidovudine before prescribing ribavirin; it is usually replaced by another drug in the same class.

Mitochondrial Toxicity

As noted in *Section 1* of this chapter, HCV can damage the “powerhouses” of liver cells, the mitochondria.⁸⁵ A significant problem in the simultaneous treatment of coinfection is the fact that certain HIV medications may also damage the mitochondria. Anti-HIV drugs that have been implicated in possible mitochondrial damage include.⁸⁶⁻⁸⁹

- zidovudine (AZT, ZDV, Retrovir[®])
- lamivudine (3TC, Epivir[®] or combination drugs Combivir[®], Epizicom[®], and Trizivir[®])
- stavudine (D4T, Zerit[®])
- didanosine (ddI, Videx[®])
- nelfinavir (Viracept[®])
- nevirapine (Viramune[®])
- zalcitabine (ddC, HIVID[®])

Lactic acidosis is a potentially life-threatening condition that may develop with severe mitochondrial toxicity. Lactic acid is a normal byproduct of the energy production process that occurs inside the mitochondria. When the mitochondria are damaged, lactic acid can build up and upset the delicate chemical balances necessary for normal body functions.

Symptoms of lactic acidosis include:

- muscular weakness – most noticeable in the arms and legs; the weakness is often severe
- nausea and/or vomiting
- abdominal pain
- breathing difficulty or shortness of breath
- numbness or tingling in the extremities

A blood test is used to confirm the diagnosis of lactic acidosis. If you develop any of the symptoms above, see your doctor immediately. This rare but very serious complication has been specifically linked to didanosine (ddI, Videx®), but has also been linked less frequently with lamivudine (3TC, Epivir®), zidovudine (AZT, Retrovir®), stavudine (D4T, Zerit®), and abacavir (Ziagen®). There have been reports of fatal reactions when didanosine and ribavirin were taken together.^{90, 91} These two drugs should not be taken at the same time.

Liver Transplantation in HCV/HIV Coinfection

Chronic HCV infection can eventually lead to end-stage liver disease. In end-stage disease, the liver is no longer capable of performing its many vital body functions. Anti-HCV treatment is not useful in such circumstances because the liver has been so severely damaged, and there are potentially life-threatening complications associated with interferon-based therapy when liver failure is present.^{92, 93} The primary treatment for patients with HCV/HIV coinfection and liver failure is liver transplantation.⁹⁴⁻⁹⁷

Prior to the introduction of HAART, coinfecting persons were not eligible for liver transplantation because the likelihood of survival was extremely low.⁹⁸ The introduction of HAART, with its ability to suppress HIV replication and the related rebound in immune function, has improved HIV prognosis to the point that coinfection is no longer a contraindication to liver transplantation.

Candidates for liver transplantation typically meet the following criteria:

- no history of opportunistic infections
- CD4 count greater than 100 cells/mm³
- undetectable HIV-RNA
- no alcohol or illicit drug consumption for at least six months

Although coinfection is not a contraindication to liver transplantation, the potential for complications after transplant are significantly greater for those with both HCV and HIV than for those with HCV alone. A recent analysis of the United Network for Organ Sharing database dating back to 1997 (during the HAART era) found that those with HCV/HIV coinfection had a significantly worse prognosis after liver transplant than those with HCV alone.⁹⁹ An earlier, smaller study found that factors associated with poor survival were post-transplant intolerance to HAART, CD4 cell counts <200 cells/mm³, detectable plasma HIV RNA and HCV infection.⁹⁷

HCV recurrence in transplanted livers occurs in 100% of people with detectable HCV-RNA prior to transplant. Up to 20% of transplanted livers that become reinfected with HCV develop cirrhosis within 5 years. People with genotype 1 HCV appear to be at greater risk for rapid fibrosis progression in transplanted livers compared to other genotypes.¹⁰⁰ Among people with both HCV and HIV, this accelerated rate of liver disease progression is often more pronounced, and makes the long-term viability of the transplanted liver an issue of great concern. Most experts recommend anti-HCV therapy

within one to three months post-transplant. A small study of 32 patients found an 18% response rate to pegylated interferon plus ribavirin in liver transplant patients who had been previous non-responders to standard interferon plus ribavirin.¹⁰¹ Although the response rate is low, it offers some hope to liver transplant recipients. Other strategies to prevent reinfection of transplanted livers are being researched in clinical trials.

Coinfection Treatment Guidelines

The management of HCV/HIV coinfection is an area of active clinical research. Recent developments in the treatment of HCV and emerging research data makes defining ideal treatment much like chasing a moving target. Nonetheless, a group of nine international experts published a series of recommendations for the care of people with hepatitis C and HIV coinfection.¹¹ A synopsis of the panel's findings and recommendations are shown in Table 1.

Table 1. Issues and Consensus Findings/Recommendations from an International Panel on Care of Patients with Hepatitis C and HIV Coinfection^{7, 64}

Treatment Issue	Panel Findings/Recommendations
Influence of hepatitis C virus infection on HIV disease progression and response to antiretroviral therapy	HCV might act as a cofactor for HIV disease progression by several mechanisms.... However, a negative impact of HCV on HIV disease progression has not been recognized in some large clinical-epidemiological studies.
Candidates for anti-hepatitis C virus treatment	All HIV-infected individuals should be screened for HCV antibodies.... Treatment should be provided to patients with repeated elevated <i>alanine aminotransferase</i> [ALT] levels, CD4 cell counts greater than 350 cells/mm ³ , relatively low plasma HIV-RNA levels (i.e., less than 50,000 copies/mL), no active consumption of illegal drugs or high alcohol intake, and no previous severe neuropsychiatric conditions.... Treatment in patients with CD4 cell counts below 350 cells/mm ³ should be prescribed cautiously.
Patients with persistently normal aminotransferases (2007 update)	Given that the prevalence of and progression to advanced liver fibrosis in patients with normal ALT is higher in HIV-positive patients, these patients should be considered for anti-HCV therapy. Treatment should be recommended based on patient's motivation, disease duration, fibrosis stage and virological profile regardless of ALT levels.
Management of patients with multiple hepatitis viruses (2007 update)	Multiple viral hepatitis is not uncommon in HIV-positive individuals and worsens liver damage. Complex and dynamic viral interactions occur and making the management of these patients difficult. When possible, treatment of all replicating viruses should be pursued.
Liver fibrosis assessment: when and how? (2007 update)	Information on liver fibrosis staging is important for therapeutic decisions in coinfecting patients. However, a liver biopsy is not mandatory for considering the treatment of chronic HCV infection. A combination of non-invasive methods to assess liver fibrosis accurately predicts hepatic fibrosis in most cases.

Treatment Issue	Panel Findings/Recommendations
Treatment of acute hepatitis C (2007 update)	Acute HCV infection in HIV-positive persons should be treated for 24 weeks with a combination of pegIFN plus weight-based ribavirin. However, responses are lower than in HIV-uninfected persons.
Treatment of chronic hepatitis C in HIV-positive patients	<p>The overall response to anti-HCV therapy is lower in patients coinfecting with HIV... Both early virologic responses and relapses are less and more frequent, respectively, in coinfecting patients compared with HCV-monoinfected individuals. The benefit of extending therapy...</p> <p>... in early virological responders should be examined in clinical trials. Moreover, treatment adherence should be considered a critical factor for the attainment of response and must be encouraged actively over the whole treatment period.</p>
Optimal dosages of pegylated interferon and ribavirin (2007 update)	The current treatment of chronic HCV infection in HIV-positive persons should be pegylated interferon at standard doses plus weight-based ribavirin (1000 mg/day if <75 kg and 1200 mg/day if >5 kg).
Optimal duration of therapy (2007 update)	The current treatment of chronic HCV infection in HIV-positive persons should be pegylated interferon plus weight-based ribavirin for 48 weeks. Patients infected with HCV genotype 2–3 and RVR could benefit from shorter (24 weeks) courses of therapy. In contrast, carriers of HCV genotypes 1 and 4 with early virological response (week 12) but not RVR (week 4) might benefit from extended (60–72 weeks) courses of therapy.
Predictors of response to hepatitis C therapy (2007 update)	The achievement of SVR can be predicted on the basis of negative serum HCV RNA at week 4 of therapy. On the other hand, a reduction <2 log IU/ml in HCV RNA at week 12 and/or the presence of detectable viremia at week 24 both predict lack of SVR; accordingly these patients should be advised to stop prematurely anti-HCV therapy.
Monitoring the response to anti-hepatitis C virus therapy in HIV-positive patients	Early virologic response to anti-HCV therapy predicts the chance of sustained response in HIV coinfecting patients as it does in HCV-monoinfected individuals. Moreover, the use of an early time point for treatment decision-making seems to be equally appropriate in coinfecting patients. Only patients showing a decline in serum HCV-RNA levels greater than 2 logs at 12 weeks on therapy will have a chance of reaching a sustained response. Therefore, treatment might be discontinued in the rest....

Treatment Issue	Panel Findings/Recommendations
Management of adverse effects of anti-hepatitis C virus therapy in HIV-positive patients	Anti-HCV therapy causes fever, malaise, asthenia, depression, etc. in the majority of cases. Patients should be informed in advance about these side effects and how to prevent and manage them... The treatment of depression should be considered as soon as symptoms begin to develop....
Interactions between anti-HIV drugs and those for hepatitis C (2007 update)	While didanosine should never be used with ribavirin, zidovudine should also be avoided when possible.
Treatment of nonresponders and/or relapsers (2007 update)	Non-responders and relapsers to prior courses of HCV therapy are a heterogeneous population and therapeutic interventions in them should be individualized.
Management of end-stage liver disease (2007 update)	HIV infection should no longer be considered a contraindication to orthotopic liver transplantation. However, coinfecting patients present unique and highly complex problems post-transplantation, including rapidly progressive recurrent HCV infection and drug interactions (mainly between immunosuppressive agents and protease inhibitors). Accordingly, orthotopic liver transplantation in this population should be limited to transplant centers experienced in the management of such patients, where a multidisciplinary team including surgeons, hepatologists, pharmacologists and infectious diseases physicians can work in concert.
Liver transplantation in HIV coinfecting patients	All HIV-infected patients with end-stage liver disease as a result of HCV should be considered candidates for liver transplantation as long as they do not have advanced HIV disease.... HIV-positive candidates should have CD4 cell counts greater than 100 cells/mm ³ and plasma HIV-RNA levels below 200 copies/mL, or the chance of becoming undetectable using optional drugs for successful treatment after transplantation. Moreover, they should have abstained from the consumption of alcohol and illegal drugs for at least 6 months....
Hepatotoxicity of antiretroviral drugs (2007 update)	Patients with chronic HCV infection have an increased risk of liver enzyme elevations following exposure to most antiretroviral drugs. The management of hepatotoxicity should be based on the knowledge of the mechanisms involved for each drug. Treatment of HCV infection may reduce the chances for further development of liver toxicity in these patients.

Adapted from: Soriano V, Puoti M, Sulkowski M, et al. Care of patients with hepatitis C and HIV coinfection. *AIDS*. 2004;18:1-12.; Soriano V, Puoti M, Sulkowski M, et al. Care of patients with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. *AIDS*. 2007;21:1073-1089.

Summary

Due to common routes of transmission and shared exposures, many people are coinfecting with HIV and HCV. Coinfection with HIV is associated with accelerated HCV disease progression and increased risk for liver cancer. Since the introduction of HAART, significant numbers of coinfecting persons are experiencing the effects of HCV-related liver disease.

The increased risks associated with coinfection raise the stakes involved in treatment decisions. The management and effective treatment of HCV/HIV coinfection are complex and should be conducted by healthcare providers experienced in this subgroup of clients. All persons being treated for both HIV and HCV must be closely monitored for potentially serious complications.

Many aspects of coinfection are currently being investigated. As these studies are completed, we hope to use the information to develop safer, more effective therapies. The ultimate goal is to reduce the disease burdens currently borne by coinfecting persons.

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