

Clinician's Guide to

**HIV** &  
**hepatitis**



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As better treatments allow HIV<sup>1</sup>-infected patients to live longer and avoid HIV-related complications, chronic viral hepatitis has become an increasingly common cause of morbidity and mortality. This guide is intended to provide a basic overview on the management of hepatitis co-infection to clinicians who care for HIV-infected patients. It is not intended to be all-inclusive or take the place of established guidelines. Readers are encouraged to refer to guidelines and seek expert consultation as needed.

*<sup>1</sup>HIV is used throughout this document to refer to HIV-1, the most common strain for infection in the U.S.*

**Table 1. Hepatitis A, Hepatitis B, and Hepatitis C: Modes of Transmission and Symptoms of Acute and Chronic Infection in HIV**

<b>Viral Hepatitis Type</b>	<b>Mode of Transmission</b>	<b>Symptoms of Acute Infection</b>	<b>Symptoms of Chronic Infection</b>
<b>Hepatitis A (HAV) infection</b>	Fecal-oral route	Acute hepatitis with fever, jaundice, anorexia, nausea, vomiting, and malaise.	No chronic infection.
<b>Hepatitis B (HBV) infection</b>	Contact with infected blood or body fluids (e.g., sexual activity, IDU, or perinatal)	Range from asymptomatic to acute hepatitis with fever, jaundice, anorexia, nausea, vomiting, and malaise.	10% of HIV-infected persons will be co-infected chronically with HBV. Symptoms frequently unnoticed until onset of end-stage liver disease (ESLD): jaundice, hepatomegaly, splenomegaly, ascites, coagulopathy, caput medusa, palmar erythema, variceal bleeding, hepatic encephalopathy, or hepatocellular cancer (HCC). Extra hepatic manifestations: polyarteritis nodosa, other vasculitides, and glomerulonephritis.
<b>Hepatitis C (HCV) infection</b>	Large or repeated percutaneous exposure to infected blood, mother-to-infant (17% if HIV co-infected); sexual activity	The majority of patients will be asymptomatic. Rarely, acute hepatitis with fever, jaundice, anorexia, nausea, vomiting, and malaise. ALT elevation is universal.	In HIV-infected people with HCV, over 80% with acute infection will develop chronic HCV. Often asymptomatic with exception of fatigue. Symptoms frequently unnoticed until onset of ESLD: jaundice, hepatomegaly, splenomegaly, ascites, coagulopathy, caput medusa, palmar erythema, variceal bleeding, hepatic encephalopathy, or HCC. Extrahepatic manifestations: leukocytoclastic vasculitis, porphyria cutanea tarda, membranous nephritis, and mixed cryoglobulinemia.

# HIV and Hepatitis A

## TRANSMISSION

Hepatitis A virus (HAV) is transmitted through fecal-oral contact. People engaging in the following activities may be at higher risk for HAV: those who eat contaminated food, men who have sex with men, travelers, people in day care centers or institutions, military personnel, injection drug users (IDU), or rarely recipients of blood transfusions.

## DIAGNOSIS

Table 2. Tests for Diagnosis of Hepatitis A

<b>Anti-HAV IgM</b>	<b>Positive</b> in Acute Infection
<b>Anti-HAV IgG</b>	<b>Positive</b> in past infection or vaccination (conferred immunity)
<b>Total anti-HAV</b> (screening test that detects IgG and IgM antibodies)	<b>Negative</b> = no evidence of acute or prior infection <b>Positive</b> = draw IgM if symptomatic to distinguish acute from prior infection or vaccination

## TREATMENT

- HAV is usually self-limited, but supportive care is indicated.

## PATIENT TEACHING

- Review the importance of proper hand washing.
- Remind patient to avoid potentially contaminated foods, including shellfish.
- Discuss the risk of HAV infection with travel.
- Use protective barrier to avoid fecal-oral contact during sexual activity.

## PREVENTION

- HAV vaccination is recommended for all HIV-infected individuals.
- 2 doses of HAV vaccine should be administered (at 0 and 6-18 months).
- Administration of HAV vaccine when the CD4 + T cell count is  $> 200$  cells/mm<sup>3</sup> improves the likelihood of response.
- HAV immune serum globulin or Hepatitis A vaccine can be given immediately after known HAV exposure for post-exposure prophylaxis.
- In patients who have received HAV vaccine, hepatitis A antibody testing (total anti-HAV) should be drawn to document seroconversion.
- In patients who received HAV vaccine and remain seronegative the series should be repeated.

# HIV AND HEPATITIS B

## OVERVIEW

- World-wide, 10% of HIV-infected people are chronically infected with hepatitis B virus (HBV) (5-10% in the United States, 20-30% in Asia and sub-Saharan Africa).
- People with HIV infection are at an increased risk of developing chronic HBV if exposed and are more likely to reactivate HBV.
- Patients with both HIV and HBV infection are more likely to have higher HBV DNA levels, and detectable Hepatitis B antigen (HBeAg).
- Patients with HIV and HBV have an increased risk for liver-related morbidity and mortality. The Multicenter AIDS Cohort Study (MACS) found an eight-fold increased risk of liver-related mortality in patients with HIV and HBV co-infection compared to patients infected only with HIV.
- Higher HBV viral loads increase the risk of hepatocellular carcinoma (HCC) and cirrhosis.
- Fulminant hepatic failure is rare and may be associated with superimposed delta hepatitis virus (HDV) infection.
- In HIV/HBV co-infected patients who are started on antiretroviral therapy (ART) for HIV, selection of drugs should contain at least two agents active against HBV.

## TRANSMISSION OF HBV

- Contact with infected blood or body fluids.
- Unprotected sexual intercourse with an HBV-infected person.
- Sharing drug paraphernalia.
- Occupational exposures to HBV-infected blood.
- Perinatal exposure.

## SCREENING AND INITIAL EVALUATION

- Initial laboratory screening tests for HBV include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc).
- Additional serologic testing for HBeAg, anti-HBe and HBV DNA level should be ordered in persons with evidence of acute or chronic HBV infection.
- Isolated anti-HBc may indicate active infection, previous infection with loss of anti-HBs especially in patients co-infected with hepatitis C virus (HCV), a false positive result, or a window period. Some experts recommend checking HBV DNA.
- Table 3 provides a guide to interpretation of these serologic tests.

**Table 3. Serologic Patterns in HBV infection**

Disease State	HBsAg	anti-HBs	anti-HBcIgG	anti-HBcIgM	HBeAg	anti-HBe
Incubating	+	-	-	-	+ / -	-
Acute Hepatitis	+	-	+ / -	+	+	-
Chronic Carrier	+	-	+	-	-	+
Chronic Hepatitis	+	-	+	-	+	-
Resolved Hepatitis	-	+	+	-	-	+
Vaccine	-	+	-	-	-	-

## TREATING THE HIV/HBV CO-INFECTED PATIENT

Therapy should be individualized. If HBV treatment is initiated, ART for HIV should be started that incorporates two drugs active against HBV with a third drug for HIV. All 3 agents should be effective against HIV. Data on HBV treatment in HIV-infected patients are limited and enrollment in clinical trials is encouraged. The optimal duration of therapy is unknown. However, most patients are treated life long as they are on life long ART. **Expert consultation is recommended** (see Resources).

### Goals of HBV Therapy:

- Sustain suppression of HBV DNA and prevent progression of liver disease.
- Reduce HBV-related morbidity and mortality.
- Reduce the risk for HCC.

### Whom to treat:

- Patients with positive HBeAg or HBV DNA levels  $> 10^5$  copies/mL ( $> 20,000$  IU/mL).
- Patients who are HBeAg-negative with abnormal ALT levels and HBV DNA levels  $> 10^4$  copies/mL ( $> 2,000$  IU/mL).
- Some experts defer therapy in patients with an ALT level  $< 2$  times the upper limit of normal. Since ALT levels fluctuate widely, a long-term pattern is most useful. Even with normal ALT levels, a significant risk of progression still exists with HBV DNA levels  $> 10^5$  copies/mL.
- Some specialists will treat anyone with a detectable HBV DNA level.
- In patients infected with HBV, HCV, and HIV, ART is the first priority. ART should preferably include two agents active against HBV. If HIV treatment is deferred, HCV treatment should be considered prior to HBV therapy as interferon

**Table 4. Evaluation and Staging of chronic HBV in HIV-infected Patients**

<b>Test</b>	<b>Initially</b>	<b>Repeat every 6 months</b>	<b>Repeat every 6-12 months</b>	<b>Consider</b>
<b>HBeAg*</b>	X			
<b>Anti-HBe IgG*</b>	X			
<b>HAV screening</b>	X			
<b>HCV screening</b>	X			
<b>HDV screening</b>	X			
<b>Liver transaminases<sup>†</sup></b>	X	X		
<b>Albumin</b>	X	X		
<b>Prothrombin time</b>	X	X		
<b>Platelet count</b>	X	X		
<b>Complete blood count</b>	X	X		
<b>Bilirubin</b>	X	X		
<b>Quantitative HBV DNA PCR</b>	X	X		
<b>Alfa-fetoprotein<sup>‡</sup></b>	X		X	
<b>Liver ultrasound<sup>‡</sup></b>	X		X	
<b>Liver biopsy<sup>§</sup></b>				X
<b>Upper-GI endoscopy &amp; therapeutic drug monitoring<sup>¶</sup></b>				X

\*HBeAg-positive patients are likely to have high HBV DNA levels, regardless of ALT levels. Anti-HBe-positive patients may not have evidence of viral replication via HBV DNA testing.

†Elevations in liver transaminases may occur: immediately prior to loss of HBeAg, after discontinuing anti-HBV therapy, with HBV drug resistance, if hepatotoxicity from medications develops, or with HAV, HCV, or HDV co-infection.

‡The effectiveness of this screening has not been determined, however it is recommended by many specialists, especially if the individual is age > 45, cirrhosis, fibrosis, or family history of HCC. If advanced cirrhosis or fibrosis consider monitoring at intervals shorter than 6 months.

§A liver biopsy may be helpful in making decisions regarding therapy as it is the most reliable method for assessing grade and stage of liver disease.

¶If liver cirrhosis is present, consider an upper-GI endoscopy every 1-2 years to evaluate for esophageal varices and, if available, therapeutic drug monitoring enables dose adjustment of antiretroviral drugs metabolized by the liver.

(IFN) may treat both. If HBV persists, treatment of chronic HBV with nucleoside or nucleotide analogs should be considered with the addition of a third agent effective against HIV.

- Some experts recommend treating anyone with biopsy results of significant fibrosis, regardless of age.

## HIV/HBV CO-INFECTION TREATMENT CONSIDERATIONS:

- Currently, there is no evidence that treatment for HBV alters the course of HIV or vice versa.
- With the recent change in Federal HIV treatment guidelines that favor immediate or early HIV therapy, the majority of co-infected patients will be on treatment for both diseases.
- Use at least 2 drugs effective against HBV to avoid resistance.
- Patients with HIV/HBV co-infection, who are initiating ART, should be treated with agents active against both viruses or with antivirals with independent activity against each virus.
- Agents that have activity against HBV and HIV may cause a flare of HBV if discontinued (see section on liver disease flare).
- Immune reconstitution may result in a flare of hepatitis.
- Indefinite continuation of HBV treatment is usually required since durable HBV treatment responses are rare and patients are on agents that simultaneously treat HIV.
- Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are associated with elevations in transaminase levels. These increases are higher with HIV/HBV co-infection. When the ALT is 5-10 times the upper limit of normal and PIs or NNRTIs are the

**Table 5. Licensed antiviral agents for the treatment of HBV**

Drug	Dose	Viral Activity	Considerations
adefovir dipivoxil* (Hepsera)	10 mg once daily	HBV, HIV	<ul style="list-style-type: none"> <li>● Not as potent as other HBV drugs</li> <li>● 12% HBeAg convert to anti-HBe antigen at 1 year in mono-infected HBV patients</li> <li>● At 10 mg daily active only against HBV</li> <li>● Due to similar toxicities, concomitant use of adefovir dipivoxil and tenofovir is not recommended</li> <li>● Active against lamivudine resistant HBV</li> <li>● Dose reduction required if creatinine clearance &lt; 50 mL/min</li> </ul>
emtricitabine (Emtriva)	200 mg once daily	HBV, HIV	<ul style="list-style-type: none"> <li>● Do NOT use as a single agent. Due to development of potential drug resistance to other NRTIs, emtricitabine must be used in combination with other NRTIs active against HIV</li> <li>● Cross resistance with entecavir and telbivudine</li> <li>● Patients with lamivudine resistance will be cross-resistant to emtricitabine</li> <li>● Dose reduction required if creatinine clearance &lt; 50 mL/min</li> </ul>
entecavir (Baraclude)	0.5 mg once daily (lamivudine-naïve)  1.0 mg once daily (lamivudine resistant)	HBV, HIV	<ul style="list-style-type: none"> <li>● 21% HBeAg seroconversion after 1 year in HBV mono-infected patients</li> <li>● Cross resistance with emtricitabine and telbivudine</li> <li>● Partial HIV RT inhibitor, may select M184 HIV mutation</li> <li>● Do NOT use as a single agent. Due to development of potential drug resistance to other NRTIs, entecavir must be used in combination with other NRTIs active against HIV</li> <li>● Dose reduction required if creatinine clearance &lt; 50 mL/min</li> </ul>

Drug	Dose	Viral Activity	Considerations
interferon (IFN) alfa (Intron A)	5 million IU SQ daily or 10 million IU SQ 3 times per week	HBV, HCV,	<ul style="list-style-type: none"> <li>● Most effective in patients with high ALT and low HBV DNA</li> <li>● IFN-alfa should not be used for patients with decompensated liver disease</li> <li>● The combination of lamivudine and IFN is currently not recommended</li> <li>● See HCV section on side effects</li> <li>● Not tested in HBV/HIV co-infection</li> <li>● Avoid in pregnancy</li> </ul>
pegylated IFN alfa-2a (pegIFN) (Pegasys)	180 mcg SQ weekly	HBV, HCV,	<ul style="list-style-type: none"> <li>● pegIFN should generally not be used for patients with decompensated liver disease</li> <li>● The combination of lamivudine and pegIFN is currently not recommended</li> <li>● See HCV section on side effects</li> <li>● Avoid in pregnancy</li> </ul>
lamivudine (Epivir)	150 mg twice daily 300 mg once daily	HBV, HIV	<ul style="list-style-type: none"> <li>● HBeAg seroconversion rate 16–18% after 1 year in mono-infection</li> <li>● The combination of lamivudine and IFN is currently not recommended</li> <li>● Do NOT use as a single agent. Lamivudine should not be used in HIV co-infected patients who are not also being treated with combination ART for HIV infection</li> <li>● Dose reduction required if creatinine clearance &lt; 50 mL/min</li> </ul>
telbivudine** (Tyzeka)	600 mg once daily	HBV, HIV	<ul style="list-style-type: none"> <li>● Not as potent as tenofovir or entecavir</li> <li>● Monotherapy not recommended</li> <li>● Patients with lamivudine resistance will have cross-resistance to telbivudine</li> <li>● Dose reduction required if creatinine clearance &lt; 50 mL/min</li> </ul>

Drug	Dose	Viral Activity	Considerations
tenofovir (Viread)	300 mg once daily	HBV, HIV	<ul style="list-style-type: none"> <li>● Potent agent: average 5-log decrease in HBV DNA</li> <li>● Effective in lamivudine experienced patients</li> <li>● Low rate of resistance after 1 year</li> <li>● Associated with decreased bone density in HIV-infected patients</li> <li>● Do NOT use as a single agent. Tenofovir should not be used in HIV co-infected patients who are not also being treated with combination ART for HIV infection</li> <li>● Due to similar toxicities, concomitant use of adefovir dipivoxil and tenofovir is not recommended</li> <li>● Dose reduction required if creatinine clearance &lt; 50 mL/min</li> </ul>
Fixed Dose Combination			
tenofovir/emtricitabine (Truvada)	200 mg/300 mg once daily	HIV, HBV	See information listed under individual components.

*\*\*some studies suggest activity against HIV*

identified cause of these elevations, discontinuation of these medications is recommended.

## LIVER DISEASE FLARE

- Discontinuation of treatment in patients with cirrhosis can result in a flare of liver disease and is not recommended.
- If discontinuing the above medications, monitor LFTs.
- If a flare occurs when discontinuing anti-HBV therapy, then anti-HBV therapy should be reinstated.
- Some flares have been reported with lamivudine resistance, in which case switching to tenofovir or adefovir dipivoxil may be beneficial.
- If lamivudine resistance is suspected as the cause of a flare, checking HBV DNA levels is recommended. If they are stable, consider an alternative cause for the flare.

## DURATION OF TREATMENT

- The optimal duration of therapy for most agents is unknown. Anti-HBV agents must be continued for at least 6 months after seroconversion, and until HBV DNA is permanently suppressed.
- Recommended length of treatment depends on the anti-HBV agent (research is ongoing in HBV mono-infection). Prolonged suppression of HBV DNA levels correlates with improved histology and reduced risk of morbidity and mortality.
- The duration of nucleoside/nucleotide therapy is driven by HIV therapy and the use of 2 concurrent nucleosides/nucleotides active against HBV is optimal to prevent drug resistance.
- HBV flares may occur upon stopping HBV therapy.

- Some experts recommend that all patients receiving ART should continue HBV therapy indefinitely, even if they have seroconverted to anti-HBe.
- If HBeAg seroconversion does not occur, but viral suppression has been achieved, treatment with anti-HBV agents should be continued indefinitely, if tolerated.
- Patients treated with pegIFN-based therapy should be treated for the standard 48-week course.
- For patients with HIV/HBV who are HBeAg positive, the goal of treatment is suppression of HBV replication with undetectable HBV DNA, loss of HBeAg, and acquisition of anti-HBeAg.
- For patients with HIV/HBV who are HBeAg negative, the treatment endpoint is not clearly defined. Goal is suppression of HBV DNA and delay of progression of liver injury.

## MARKERS OF VIROLOGIC RESPONSE AND SUSTAINED VIROLOGIC RESPONSE:

- **Virologic response** - a decrease in HBV DNA ( $> 2 \log_{10}$  copies/mL) and loss of HBeAg at the end of treatment.
- **Sustained virologic response (SVR)** - suppression of HBV DNA and loss of HBeAg 6 months after treatment is stopped; although rare, loss of HBsAg with development of anti-HBs can occur.
- **Other markers of response** - improved liver histology, normal hepatic transaminases, and the development of anti-HBe if HBeAg is lost.

## SITUATIONS TO REFER OR SEEK EXPERT CONSULTATION

- Pregnancy
- Drug resistance
- Advanced cirrhosis

## PATIENT EDUCATION

- Discuss the importance of reducing alcohol consumption and drug use.
- Discuss how to prevent transmission of HBV, including the use of condoms to prevent sexual transmission, safer drug use activity, and encouraging partners and household contacts to receive the HBV vaccine.
- Recommend HAV vaccine if not HAV immune.
- If not HCV-infected, review prevention and risk reduction.
- Review the importance of not stopping medications without first discussing with medical provider. Reiterate the potential of a liver flare if medications stopped.

## PREVENTION OF DISEASE

- HBV vaccine is recommended for all HIV-infected adults.
- HBV vaccine efficacy is poor with CD4 + T cell count  $< 200$  cells/mm<sup>3</sup>. Better response with CD4 + T cell count  $> 500$  cells/mm<sup>3</sup>.
- Anti-HBs following vaccination occurs less frequently in HIV co-infected patients (18-59%) compared to HBV mono-infected patients ( $> 90\%$ ).
- Loss of anti-HBs occurs more rapidly after vaccination in co-infected patients.
- If low anti-HBs after initial series, repeat with additional 3 dose series.
- HBV immune serum globulin within 1 week after known HBV exposure if not previously immune.
- Behavior modification and risk reduction counseling to decrease contact with infected or other body fluids (i.e., not sharing drug-using equipment and using condoms during sexual intercourse).



# HIV AND HEPATITIS C

## OVERVIEW

- In the United States, 30% of HIV-infected people are co-infected with HCV. Co-infection rates are highly dependent on risk factors. For those who acquired HIV through injection drug use (IDU), the rate of HIV/HCV co-infection is 50-90%. Unlike HIV, HCV can be cured in up to 30% of co-infected patients. There are 6 HCV genotypes which vary geographically. HCV genotype 1 is the predominate type found in North America and is associated with a decreased response to HCV treatment.
- Spontaneous HCV RNA clearance in acute HCV infection occurs less frequently in co-infected individuals.
- Co-infected individuals tend to have higher HCV viral loads, which can increase the risk of transmission. HIV accelerates the progression of chronic HCV to end-stage liver disease (ESLD).
- HCV infection may increase the risk of hepatotoxicity related to ART.
- Use of ddI is contraindicated due to increased potential of mitochondrial toxicity, lactic acidosis, and death when used in combination with ribavirin (RBV). Zidovudine should be avoided due to risk of anemia with concurrent RBV administration.
- A multi-disciplinary healthcare team can optimize support for patients during treatment.

## TRANSMISSION

- HCV is primarily transmitted via blood contact. Sexual and perinatal transmissions are less common although the risk of sexual transmission is higher in co-infected patients and patients at risk (see below).

- Risk factors include blood transfusion prior to 1992, receiving clotting factor prior to 1987, hemodialysis, sharing intimate items containing blood with someone who is infected with HCV, current or previous sharing of drug paraphernalia (including syringes, needles, contaminated preparation materials such as cookers or cotton, rinse water, straws for snorting, pipes for smoking, or even the drug itself), a history of body piercing or tattooing without proper sterilization, and a history of occupational exposure to HCV-infected blood.
- HCV transmission through sexual activity is less efficient than blood contact. HIV/HCV co-infection increases the risk of sexual transmission of both HCV and HIV. A history of unprotected sex with an HCV-infected person, especially with traumatic sexual practices (anal, fisting, douching or enema prior to sex) may increase the risk of transmission.
- Perinatal exposure to HCV is more common among co-infected individuals. Some studies have demonstrated an increased risk of HIV vertical transmission in women co-infected with HCV. Breastfeeding has not been observed to transmit HCV.

## SCREENING AND INITIAL EVALUATION

Who should be tested for HCV antibodies?

- All HIV-infected patients
- Patients at risk for infection with HCV: those with a history of IDU, blood transfusion prior to 1992 (clotting factor prior to 1987), snorting drugs, body piercing or tattooing without proper sterilization, multiple sexual partners (studies are not unanimous, but certain kinds of sexual activity may increase risk), or known exposure to HCV
- Long-term hemodialysis patients
- Individuals with history of occupational exposure (secondary to percutaneous injury)

- Infants born to HCV-infected mothers
- Patients with elevated liver function enzymes

## **TREATING THE HIV/HCV CO-INFECTED PATIENT**

Therapy should be individualized. A team approach incorporating physicians and nurses trained in HCV treatment with frequent psychiatric consultation is helpful. Psychosocial and economic issues may be more frequent in HIV/HCV co-infected clients. Multidisciplinary care is recommended.

### **GOALS OF HCV THERAPY:**

- Eradicate HCV infection (occurs less frequently with HIV co-infection and/or HCV genotype 1).
- Delay, and in some cases reverse, histologic progression of HCV-related hepatic fibrosis, which can occur even without SVR.

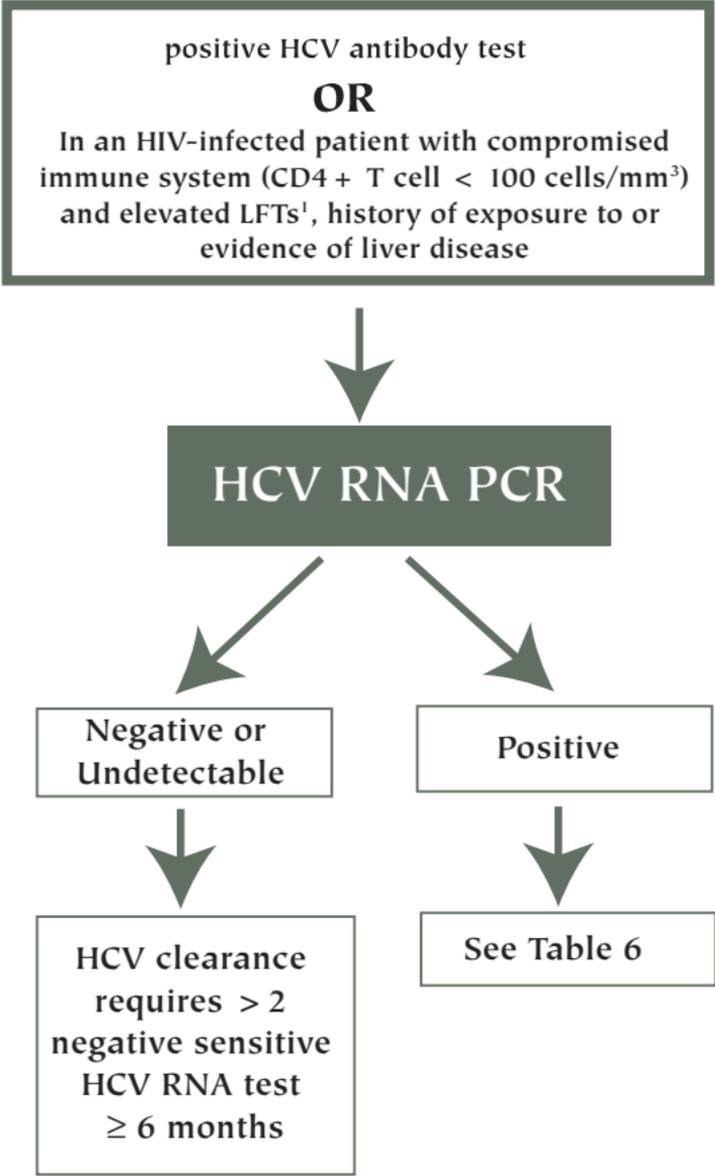
### **WHOM TO TREAT**

All patients with positive HCV RNA should be evaluated for treatment. IDU and opiate replacement therapy are not absolute contraindications.

### **HIV/HCV TREATMENT CONSIDERATIONS**

- Studies demonstrate a 14-29% rate of sustained virologic response (SVR) to HCV therapy in HIV-infected patients with HCV genotype 1 when treated with a combination of pegIFN and oral RBV.
- HIV-infected patients with HCV genotype 2 or 3 exhibited a 43-73% SVR with the same treatment.
- Low HCV viral load and CD4+ T cell counts > 500 cells/mm<sup>3</sup> are factors that may improve response to treatment. Thus, consider initiating HCV treatment when the CD4+ T cell count is

# Figure 1. Initial HCV Screening and Evaluation in the HIV-infected patient



<sup>1</sup>HIV-infected individuals with a compromised immune system may have a false negative antibody test; LFTs must be evaluated repeatedly as they may be normal despite active HCV infection

> 500 cells/mm<sup>3</sup>, or initiating ART prior to HCV treatment when the CD4 + T cell count is < 500 cells/mm<sup>3</sup>.

- Patients with insulin resistance, older age, black race, male sex, advanced fibrosis and high BMI have lower rates of SVR.

**Table 6. Initial HCV Screening and Evaluation with a Positive HCV RNA PCR Test**

Positive HCV RNA PCR test
<p><i>Obtain</i> CBC, hepatic function panel, hepatitis A &amp; B profiles, basic metabolic panel, PT, PTT, ANA, HCV genotyping, pregnancy test when appropriate.</p>
<p><i>Consider</i> liver biopsy to assist with treatment decisions. Screen for HCC with serum alfa-fetoprotein and abdominal ultrasound at 6-12 month intervals (every 6 months in cirrhosis and fibrosis).</p>
<p><i>Provide</i> patient education about transmissibility of HCV, natural history of HCV infection, significance of test results &amp; option for liver biopsy (prognosis and assistance with treatment recommendation), options for treatment &amp; treatment overview, teach to abstain from alcohol.</p>
<p><i>Provide</i> vaccinations for hepatitis A and B if needed.</p>
<p><i>Evaluate</i> for HCV treatment<sup>1</sup> by considering patient goals (long-term considerations, concerns about transmission), history (symptomatology, likely duration of disease including acute vs. chronic), labs (high HCV viremia &gt; 2 million copies/mL and genotype 1 are more difficult to cure), physical (signs of cirrhosis), and diagnostic findings (liver biopsy results if available). Thorough history including other medical issues, other causes of liver disease<sup>2</sup> (auto-immune disease, seizure disorder, thyroid abnormalities, diabetes, cardiac disease, renal disease, hematologic abnormalities, pulmonary disease) and psychosocial screening.</p>
<p><i>Evaluate</i> HIV status (HIV RNA, CD4 + T cell profile) and consider ART according to DHHS/IAS-USA Guidelines. Do not start both treatments at once; treat any toxicities before starting 2<sup>nd</sup> therapy; if ART deferred, consider treating HCV first; before starting HCV treatment, consider HIV disease stability &amp; current ART issues (i.e., side effects, adherence). Consider ART first to increase CD4 + T cell count and improve response of HCV therapy.</p>
<p><sup>1</sup>Treatment for HIV/HCV co-infection is evolving rapidly; clinicians without expertise in treating these patients are encouraged to seek consultation with and, if possible, referral to HIV-expert clinicians.</p>
<p><sup>2</sup>Rule out other causes of liver disease including serum hemochromatosis, (serum iron, TIBC) in all patients, auto-immune hepatitis, Wilson's disease, and alfa-1 antitrypsin deficiency as individually indicated.</p>

- HCV treatment is less effective and more dangerous once decompensated liver disease and related complications develop. Hepatology consultation is strongly advised.
- Adverse effects to HCV treatment, including decreased white and red blood cells, severe depression, and lactic acidosis, are more common in co-infected patients.
- Consider the patient's sources for medications prior to the initiation of therapy.
- Although treatment for HIV can cause an increase in HCV RNA in some patients, it is not a reason to withhold ART.
- If also treating HIV, review possible drug interactions, provide adherence counseling, and warn about CD4 + T cell effect (decline in absolute number, but CD4% remains stable).

**Table 7. Medication Dosing**

<b>PEGINTERFERONS</b>	
<b>PegIFN alpha-2a<sup>†</sup></b>	<b>PegIFN alpha-2b</b>
180 mcg SC weekly x 48 weeks	Weight based dosing of 1.5 mcg/kg SC weekly x 48 weeks
<b>PLUS</b>	
<b>Ribavirin orally twice daily with food using the following dosing schedule</b>	
<b>For HCV genotypes 1, 4, 5, and 6</b>	<b>For HCV genotypes 2 &amp; 3</b>
≤ 75 kg* = 1000 mg/day: 600 mg in AM 400 mg in PM	400 mg in AM 400 mg in PM
> 75 kg* = 1200 mg/day: 600 mg in AM 600 mg in PM	
<sup>†</sup> Peg IFN alfa-2a is currently the only form of pegIFN FDA indicated for HIV and HCV co-infection. *Doses meant to approximate > 10.6 mg/kg/D, and patients at extremes of weight may require individualized dosing.	

### Table 8. Treatment Monitoring

(Duration of Therapy 48 Weeks – Evaluate at 12 and 24 weeks)

Monitor:	at baseline	at 2 weeks	at 4 weeks	at 8 weeks	at 12 weeks	at 16 weeks	at 20 weeks	at 24 weeks	at 24-48 weeks
CBC	X	X	X	X	X	X	X	X	q 4 wks
Hepatic function and basic metabolic panels	X		X	X	X	X	X	X	q 4 wks
HCV RNA	X				X <sup>1</sup>			X <sup>2</sup>	q 12 wks <sup>3</sup>
HIV RNA & CD4 + T cell profile	X				X <sup>4</sup>			X	q 12 wks
TSH	X				X			X	q 12 wks
Lipids	X								q 24 wks
Depression	X	X	X	X	X	X	X	X	ongoing
Ophthalmologic exam	X <sup>5</sup>				X			X	q 3 months
PT/INR	X				X			X	q 12 wks
Pregnancy Test	Perform at regular intervals if appropriate								

<sup>1</sup> Those patients who have not dropped  $\geq 2$  logs from baseline HCV RNA at 12 weeks will have  $< 3\%$  chance of obtaining SVR (undetectable HCV RNA 6 mos. post-treatment); implications for continuing therapy for patients with tolerance issues and maintaining preferred dosing of HCV medications. Discontinuation of therapy should be based on goal of treatment (i.e., viral eradication vs. histologic improvement).

<sup>2</sup> If undetectable HCV RNA @24 weeks, continue therapy for an additional 24 weeks (genotype 2 or 3, discuss option to stop, but experts agree co-infected patients should continue treatment for 48 weeks to decrease risk of relapse); if HCV RNA positive at 24 weeks consider discontinuing HCV therapy.

<sup>3</sup> For patients who achieve end of treatment response (ETR) continue to check HCV RNA every 6-12 months for 1-5 years after ETR.

<sup>4</sup> Anticipate decrease in absolute cell count but stable CD4%.

<sup>5</sup> Interferon (IFN) associated with ischemic retinopathy. Ophthalmologic exam necessary for patients with a history of retinopathy, strongly recommended in patients with diabetes, hypertension. IFN package insert recommends screening all patients prior to treatment. Many clinicians choose to defer initial exam & monitor for disturbances in vision and loss of color perception.

**Table 9a. Peginterferon (PegIFN): Management of Adverse Effects \***

<b>Side Effect</b>	<b>Interventions</b>
<b>Influenza-like symptoms</b>	NSAIDs can help relieve flu-like symptoms if administered prophylactically.
<b>Depression Emotional lability</b>	Consider initiating selective serotonin reuptake inhibitors (SSRIs) or venlafaxine prior to starting therapy. Once therapy is initiated, monitor mood closely and have a low threshold for use of antidepressants. Psychotropic drugs should be used for neuropsychiatric effects. Consultation and collaboration with psychiatry are advised. Severe symptoms including suicidal ideation should prompt treatment discontinuation. Support groups and family may be helpful.
<b>Neutropenia</b>	Consider G-CSF 300mcg SC weekly and titrate to maintain ANC $\geq$ 750/mm <sup>3</sup> . Interferon dose reduction may ultimately be required.**
<b>Thrombocytopenia***</b>	Dose reduce interferon if platelet count < 80,000/mm <sup>3</sup> ; some experts are comfortable with lower thresholds (40,000/mm <sup>3</sup> ).** May need to institute platelet precautions.
<b>Retinopathy</b>	Patients must report any changes in vision. Refer to ophthalmologist, discontinue treatment.
<b>Respiratory problems with pulmonary infiltrates of unknown origin</b>	Discontinue therapy.
<b>Fatigue Insomnia</b>	Encourage moderate exercise and routine sleep patterns; discuss need for frequent rest periods during the day but be aware that this may contribute to nighttime sleep problems. Avoid caffeine, alcohol, and tobacco late in the day. May consider use of short-acting sedatives-hypnotics but limit use to 1-3 weeks.
<b>Anorexia Weight loss</b>	Encourage intake of several small, nutrient rich meals or snacks every few hours while awake. Focus on foods that appeal to the patient. Consult with dietitian.
<b>Diarrhea</b>	Encourage use of over-the-counter medications when appropriate. Prescribe anti-diarrheal medications as needed.
<b>Alopecia</b>	Reversible, most hair will grow back after treatment.
<b>Neuropathy</b>	Warn about possible occurrence.
<b>Hearing loss</b>	Provide patient with list of signs and symptoms.
<b>Thyroid dysfunction</b>	Provide clear information about contacting the provider/ clinic when symptoms occur.

*\*IFN can also exacerbate existing skin conditions and autoimmune diseases. Caution should be exercised with preexisting seizure disorder, cardiovascular disease, pulmonary disease, coagulation disorders, severe myelosuppression, and diabetes.*

*\*\*Dose reductions may decrease effectiveness of therapy.*

*\*\*\*For co-infected hemophiliacs management should be in collaboration with hematology.*

*Some studies have shown benefits of exogenous recombinant human IL-11.*

**Table 9b. Ribavirin (RBV):  
Management of Adverse Effects\***

Side Effect	Interventions
Dose-dependent hemolytic anemia, associated indirect hyperbilirubinemia and related fatigue and exercise intolerance	Hgb needs to be monitored regularly. <ul style="list-style-type: none"> <li>• If Hgb is low (10-12g/dL) due to HIV, consider initiating epoetin alpha prior to HCV treatment to proactively ameliorate effects of therapy.</li> <li>• If Hgb drops 25% from baseline, or &lt; 10g/dL add epoetin alpha 40,000 U SC if available; or reduce RBV dose.**</li> <li>• If Hgb decreases &gt; 2g/dL add epoetin or reduce RBV dose. If Hgb &lt; 8.5g/dL discontinue therapy. Hgb returns to baseline within 4 weeks after RBV is stopped. In cardiac patients reduce RBV for Hgb &lt; 12g/dL.</li> </ul>
Nausea	Prescribe PRN anti-nausea medications.
Insomnia	Take RBV at least 3 hours before going to bed.
Rash, dry pruritic skin	Steroid cream may be used for localized rash & pruritis. Recommend skin moisturizers.
Noncardiac chest pain Dry cough Dyspnea	Warn about possible occurrence, provide with list of signs and symptoms to watch for, provide clear information about contacting the provider/clinic when symptoms occur.
*Lab parameters are based on data from HIV-uninfected patients.	
**Dose reductions can lead to decreased therapeutic response.	
RBV is teratogenic in animal studies. Avoid pregnancy during therapy and for 6 mos. after completion.	

- ddl is contraindicated for use with RBV due to a drug interaction that greatly increases ddl levels and toxicities.
- Consider replacing medications that may lead to myelosuppression, especially zidovudine (ZDV).
- Consider replacing nevirapine in the HIV regimen secondary to the possibility of hepatotoxicity.
- Immune reconstitution may result in a flare of hepatitis.
- For mild cases of anemia and neutropenia, growth factor support (erythropoietin or recombinant granulocyte colony stimulating factor [G-CSF]) should be considered prior to dose reductions of HCV medications.

- HCV treatment can delay clinical progression to ESLD, HCC, and death.
- Successful HCV treatment may reduce risk of current or future ART-related hepatotoxicity.

## **DURATION OF TREATMENT**

- Chronic HCV should be treated for at least 48 weeks regardless of genotype.
- Acute HCV (less than 6 months duration) should be treated for greater than or equal to 24 weeks with pegIFN and weight-based RBV (based on HCV mono-infection). Treatment should be started in eligible patients no earlier than 8-12 weeks after acute HCV exposure to allow for spontaneous HCV clearance.
- Most clinicians agree HCV treatment should be discontinued for patients who fail to achieve  $> 2$  log reduction of viral load at 12 weeks of treatment.
- Treatment for HIV/HCV co-infection is evolving rapidly; clinicians without expertise in treating these patients are encouraged to seek consultation with and referral to HIV-expert clinicians (See Resources).

## **ROLE OF THE SPECIALIST**

- Whenever possible, consult, refer to and/or co-manage with experts in treating HIV/HCV co-infection.
- As with liver biopsy, access to specialists may be limited secondary to patient resources.

## **ROLE OF LIVER BIOPSY**

- Biopsy is not needed to confirm diagnosis or required to initiate therapy but may be necessary to identify cirrhosis in some patients.

- Histologic stage of disease coupled with the estimated duration of infection can help to understand risk for disease progression. Mild disease may support deferring therapy or discontinuing problematic treatment; advanced fibrosis is an indication for therapy and a motivation for more complicated management. However, patients with early fibrosis may respond better to treatment.
- The high response rate of genotypes 2 & 3 may justify offering treatment without a liver biopsy.
- For those who defer therapy or for whom therapy is unsuccessful, liver biopsy should be repeated every 2-5 years to assess disease progression.
- Use of non-invasive testing to assess liver fibrosis such as transient elastography or other laboratory assays are used by some clinicians. Studies are underway to determine which methodology has the best predictive value for disease progression.

## **CONTRAINDICATIONS TO TREATMENT**

Anti-HCV treatment is contraindicated in patients with known hypersensitivity to HCV medications, pregnancy, autoimmune hepatitis, hepatic decompensation before or during treatment, and for patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia), and unstable or significant cardiac disease. Other medical conditions such as diabetes, thyroid problems, seizure disorders, and pulmonary, cardiac, and psychiatric diseases should be stabilized prior to initiating therapy. Cardiac stress testing is recommended for those with cardiac risk factors. Use with extreme caution and psychiatric consultation in those with a history of severe depression or suicidal tendencies. Interferon has been associated with risk of drug relapse among IDU. RBV is teratogenic in animal studies; pregnancy should be avoided by patient or patient's partners during therapy and for 6 months after completion of therapy.

**Table 10. Staging and Grading of Chronic Hepatitis\***

Staging (Fibrosis)		Grading (Inflammation)	
Score	Stages of Fibrosis	Grade	Grade of Inflammation or Necrosis
0	No fibrosis	0- no activity	None – very mild
1	Mild fibrosis (portal)	1 – minimal	Portal inflammation
2	Moderate fibrosis	2 – mild	Mild periportal inflammation (piecemeal)
3	Severe fibrosis (septal)	3 – moderate	Moderate portal/periportal inflammation all tracts and piecemeal necrosis
4	Cirrhosis	4 – severe	Severe inflammation plus piecemeal necrosis

\* *Ishak K, et al. (1995). Journal of Hepatology, 22, 696-699.*

Table 7 provides information about medication dosing for HCV treatment; Table 8 gives information about parameters to monitor during therapy; Tables 9a and 9b give information on managing adverse effects of therapy.

## PATIENT EDUCATION

All patients with HCV need to know about the natural history of HCV, long-term effects on the liver, treatment options, and prognosis. Patients who are co-infected with HIV should understand how the two diseases interact and the potential for increased risk of complications.

### Key points to discuss with patients include:

- Emphasize need for lab evaluations prior to initiating therapy and periodically thereafter. Discuss significance of diagnostic tests:

- LFTs – do not reflect stage of disease, may not correlate with severity of disease, inexpensive and easy to monitor, severe elevations may indicate acute problem
- HCV RNA PCR – level of viremia does not correlate with degree of liver damage
- Other diagnostics if appropriate – i.e., imaging to rule out malignancy
- Liver biopsy – access to biopsy may be limited secondary to resources. Discuss option with patient and consider deferring if patient absolutely wants to treat HCV (and there are no signs/symptoms of decompensated cirrhosis), or absolutely does not want to pursue therapy. This should be documented clearly in the patient chart

### **Making the decision to accept treatment**

- Treatment options including risks and benefits – discuss likely efficacy of HCV treatment based on patient’s HIV disease, possible duration of HCV infection, HCV viral titer, stage of liver disease (if known), HCV genotype (75% genotype 1 in United States).
- Table 11 lists the benefits and challenges of HCV therapy.

### **Prior to initiation of therapy**

- Prepare patients for potential side effects of therapy and provide instructions for addressing problems promptly (see Tables 9a and 9b).
  - Encourage patient to report all side effects and counsel patient that most side effects are manageable. More severe adverse effects may require dose reductions or discontinuation.
  - Discuss potential mental and emotional side effects of medication. Discuss starting antidepressant therapy prior to treatment (3-4

weeks for effective levels). SSRIs and venlafaxine are common choices.

- Most side effects are attributed to pegIFN, but RBV also has specific side effects. It is usually possible to determine which drug is the predominant cause of problems, allowing for dose reduction of the offending drug.
- Prepare patient for probable CD4 + T cell drop, percentage will remain relatively stable.
- General measures for managing side effects include injection timing, use of NSAIDs, increased daily fluid intake, light aerobic exercise, and comfort measures. Injections of pegIFN may be best scheduled before a weekend, a day off, or prior to bedtime.
- Stress importance of adequate hydration (> 10 glasses water/day) and mild exercise.
- Encourage adequate rest and caloric intake. Prepare patient for potential weight loss.
- Discuss methods to avoid pregnancy when using RBV; two forms of birth control for patient and/or partner (including condoms) during treatment and for 6 months after therapy is completed are recommended.

**Table 11. Benefits and Challenges of HCV Therapy**

Potential Benefits	Potential Challenges
<ul style="list-style-type: none"> <li>• Viral eradication</li> <li>• Delay or reverse fibrosis</li> <li>• Prevent disease progression</li> <li>• Improve tolerance &amp; effectiveness of ART</li> <li>• Improve extra-hepatic manifestations of HIV</li> </ul>	<ul style="list-style-type: none"> <li>• Toxicities of medications</li> <li>• Adherence difficulties</li> <li>• Lack of data on effectiveness &amp; treatment guidelines for co-infected individuals</li> <li>• Exacerbation of other medical conditions</li> </ul>

- Adherence to HCV treatment > 80% (administration, dosage, duration) will increase chances of achieving SVR.
- Teach methods of medication administration
  - Demonstrate injection techniques and ask for return demonstration.
  - Emphasize proper disposal of injection equipment.
- Encourage patient to enlist the help and support of friends and family.
- Develop individualized medication schedule to best fit into patient's usual activities.
- Emphasize positive aspects of treatment.

### After treatment

- Assess HCV-RNA periodically (every 6-12 months) for 1-5 years to exclude late relapse or reinfection.
- Counsel and reinforce the importance of avoiding reinfection.

### PREVENTION

- HCV antibodies are not protective therefore reinfection can occur following SVR or with acquisition of other genotypes.
- Risk reduction strategies include:
  - Discussion of current drug use and determination of changes the patient is willing to make: such as abstinence; treatment for substance use; using only clean equipment to inject, snort, or smoke drugs; cleaning equipment prior to use.
  - Discussion of current risk related to sexual activity and determination of changes the patient is willing to make: abstaining (or maintaining abstinence) from risky sex or using condoms and other barriers consistently

and correctly with sexual encounters.

- Education regarding the importance of protecting the liver from further damage. Use of alcohol and other hepatotoxic drugs is of primary concern, as even small amounts can make a major difference in liver health. Information about abstaining from these chemicals needs to be provided along with resources for withdrawal and long-term support as needed.
- HAV and HBV vaccination to prevent acute hepatitis A or B which can be life-threatening when superimposed on chronic hepatitis.
- No HCV vaccine is currently available.

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Information on HBV and HCV in patients with HIV infection was also obtained from [www.clinicalcareoptions.com](http://www.clinicalcareoptions.com) and [www.uptodate.com](http://www.uptodate.com).

## **RESOURCES:**

### **Mountain Plains AIDS Education and Training Center HIV & Hepatitis Resources**

[www.mpaetc.org](http://www.mpaetc.org)

The Web site offers access to hepatitis and HIV co-infection specific resources including the pocket guide, clinical consultation, and links to other resources.

### **AIDS Education and Training Centers National Resource Center**

[www.aids-ed.org](http://www.aids-ed.org)

A central Web site for education and training materials designed by the AETCs.

### **AIDSinfo**

[www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov)

A service of the U.S. Department of Health and Human Services providing information about federally approved treatment guidelines for HIV and AIDS.

### **AIDS InfoNet**

[www.aidsinfonet.org](http://www.aidsinfonet.org)

A project of the New Mexico AIDS Education and Training Center that offers information for patients, caregivers, and first-line treatment providers. Fact sheets are available in several languages.

### **The American Association for the Study of Liver Diseases**

[www.aasld.org](http://www.aasld.org)

An organization focused on hepatology. Various live CME and written materials are offered.

### **Chronic Hepatitis C: Current Disease Management**

[www.niddk.nih.gov/](http://www.niddk.nih.gov/)

Produced by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

### **Clinical Care Options**

[www.clinicalcareoptions.com](http://www.clinicalcareoptions.com)

Provides information for health care providers on HIV, hepatitis, and oncology.

### **Hep C Connection**

**[www.hepc-connection.org](http://www.hepc-connection.org)**

A unique network and support system for patients with HCV. Hep C Connection was established in Denver, CO to provide education and support to patients with HCV and HCV/HIV co-infection through materials, programs, and the hepatitis helpline (1-800-522-HEPC).

### **HIV and Hepatitis.com**

**[www.hivandhepatitis.com](http://www.hivandhepatitis.com)**

Provides cutting-edge information about treatment for HIV, chronic HBV and HCV, and co-infection with HIV/HCV and HIV/HBV.

### **National HIV/AIDS Clinicians' Consultation Center**

**[www.nccc.ucsf.edu](http://www.nccc.ucsf.edu)**

Provides expert advice for health care providers caring for people with HIV or managing occupational exposures. Warmline: 1-800-933-3413 PEpline: 1-888-448-4911 Perinatal HIV Hotline: 1-888-448-8765.

### **The National AIDS Treatment Advocacy Project**

**[www.natap.org](http://www.natap.org)**

A non-profit corporation created to educate individuals about HIV and hepatitis treatments, and to advocate on the behalf of people living with HCV, especially with HIV/HCV co-infection. NATAP offers up-to-date treatment information suitable for health care professionals through a variety of printed and electronic formats.

### **Projects in Knowledge**

**[www.projectsinknowledge.com](http://www.projectsinknowledge.com)**

Developed to improve the quality of healthcare in the United States; provides free CME activities in a variety of areas. For HIV/HCV co-infection, activities include printed materials and meetings that convene clinical experts to network and develop materials.





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