

Clinician's Guide to

HIV &
hepatitis

January 2007



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As better treatments allow HIV¹-infected patients to live longer and avoid HIV-related complications, other diseases, including Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infection are increasingly common causes of morbidity and mortality. This guide is intended to provide basic information related to care of patients infected with HIV and either infected with or at risk for Hepatitis A, B and/or C. 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. Table 1 provides an overview of Hepatitis A, B, and C.

HIV/HAV CO-INFECTION

INTRODUCTION

For most patients, Hepatitis A virus (HAV) is a self-limiting infection; however, fulminant hepatic failure from HAV infection may occur and is more frequent in individuals with chronic liver disease. Current recommendations encourage screening all HIV-infected patients for HAV. See Table 2 for HAV screening information.

TRANSMISSION

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, and rarely, recipients of blood transfusions or injection drug users (IDU).

¹HIV 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**

<i>Viral Hepatitis Type</i>	<i>Mode of Transmission</i>	<i>Symptoms of Acute Infection</i>	<i>Symptoms of Chronic Infection</i>
Hepatitis A (HAV) infection	Fecal-oral route	Acute hepatitis with fever, jaundice, anorexia, nausea, vomiting, and malaise.	No chronic infection.
Hepatitis B (HBV) infection	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.	In HIV-infected people with HBV, ~ 10% will develop chronic HBV infection. 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.
Hepatitis C (HCV) infection	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.

SCREENING

Table 2. HAV Screening

<i>Anti-HAV IgM</i>	positive in acute infection, recent infection, asymptomatic infection, or false-positive result
<i>Anti-HAV IgG</i>	positive in past infection or vaccination (conferred immunity)
<i>Total anti-HAV antibody</i> (screening test that detects IgG and IgM antibodies)	negative = no evidence of acute or prior infection positive = draw IgM to distinguish acute from prior infection or vaccination

TREATMENT

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

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/ μ L improves the likelihood of response.
- HAV immune serum globulin can be given immediately after known HAV exposure.

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.

HIV/HBV CO-INFECTION

INTRODUCTION

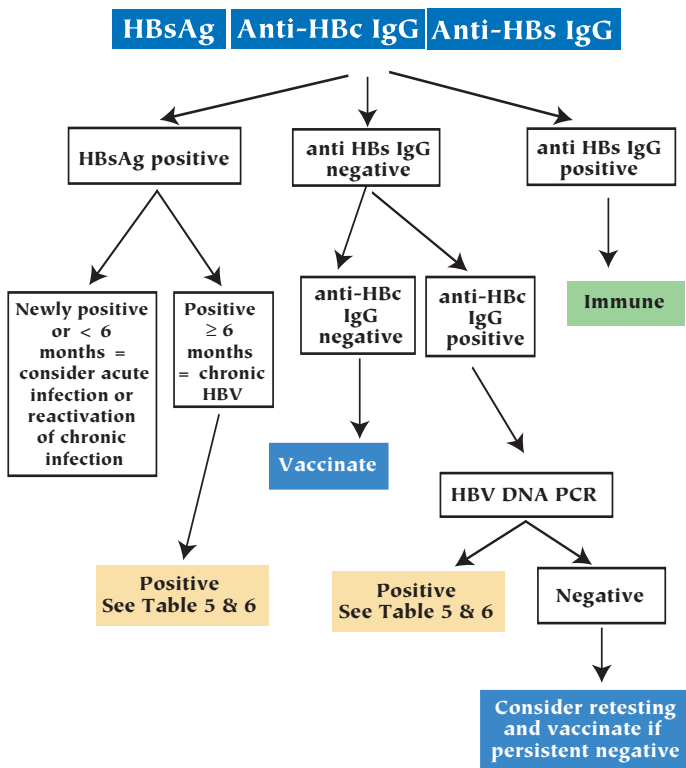
- World-wide, 10% of HIV-infected people are chronically infected with HBV.
- People with HIV infection are at an increased risk of developing chronic HBV if exposed.
- Patients with both HIV and HBV infection are more likely to have higher HBV DNA levels, and detectable Hepatitis B e antigen (HBeAg). Co-infected patients also lose the Hepatitis B surface antibody (antiHBs) rapidly and have an increased risk for liver-related morbidity and mortality.
- Recent research indicates that 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.

TRANSMISSION OF HBV

HBV is transmitted through contact with infected blood or body fluids. Risk factors include unprotected sexual intercourse with an HBV-infected person, sharing drug paraphernalia, and occupational exposures to HBV-infected blood. HBV is also transmitted through perinatal exposure and can be spread through household contacts. Tables 3 and 4 discuss screening and evaluation for HBV.

SCREENING AND INITIAL EVALUATION

Table 3. Initial Screening and Evaluation for HBV



Vaccination

- Vaccination with 3 doses of HBV vaccine, at 0, 1 and 6 months, is recommended for all HIV-infected persons who are not HBV immune or infected.
- Measure anti-HBs level 1-6 months following 3rd dose. If < 10 IU/mL repeat series.

Isolated anti-HBc IgG positive:

- More common in patients with HIV infection
May occur in the following settings:
- Window period of acute hepatitis B
 - Many years following recovery when anti-HBs IgG is no longer detectable
 - Low level HBV replication with HBsAg clearance

Table 4. Screening and Evaluation for chronic HBV Prior to Treatment

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

*HBe Ag-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, including anti-HIV therapy, or with HAV, HCV, or HDV co-infection.

‡The effectiveness of this screening has not been determined, however it is recommended by many specialists, specifically if the individual is in a high-risk group (age > 45, cirrhosis, or family history of HCC carcinoma). If advanced fibrosis/cirrhosis 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, an upper-GI endoscopy every 1-2 years can be considered to evaluate for esophageal varices and, if available, therapeutic drug monitoring enables dose adjustment of antiretroviral drugs metabolized by the liver.

TREATING THE HIV/HBV CO-INFECTED PATIENT

Therapy should be individualized. Data on HBV treatment in HIV-infected patients are limited and enrollment in clinical trials is encouraged. The optimal duration of therapy is unknown and the rate of relapse is high. **Expert consultation is recommended** (see Resources).

Goals of Therapy:

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

Who to treat:

- Patients with positive HBeAg or HBV DNA levels $> 10^5$ copies/mL and liver disease (serum ALT elevated to 2 times the upper limits of normal or a liver biopsy showing evidence of moderate liver disease activity and/or fibrosis).
- 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 and advanced fibrosis or cirrhosis on a liver biopsy (if other causes have been eliminated).
- In patients infected with HBV, HCV and HIV, anti-retroviral therapy (ART) is the first priority. If HIV treatment is not necessary, HCV treatment should be considered prior to HBV therapy as interferon (IFN) may treat both. If HBV persists, treatment of chronic HBV with nucleoside or nucleotide analogs should be considered.
- Treatment of chronic HBV is generally not recommended during pregnancy.

Duration of treatment:

The optimal duration of therapy for most agents is unknown. 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 active therapy.

Duration of Interferon-based therapy²:

- If HBeAg positive – 16-24 weeks
- If HBeAg negative – 12 months minimum
- If $> 2 \log_{10}$ copies/mL reduction or clearance of HBV DNA at week 16 but still HBeAg positive may be candidates for treatment of 12 months or longer

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 (threshold not yet defined) and loss of HBeAg 6 months after treatment is stopped; although rare, loss of HBsAg with positive HBsAb.
- Other Markers of Response – improved liver histology, normal hepatic transaminases, and the development of anti-HBe if HBeAg is lost.

²From *Treating Opportunistic Infections Among HIV-Infected Adults and Adolescents: Recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America* (December 17, 2004); Available at <http://aidsinfo.nih.gov/guidelines/>. Other experts may vary in opinion.

HBV Treatment Options:

Table 5. HBV Treatment Options*

Drug	Dose	Viral Activity	Considerations
adefovir dipivoxil	10 mg daily	HBV, HIV	<ul style="list-style-type: none"> • Due to similar toxicities, concomitant use of adefovir dipivoxil and tenofovir is not recommended • Dose reduction required if creatinine clearance < 50 mL/min
emtricitabine	200 mg once daily	HBV, HIV	<ul style="list-style-type: none"> • Dose reduction required if creatinine clearance < 50 mL/min
entecavir	0.5 mg daily (if lamivudine-naïve), 1.0 mg daily (lamivudine resistant)	HBV	<ul style="list-style-type: none"> • Dose reduction required if creatinine clearance < 50 mL/min
interferon (IFN) alfa	5 MU SQ daily or 10 MU SQ 3 times a week	HBV, HCV, HIV	<ul style="list-style-type: none"> • IFN-alfa should not be used for patients with decompensated liver disease • The combination of lamivudine and INF is currently not recommended • See HCV section on side effects
pegylated IFN alfa-2a	180 µg SQ weekly	HBV, HCV, HIV	<ul style="list-style-type: none"> • The combination of lamivudine and INF is currently not recommended • See HCV section on side effects
lamivudine	150 mg twice daily 300 mg daily	HBV, HIV	<ul style="list-style-type: none"> • The combination of lamivudine and INF is currently not recommended • Dose reduction required if creatinine clearance < 50 mL/min
telbivudine	600 mg daily	HBV	<ul style="list-style-type: none"> • Dose reduction required if creatinine clearance < 50 mL/min
tenofovir	300 mg daily	HBV, HIV	<ul style="list-style-type: none"> • Due to similar toxicities, concomitant use of adefovir dipivoxil and tenofovir is not recommended

*Of these medications, only entecavir is currently indicated by the FDA for treatment of chronic HBV infection in HIV-infected persons.

Table 6. HBV and HIV Treatment Considerations

<i>HIV Treatment Indicated</i>	<i>HBV Treatment Indicated</i>	<i>Treatment Consideration</i>
YES	YES	<ul style="list-style-type: none"> • Tenofovir + emtricitabine or lamivudine 1st choice as NRTI backbone • Consider entecavir alone or in combination with one of these NRTIs • Avoid sole use of one of these NRTIs to avoid HBV resistance
YES	NO	<ul style="list-style-type: none"> • Consider tenofovir + emtricitabine or lamivudine as NRTI backbone • Avoid sole use of one of these NRTIs to avoid HBV resistance
NO	YES	<p>To avoid HIV-related drug resistance, consider:</p> <ul style="list-style-type: none"> • Pegylated IFN alfa • Entecavir • Some experts avoid adefovir dipivoxil (no anti-HIV activity at HBV doses, but related to tenofovir) • Avoid emtricitabine, lamivudine and tenofovir except as components of fully-suppressive ART

HIV/HBV CO-INFECTION TREATMENT CONSIDERATIONS:

- Currently, there is no evidence that treatment for HBV alters the course of HIV or vice versa.
- Emtricitabine, lamivudine, and tenofovir are active against both HIV and HBV. Discontinuation of these may cause a flare of HBV resulting in hepatocellular damage (see section on liver flare).
- HBV lamivudine resistance is approximately 40% at 2 years and 90% at 4 years when used as HBV monotherapy in HIV/HBV co-infected patients.
- Immune reconstitution may result in deterioration in LFTs, as well as loss of HBeAg, associated with a flare of hepatitis.

- 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 the cause of these elevations is found to be due to the PIs or NNRTIs, discontinuation of these medications is recommended.

LIVER DISEASE FLARE

- Discontinuation of lamivudine, adefovir dipivoxil, tenofovir or emtricitabine can result in a flare of liver disease in 15% of cases with loss of benefits gained from HBV treatment.
- If discontinuing the above medications, monitor LFTs.
- If discontinuing lamivudine, tenofovir, or emtricitabine, consider the use of adefovir dipivoxil or entecavir to prevent flares.
- If a flare occurs, reinstatement of treatment is recommended.
- 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.

Table 7 discusses monitoring considerations with HBV infection.

MONITORING CONSIDERATIONS DURING AND AFTER HBV TREATMENT

Table 7. Monitoring Considerations for HBV Treatment

After treatment	During treatment	If no treatment
HBV DNA, HBeAg, HBeAb, ALT, AST, consider markers for liver histology	If on INF follow INF monitoring guidelines listed under HCV treatment recommendations If on adefovir dipivoxil or tenofovir monitor for renal toxicity	ALT every 4-6 months

PREVENTION

- HBV vaccine is recommended for all HIV-infected adults.
- Consider revaccination if low anti-HBs titer.
- HBV immune serum globulin within 1 week after known HBV exposure.
- 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).

PATIENT TEACHING

- Discuss the importance of reducing alcohol consumption and drug use.
- Discuss how to prevent transmission of HBV, including the use of condoms to prevent sexu-

al 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.

HIV/HCV CO-INFECTION

INTRODUCTION

- In the United States, 15-30% 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 may be 50-90%. Unlike HIV, HCV can be cured, but immunodeficiency caused by HIV may decrease the efficacy of HCV therapy. HCV genotype 1, the predominate type found in the United States, is also associated with a decreased response to HCV treatment.
- Co-infected individuals tend to have higher HCV viral loads, which can increase the risk of transmission. HIV also appears to accelerate the progression of chronic HCV to end-stage liver disease (ESLD).
- HCV disease can complicate HIV treatment, and may increase the risk of hepatotoxicity related to ART. Co-infected individuals may have a blunted immune response following initiation of ART. Direct effects of HCV on HIV disease progression are being investigated.

TRANSMISSION

HCV is transmitted via blood contact. Sexual and perinatal transmissions appear to be less common although studies indicate that these are viable routes of transmission.

- 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, a history of sharing equipment to use drugs, a history of body piercing or tattooing

without proper sterilization, and a history of occupational exposure to HCV-infected blood.

- The greatest risk of transmission occurs when IDUs share injection equipment; this accounts for the majority of cases. Sharing 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) can transmit HCV through exposure to blood.
- A history of unprotected sex with an HCV-infected person, as well as engaging in certain kinds of sex (anal, fisting, douching or enema prior to sex) may increase the risk of transmission. HCV transmission through sexual activity is less efficient than blood contact. HIV/HCV co-infection may increase the risk of sexual transmission of both HCV and HIV.
- Perinatal exposure to HCV is also a mode of transmission. 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.

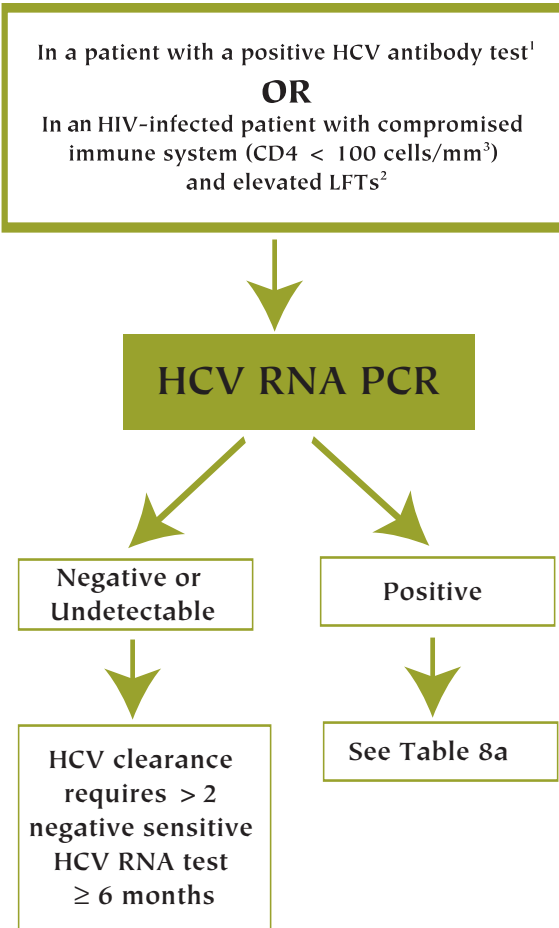
SCREENING AND INITIAL EVALUATION

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
- See Tables 8 and 8a for information on the initial screening and evaluation process.

Table 8. Initial HCV Screening and Evaluation



¹HCV screening should be done with 3rd generation EIA.

²HIV-infected individuals with a compromised immune system may have a false negative antibody test.

Table 8a. Initial HCV Screening and Evaluation with a Positive HCV RNA PCR Test

<p align="center">Positive HCV RNA PCR test</p>
<p><i>Obtain</i> CBC, hepatic function panel, hepatitis A & 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. Many experts also recommend periodic screening for HCC with serum alfa-fetoprotein and abdominal ultrasound at 6-12 month intervals.</p>
<p><i>Provide</i> patient education about transmissibility of HCV, natural history of HCV infection, significance of test results & option for liver biopsy (prognosis and assistance with treatment recommendation), options for treatment & 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 treatment¹ by considering patient goals (long-term considerations, concerns about transmission), history (symptomatology, likely duration of disease), labs (high HCV viremia > 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 (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 profile) and consider ART according to DHHS/IAS-USA Guidelines. Do not start both treatments at once; treat any toxicities before starting 2nd therapy; if ART deferred, consider treating HCV first; before starting HCV treatment, consider HIV disease stability & current ART issues (i.e., side effects, adherence). Consider ART first to increase CD4 count and improve response of HCV therapy.</p>
<p>¹<i>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.</i></p>

TREATING THE HIV/HCV CO-INFECTED PATIENT

More research is needed on how HIV/HCV co-infected individuals respond to HCV therapy, but new treatments may improve response rates.

Recent studies demonstrate a 14-30% rate of sustained virologic response (SVR) to HCV therapy in HIV-infected patients with HCV genotype 1 when treated with a combination of injected pegylated interferon (PEG IFN) and oral ribavirin (RBV).

HIV-infected patients with HCV genotype 2 or 3 exhibited a 44-73% SVR with the same treatment.

Low HCV viral load and CD4 counts > 500

cells/mm³ are factors that may improve response to treatment. Thus, consider initiating HCV treatment when the CD4 count is > 500 cells/mm³, or initiating ART prior to HCV treatment when the CD4 count is < 500 cells/mm³.

- 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.
- Many psychosocial and economic issues that can complicate treatment are frequently present in HIV/HCV co-infected clients. Multidisciplinary care is recommended when treatment for HCV is anticipated. 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 effect (decline in absolute number, but CD4% remains stable).

- Didanosine (ddI) 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 AZT.
- Consider replacing nevirapine in the HIV regimen secondary to the possibility of hepatotoxicity.
- Most clinicians agree that HCV treatment in co-infected patients should continue for at least 48 weeks regardless of genotype.
- Most clinicians agree HCV treatment should be discontinued for patients who fail to achieve an early virologic response at 12 weeks of treatment.
- 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.
- 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).

Goals of 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.

- Delay clinical progression to ESLD, HCC, and death.
- Reduce risk of current or future ART-related hepatotoxicity.

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. 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 9 provides information about medication dosing for HCV treatment; Table 10 gives information about parameters to monitor during therapy; Tables 11a and 11b give information on managing adverse effects of therapy.

Table 9. Medication Dosing

Pegylated interferon alfa-2b			OR	Pegylated interferon alfa-2a[†] 180 µg SC weekly X 48 weeks
1.5 µg/kg SC weekly X 48 weeks consider weight-based dosing:				
Weight kg (lb)	Peg-Intron vial strength	Peg-Intron volume		
< 40 (< 88)	100 µg/mL	0.5		
40-50 (88-110)	160 µg/mL	0.4		
51-60 (112 -132)	160 µg/mL	0.5		
61-75 (134.2 -166)	240 µg/mL	0.4		
76-85 (167-187)	240 µg/mL	0.5		
> 85 (> 187)	300 µg/mL	0.5		
PLUS				
Ribavirin PO daily (with food) in BID dosing				
≤ 75 kg* = 1000 mg/day: • 2 x 200 mg capsules AM • 3 x 200 mg capsules PM				
> 75 kg* = 1200 mg/day: • 3 x 200 mg capsules AM • 3 x 200 mg capsules PM				
Genotypes 2 & 3: may consider 800 mg/day				
†Pegylated INF alfa-2a is currently the only form of PEG INF FDA indicated for HIV and HCV Co-infection.				
*Doses meant to approximate > 10.6mg/kg/D, and patients at extremes of weight may require individualized dosing.				

Table 10. 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 ¹			X ²	q 12 wks
HIV RNA & CD4 profile	X				X ³			X	q 12 wks
TSH	X				X			X	q 12 wks
Depression	X	X	X	X	X	X	X	X	ongoing
Ophthalmologic exam	X ⁴				X			X	q 3 mon
PT	X				X			X	q 12 wks
Pregnancy Test	Perform at regular intervals if appropriate								

¹ Those patients who have not dropped ≥ 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).

² If undetectable HCV RNA @24 weeks, continue therapy for an additional 24 weeks (if known genotype 2 or 3, discuss option to stop, but some 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 or using maintenance Peg IFN in the presence of advanced fibrosis (studies pending) and pursue liver biopsy if not done within last 2 years. Even in patients without viral response, treatment can improve liver histology.

³ Anticipate decrease in absolute cell count but stable CD4%.

⁴ Necessary for patients with a history of retinopathy, 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 11a. Interferon (IFN): Management of Adverse Effects*

Side Effect	Interventions
Influenza-like symptoms	Acetaminophen or NSAIDs can help relieve flu-like symptoms if administered prophylactically.
Depression Emotional lability	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.
Neutropenia	Consider G-CSF 300ug SC t.i.w. and titrate to maintain ANC $\geq 750/\text{mm}^3$. Interferon dose reduction may ultimately be required.**
Thrombocytopenia***	Dose reduce interferon if platelet count $< 80,000/\text{mm}^3$; some experts are comfortable with lower thresholds ($40,000/\text{mm}^3$).** May need to institute platelet precautions.
Retinopathy	Patients must report any changes in vision. Refer to ophthalmologist, discontinue treatment.
Respiratory problems with pulmonary infiltrates of unknown origin	Discontinue therapy.
Fatigue Insomnia	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.
Anorexia Weight loss	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.
Diarrhea	Encourage use of over-the-counter medications when appropriate. Prescribe anti-diarrheal medications as needed.
Alopecia	Reversible, most hair will grow back after treatment.
Neuropathy Hearing loss Thyroid dysfunction	Warn about possible occurrence. Provide patient with list of signs and symptoms. 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 11b. Ribavirin (RBV):
Management of Adverse Effects***

Side Effect	Interventions
Dose-dependent hemolytic anemia, associated indirect hyperbilirubinemia and related fatigue and exercise intolerance	<p>Hgb needs to be monitored regularly.</p> <ul style="list-style-type: none"> • If Hgb is low (10-12g/dL) due to HIV, consider initiating epoetin alpha prior to HCV treatment to proactively ameliorate effects of therapy. • If Hgb drops 25% from baseline, or < 10g/dL add epoetin alpha 40,000 U SC if available; or reduce RBV dose.** • If Hgb decreases > 2g/dL add epoetin or reduce RBV dose. If Hgb < 8.5g/dL discontinue therapy. Hgb returns to baseline within 4 weeks after RBV is stopped. In cardiac patients reduce RBV for Hgb < 12g/dL.
Nausea	Prescribe PRN anti-nausea medications and explain use.
Insomnia	Take RBV at least 3 hours before going to bed.
Rash, dry pruritic skin	Steroid cream may be used for localized rash & pruritis.
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.
<p>*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.</p>	

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.
- Many HIV providers are becoming proficient in caring for co-infected patients out of necessity. Resources for increasing knowledge and skills in this area are available (See Resources).

ROLE OF LIVER BIOPSY

- Biopsy is not needed to confirm diagnosis or required to initiate therapy.
- Discuss as an option, but encourage if accessible as biopsy is the only prognostic tool available and would be extremely helpful in making treatment decisions (see Table 12). 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.
- 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.
- For those who defer therapy or for whom therapy is unsuccessful, liver biopsy should be repeated every 2-5 years to assess disease progression.
- The high response rate of genotypes 2 & 3 may justify offering treatment without a liver biopsy.

PREVENTION

- Emphasize need for measures to prevent transmission to others and to prevent personal re-infection with HCV and/or exposure to other blood-borne diseases. Use risk reduction strategies to help clients meet prevention goals:
 - Discuss current drug use and determine changes the patient is willing to make: abstaining (or maintaining abstinence) from use; enrolling in treatment for substance use; using only clean equipment to inject, snort, or smoke drugs; cleaning equipment prior to use, etc.

Table 12. 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.

- Discuss current risk related to sexual activity and determine 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.
- Patients need to know 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.
- Encourage HAV and HBV vaccination to prevent acute infection with these organisms,

which can be life-threatening in the face of chronic hepatitis. No HCV vaccine is currently available.

PATIENT EDUCATION

All patients with HCV need to know about the disease. They 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 not prognostic, but high viral titer (> 2 million copies/mL) may be more difficult to cure; used to establish chronic infection and monitor treatment response
 - 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 U.S.).
- Table 13 lists the benefits and challenges of HCV therapy.

Table 13. Benefits and Challenges of HCV Therapy

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

Prior to initiation of therapy

- Prepare patients for potential side effects of therapy and provide instructions for addressing problems promptly (see Tables 11a and 11b).
 - 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 treat-

ment (3-4 weeks for effective levels). SSRIs and venlafaxine are common choices.

- Most side effects are attributed to IFN, 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 potential CD4 cell drop.
- General measures for managing side effects include injection timing, use of acetaminophen or NSAIDs, increased daily fluid intake, light aerobic exercise, and comfort measures. Injections of IFN 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 six months after therapy is completed are recommended.
- 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.

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Information on HBV and HCV in patients with HIV infection was also obtained from www.clinicalcareoptions.com and www.uptodate.com.

RESOURCES:

Mountain Plains AIDS Education and Training Centers HIV & Hepatitis Resources

www.mpaetc.org

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

AIDS Education and Training Centers National Resource Center

www.aids-ed.org

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

AIDSinfo

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.

The American Association for the Study of Liver Diseases

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/

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

Clinical Care Options

www.clinicalcareoptions.com

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

Hep C Connection

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 help-line (1-800-522-HEPC).

Hepatitis Resource Network (HRN)

www.h-r-n.org

A non-profit alliance for research, prevention, and treatment. HRN provides a variety of education opportunities including printed materials, and presentation support.

HIV and Hepatitis.com

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.ucsf.edu/hivcntr

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

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

Developed to improve the quality of healthcare in the U.S.; 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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**Developed by Mountain Plains
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