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Clinician's Guide to **HIV & HEPATITIS**

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CLINICIAN'S GUIDE TO HIV & HEPATITIS • 2013

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As better treatments allow HIV¹-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 of the management of viral hepatitis for 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.

¹HIV is used throughout this document to refer to HIV-1, the most common HIV strain in the United States.

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TABLE 1. HEPATITIS A THROUGH E: MODES OF TRANSMISSION AND SYMPTOMS OF ACUTE AND CHRONIC INFECTION IN PATIENTS INFECTED WITH HIV

Viral Hepatitis Type	Mode of Transmission	Symptoms of Acute Infection	Symptoms of Chronic Infection in HIV
HAV & HEV Infection	Fecal-oral route	Elevated liver enzymes (ALT) with fever, jaundice, anorexia, nausea, vomiting and malaise. Aggressive liver disease has been described with HEV in HIV-infected patients	HAV - No chronic infection. HEV – Chronic HEV infection has been described in transplant recipients taking immunosuppressive drugs.
HBV & HDV Infection	Contact with infected blood or body fluids (e.g., sexual activity, IDU, vertical [mother to neonate] or perinatal transmission, or occupational exposures)	Ranges from asymptomatic infection 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 go unnoticed until the onset of ESLD including jaundice, hepatomegaly, splenomegaly, ascites, coagulopathy, caput medusa, palmar erythema, variceal bleeding, hepatic encephalopathy or HCC. Extra-hepatic manifestations include polyarteritis nodosa, other vasculitides and glomerulonephritis. Delta hepatitis (HDV) may complicate HBV infection and contribute to more severe disease.
HCV Infection	Contact with infected blood or body fluids (e.g., IDU, vertical transmission, and possible sexual activity)	The majority of patients will be asymptomatic. Rarely, acute hepatitis can present with fever, jaundice, anorexia, nausea, vomiting and malaise.	Approximately 25% of HIV-infected persons are co-infected with HCV. In HIV/HCV co-infected persons, more than 80% with acute infection will develop chronic HCV. Often asymptomatic with the 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. Extra-hepatic manifestations: autoimmune thyroiditis, leukocytoclastic vasculitis, porphyria cutanea tarda, membranous nephritis and mixed cryoglobulinemia.

Note. HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D (delta) virus; HEV = hepatitis E virus; IDU = injection drug use; ALT = alanine transaminase; ESLD = end-stage liver disease; HCC = hepatocellular cancer

HIV & 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, participation in sexual practices involving anal/oral contact, travelers to areas where HAV is prevalent, injection drug users (IDU), and those in institutions, such as rehabilitation centers, nursing homes, day care centers, and military barracks.

Symptoms and Clinical Presentation

- Symptoms appear 2-6 weeks after exposure
- Fatigue
- Nausea and vomiting
- Fever
- Anorexia
- Right upper quadrant pain
- Dark urine
- Light-colored stools
- Jaundice
- Pruritus
- See Table 2 for diagnostic tests for HAV

Treatment

- HAV is usually self-limited, but supportive care is indicated.
- Contacts of an infected individual may require treatment with immune globulin and HAV vaccine.

TABLE 2. TESTS FOR DIAGNOSIS OF HEPATITIS A INFECTION

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

Note. HAV = hepatitis A virus; IgM = immunoglobulin M; IgG = immunoglobulin G

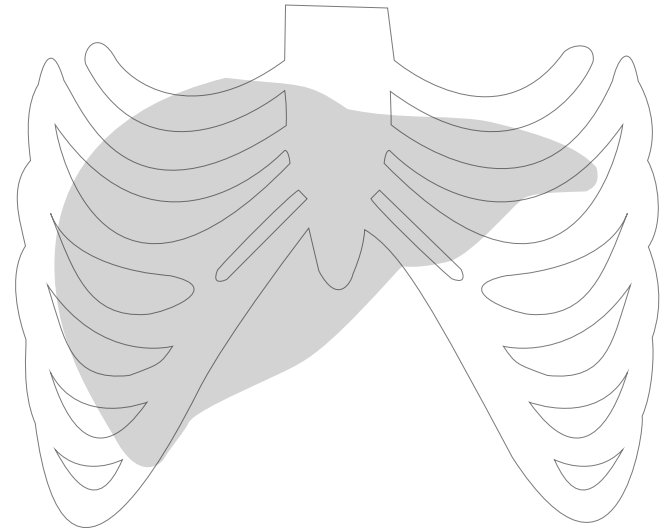
Patient Teaching

- Review the importance of proper hand washing.
- HAV can survive outside the body for months.
- Remind patient to avoid potentially contaminated foods, including shellfish.
- Extremely high temperatures kill the virus.
- 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, the second dose 6 months or more after the first dose. HAV is commonly administered with HBV vaccine.
- Administration of HAV vaccine when the CD4+ T cell count is > 200 cells/mm³ improves the likelihood of response.
- HAV immune serum globulin and Hepatitis A vaccine should be given as soon as possible after known HAV exposure for post-exposure prophylaxis. Post-exposure prophylaxis is most effective when administered within two weeks of exposure.

- In patients who have received HAV vaccine, hepatitis A antibody testing (total anti-HAV) should be drawn to document seroconversion.
- In patients who have received HAV vaccine and remain seronegative, the series should be repeated.
- Natural or acquired immunity is usually life-long.
- Receiving an extra dose of the hepatitis A vaccine is not harmful.
- Additional information on the hepatitis A vaccine can be accessed at:
<http://www.cdc.gov/vaccines/pubs/vis/downloads/vis-hep-a.pdf>



HIV & HEPATITIS B & HEPATITIS D

Overview

- Worldwide, 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 (HBsAg).
- Patients with HIV and HBV have an increased risk for liver-related morbidity and mortality. The Multicenter AIDS Cohort Study (MACS) found an 8-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.
- Acute liver failure from severe acute hepatitis B is rare but can result in death or need for liver transplantation.
- Hepatitis D (delta) is due to an incomplete RNA virus that requires HBsAg to complete its life cycle – that is why hepatitis D only occurs in patients who are also infected with HBV and express HBsAg. Co-infection with HDV is associated with more severe acute and chronic infection and higher risk for HCC.
- Fulminant hepatic failure is rare and may be associated with superimposed delta hepatitis virus (HDV) infection.

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

Prevention of Disease

- HBV vaccine is recommended for all HIV-infected adults.
- HBV vaccine efficacy is improved with a CD4+ Tcell count > 200 cells/mm³.
- 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 HIV co-infected patients.
- Vaccination in individuals with immunocompromising conditions, such as HIV infection, is recommended using a 3- or 4-dose series, either with 40 µg/mL of Recombivax HB on a 3 dose schedule (at 0, 1, and 6 months), or alternately, a 4-dose schedule using 20 µg/mL of Engerix-B, to be given on a schedule of 0, 1, 2, and 6 months.
- HBV immune serum globulin is recommended within 2 weeks after known HBV exposure if not previously immune.
- Behavior modification and risk reduction counseling to decrease contact with infected or other bodily fluids (i.e., not sharing drug-using equipment and using condoms during sexual intercourse) should be offered in all cases.

Screening and Initial Evaluation

- Initial laboratory screening tests for HBV include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb).
- Additional serologic testing for HBeAg, HBeAb, and HBV DNA levels should be ordered in persons with evidence of acute or chronic HBV infection. Anti-HDV testing is recommended for persons from regions of the world endemic for HDV, such as the Mediterranean and sub-Saharan Africa.
- A positive HBcAb may indicate (a) active infection; (b) previous infection with loss of HBsAb, especially in patients co-infected with hepatitis C virus (HCV); (c) a false positive result; or (d) the window period soon after acute infection and before anti-HBs emerges. Checking HBV DNA is recommended. Patients with isolated anti-HBcAb are at risk for reactivation of HBV infection during treatment with chemotherapy or while on immunosuppression after transplantation.
- Table 3 provides a guide to interpretation of these serologic tests.

TABLE 3. SEROLOGIC PATTERNS IN HBV INFECTION

Disease State	HBsAg	HBsAb	HBcAb IgG	HBcAb IgM	HBeAg	HBsAb
Incubating	+	-	-	-	+/-	-
Acute Hepatitis*	+/-	-	+/-	+	+/-	+/-
Chronic Carrier**	+	-	+	-	+/-	+/-
Chronic Hepatitis**	+	-	+	-	+/-	+/-
Resolved Hepatitis	-	+	+	-	-	-
Vaccine	-	+	-	-	-	-

Note. HBsAg = hepatitis B surface antigen; HBsAb = hepatitis B surface antibody; HBcAb IgG = immunoglobulin G antibody to hepatitis B core antigen; HBcAb IgM = immunoglobulin M antibody to hepatitis B core antigen; HBeAg = hepatitis B antigen; HBeAb = hepatitis B antibody

*The single most diagnostic test for acute hepatitis B is a positive anti-HBc-IgM.

**Chronic carriers have normal ALT and lack inflammatory or fibrotic changes on liver biopsy. Patients with chronic hepatitis usually have elevated ALT (not always) and liver biopsy shows active inflammation and various stages of fibrosis.

Treating the HIV/HBV Co-Infected Patient

Therapy should be individualized for the HIV/HBV infected patient. The treatment options for HBV in the setting of HIV are dictated, in part, by the choice of ART. Tenofovir is highly effective as monotherapy for HBV. If tenofovir is a component of the chosen ART, then no additional treatment may be needed for the HBV. However, if only lamivudine is a component of ART, then a second agent, such as tenofovir, is required for treating HBV. Treatment of hepatitis B and HIV infection is lifelong. HDV infection, complicating HIV/HBV co-infection, may not be adequately controlled by the antivirals against HBV. Peginterferon may be required to control HDV infection. Decisions regarding use of treatments for HIV/HBV coinfection and HDV require proper patient evaluation and assessment of multiple treatment options. **Expert consultation is recommended** (see Resources).

Goals of HBV Therapy

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

Treatment Recommendations

- Most chronic carriers (normal ALT on multiple determinations and normal liver biopsy) and patients with undetectable HBV DNA are not treated.
- Patients with chronic hepatitis and positive HBeAg or HBV DNA levels > 2 x 10⁴ copies/mL (> 20,000 IU/mL) should be treated.
- Patients with chronic hepatitis who are HBeAg-negative with HBV DNA levels > 2 x 10⁴ copies/mL (> 2,000 IU/mL) should be treated.
- Some experts defer therapy in patients with an ALT level < 2 times the upper limit of normal (ULN). Because ALT levels fluctuate widely, a long-term pattern is most useful. Sporadically, normal ALT levels are common, even in those with chronic hepatitis who may have a significant risk of progression, especially with HBV DNA levels > 10⁵ copies/mL.
- In patients infected with HBV, HCV, and HIV, ART is the first priority. ART should preferably include agents with activity against HBV. HBV can be treated effectively with monotherapy with either tenofovir or entecavir, although tenofovir may be preferred in the setting of HIV. The treatment of HCV is rapidly evolving given the recent advent of direct-acting antivirals specific for HCV. Current options include interferon and ribavirin with HCV-specific protease inhibitors. In the near future, interferon-free and possibly ribavirin-free treatments may be available. Selection of appropriate therapy for HCV will be individualized.

- Some experts recommend treating anyone with detectable HBV DNA whose liver biopsy demonstrates significant fibrosis, regardless of age.
- See Table 4.

HIV/HBV Co-Infection Treatment Considerations

- 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.

- Current recommendations are to use at least 2 drugs that are effective against HBV to avoid the development of 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. Similarly, if ART needs to be changed, two active agents against HBV need to remain.
- 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.

TABLE 4. EVALUATION AND STAGING OF CHRONIC HBV IN HIV-INFECTED PATIENTS

Test	Initially	Repeat every 6 months	Repeat every 6-12 months	Additional Considerations
HBeAg*	x			
HBeAb IgG*	x			
HAV screening	x			
HCV screening [¶]	x			x [¶]
HDV screening	x			
Liver transaminases [†]	x	x		
Albumin	x	x		
Prothrombin time	x	x		
Complete blood count	x	x		
Bilirubin	x	x		
Quantitative HBV DNA PCR	x	x		The frequency of testing depends on clinical status and treatments.
Alpha-fetoprotein [‡]	x		x	
Liver ultrasound [‡]	x		x	
Liver biopsy [§]				x [§]
Upper-GI endoscopy [¶]				x [¶]

Note. HBV = hepatitis B virus; HBeAg = hepatitis B antigen; DNA = deoxyribonucleic acid; PCR = polymerase chain reaction; GI = gastrointestinal

*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.

¶ Consider repeat screening in high-risk individuals.

†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 yet been determined, however it is recommended by many specialists, especially if the individual is ≥ 45 years of age, or has cirrhosis, fibrosis, or a family history of HCC. If the patient has advanced cirrhosis or fibrosis consider monitoring at intervals shorter than 6 months.

§A liver biopsy to define grade of inflammation and stage of fibrosis may be helpful in making decisions regarding therapy or for selecting patients for surveillance with ultrasound or CT for detection of hepatocellular carcinoma. In the future, noninvasive tests such as serum fibrosis tests, quantitative tests of liver function, or hepatic elastography may replace liver for staging.

¶If liver cirrhosis is present, consider an upper-GI endoscopy every 1-2 years to evaluate for esophageal varices in patients with cirrhosis.

TABLE 5. LICENSED ANTIVIRAL AGENTS FOR THE TREATMENT OF HBV

Test	Dose	Antiviral Activity	Considerations
adefovir dipivoxil** (Hepsera)	10 mg once daily	HBV	<ul style="list-style-type: none"> • Not as potent as other HIV drugs, and not recommended for treatment of HIV. • 12% HBeAg convert to anti-HBe antigen at 1 year in mono-infected HBV patients • At 10 mg daily active only against HBV • Due to similar toxicities, concomitant use of adefovir dipivoxil and tenofovir is not recommended • Active against lamivudine-resistant HBV
emtricitabine (Emtriva)	200 mg once daily	HBV, HIV	<ul style="list-style-type: none"> • 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 • Cross resistance with entecavir and telbivudine • Patients with lamivudine resistance will be cross-resistant to emtricitabine • Dose reduction required if creatinine clearance < 50 mL/min
entecavir (Baraclude)	0.5 mg once daily (lamivudine-naive) 1.0 mg once daily (lamivudine resistant)	HBV	<ul style="list-style-type: none"> • 21% HBeAg seroconversion after 1 year in HBV mono-infected patients • Cross resistance with emtricitabine and telbivudine • Partial HIV RT inhibitor, may select M184 HIV mutation • Do NOT use as a single agent. Due to development of potential drug resistance to other NRTIs, entecavir must be used in combination with 2 other NRTIs active against HIV; entecavir is not indicated for HIV treatment. • Dose reduction required if creatinine clearance < 50 mL/min
pegylated IFN alfa-2a (pegIFN) (Pegasys)	180 mcg SQ weekly	HBV, HCV	<ul style="list-style-type: none"> • HBV: Most effective in patients with high ALT and relatively low HBV DNA blood levels • pegIFN should generally not be used for patients with decompensated liver disease • Most effective in HBV genotypes A and B • Most effective in HCV genotypes 2 and 3 • The combination of lamivudine and pegIFN is currently not recommended • See HCV section on side effects • Avoid in pregnancy
lamivudine (Epivir)	150 mg twice daily	HBV, HIV	<ul style="list-style-type: none"> • HBeAg seroconversion rate 16-18% after 1 year in mono-infection • The combination of lamivudine and pegIFN is currently not recommended • 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 • Dose reduction required if creatinine clearance < 50 mL/min
telbivudine** (Tyzeka)	300 mg once daily	HBV	<ul style="list-style-type: none"> • Not as potent as tenofovir or entecavir • Monotherapy not recommended • Patients with lamivudine resistance will have cross-resistance to telbivudine and emtricitabine • Dose reduction required if creatinine clearance < 50 mL/min

tenofovir (Viread)		HBV, HIV	<ul style="list-style-type: none"> • Potent agent: average 5-log decrease in HBV DNA • Effective in lamivudine-experienced patients • Low rate of resistance after 1 year • Associated with decreased bone density in HIV-infected patients • 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 • Due to similar toxicities, concomitant use of adefovir dipivoxil and tenofovir is not recommended • Dose reduction required if creatinine clearance < 50 mL/min
Fixed Dose Combination			
tenofovir/ emtricitabine (Truvada)	300 mg once daily	HIV, HBV	See information listed under individual components.

Note. HBV = hepatitis B virus; HBeAg = hepatitis B e antigen; NRTI = nucleoside reverse transcriptase inhibitor; IU = international units; ALT = alanine aminotransferase; IFN = interferon; HCV = hepatitis C virus; pegIFN = pegylated interferon; SQ = subcutaneous; BID = twice daily; ART = antiretroviral therapy

** Some studies suggest activity against HIV

- Indefinite continuation of HBV treatment is usually required because 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 identified cause of these elevations, discontinuation of these medications is recommended.
- See Table 5 for an overview of medications used to treat HBV.

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 treatment for HBV, monitor liver function tests (LFTs).
- If a flare occurs when discontinuing anti-HBV therapy, then anti-HBV therapy should be reinstituted.
- 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 2 years after eAg to eAb seroconversion, documenting HBV DNA has been continually suppressed.
- Recommended length of treatment depends on the anti-HBV agent. Peginterferon is typically 12 months, and nucleoside/nucleotide therapy is typically life long. 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 concurrent nucleosides/nucleotides active against HBV is optimal to prevent drug resistance.
- HBV flares may occur when 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 pegylated interferon (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 serologically. The goal of therapy is suppression of HBV DNA and delay of progression of liver injury.

Markers of Virologic Response and Sustained Virologic Response

- **Virologic response** – during treatment, achieving undetectable HBV DNA and loss of HBeAg and development of HBeAb at the end of treatment. Rarely, patients may lose HBsAg and develop HBsAb.
- **Sustained virologic response (SVR)** – after discontinuing treatment, maintenance of undetectable HBV DNA and negative HBeAg 6 months or more after treatment is stopped. Although rare, loss of HBsAg with development of HBsAb can occur.
- **Other markers of response** – improved liver histology, improved hepatic transaminases and the development of anti-HBe if HBeAg is lost.

Seek Expert Consultation in the Following Areas:

- Pregnancy
- Drug resistance
- Advanced cirrhosis
- Transplantation

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.
- Review the importance of not stopping medications without first discussing with medical provider. Reiterate the potential of a liver flare if medications are stopped.

HIV & HEPATITIS C

Transmission of HCV

- HCV is primarily transmitted via blood to blood contact. Sexual and perinatal transmissions are less common, although the risk of both vertical and sexual transmission is higher in HIV co-infected patients and patients at risk (see below).
- Risk factors for acquisition of HCV include blood transfusion prior to 1992, receiving clotting factor prior to 1987, hemodialysis, sharing personal care items such as razors and nail clippers 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 sex practices (anal sex, fisting, douching, or enema prior to sex) may increase the risk of transmission.
- Perinatal exposure to HCV is more common among HIV/HCV co-infected individuals. Additionally, some studies have demonstrated an increased risk of HIV vertical transmission and in women co-infected with HIV/HCV. Breastfeeding has not been determined to transmit HCV infection.

Prevention of Disease

- Avoid contact with known HCV-infected blood.
- Do not share dental equipment, including tooth brushes, with a known HCV-infected person.
- Use clean works to inject drugs. Do not share rinse water or cotton.
- Universal precautions should be used when there is potential for contact with blood or blood products.
- HCV-infected individuals should be counseled regarding methods to avoid potential transmission to others.

Screening and Initial Evaluation

The CDC currently recommends testing for any individual born between 1945-1965, the so-called baby boomers.

Other identifiable risk factors for exposure to HCV that indicate a need for screening, include:

- All HIV-infected patients
- Anyone with a history of IDU
- Anyone with a history of drug use with a straw (for snorting) or pipe (for smoking)
- Long-term hemodialysis patients
- Anyone who had a blood transfusion or organ transplantation prior to 1992, or who used clotting factor prior to 1987
- Anyone with a history of hemophilia
- Infants born to HCV-infected mothers
- Anyone who obtained body piercings or tattoos without proper sterilization
- Any individual with a known exposure to HCV
- Sexual partners of known HCV-infected individuals
- Individuals with history of occupational exposure (secondary to percutaneous injury or mucosal exposure to HCV-infected source)
- Patients with unexplained elevated liver function enzymes
- See Figure 1 for an overview of the HCV testing process, Table 6 for a review of HCV testing interpretation, and Table 7 for initial screening and evaluation.

Treating the HIV/HCV Co-Infected Patient

Therapy should be individualized. A multi-disciplinary team approach incorporating physicians, nurse practitioners, nurses, and pharmacists trained in HCV treatment with frequent psychiatric consultation is helpful. The team should also include mental health professionals, social workers, and case managers, because psychosocial and economic issues may be more frequent in HIV/HCV co-infected clients. Evaluation for treatment should include consideration of the following:

- Hepatitis C RNA
- Hepatitis C genotype
- Degree of impaired immunity related to HIV
- Current ART and past resistance patterns
- Mental health evaluation
- Access to direct-acting antivirals for hepatitis C
- Willingness of the patient to adjust the HIV regimen as needed to avoid drug-drug interactions
- Readiness and capability of the patient to commit to intensive medication regimens, requiring frequent monitoring and specific dosing of medications, with potentially significant side effects to therapy.

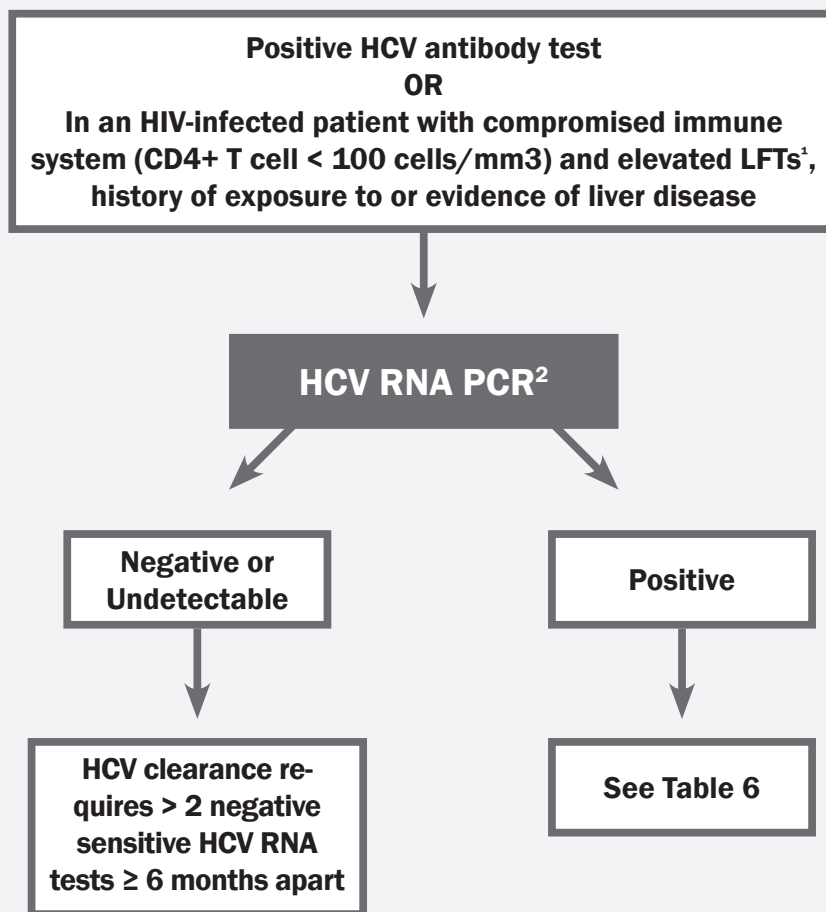
TABLE 6. INTERPRETATION OF HCV SEROLOGIC TESTING

Hep C Ab	HCV RNA	Disease state and interpretation
Positive	Positive	Acute or chronic HCV infection. Clinical correlation is needed.
Positive	Negative	Evidence of exposure to HCV and clearance of viremia either spontaneously or post-treatment, and requires repeat testing in 4-6 months; may also represent acute HCV infection.
Negative	Positive	Acute HCV infection; may also represent chronic HCV infection in an immunosuppressed state; may be false positive.
Negative	Negative	HCV infection is absent.

Note. HCV = hepatitis C infection; Ab = antibody; RNA = ribonucleic acid

Table adapted from: Ghany, M. G., Strader, D. B., Thomas, D. L., & Seeff, L. B. (2009). Diagnosis, management, and treatment of Hepatitis C: An update. *Hepatology*, 49(4), 1335-1374. doi:10.1002/hep.22759

FIGURE 1. INITIAL HCV SCREENING AND EVALUATION IN THE HIV-INFECTED PATIENT



Note. LFT = liver function test; HCV = hepatitis C virus; RNA = ribonucleic acid;

PCR = polymerase chain reaction

¹HIV-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

²HCV RNA is usually detectable within 2 weeks of an exposure

TABLE 7. INITIAL HCV SCREENING AND EVALUATION WITH A POSITIVE HCV RNA PCR TEST

Positive HCV RNA PCR test
Obtain CBC, hepatic function panel, hepatitis A & B profiles, basic metabolic panel, PT, PTT, ANA, HCV genotyping, pregnancy test when appropriate. HCV genotyping is needed to determine optimal treatment regimens, predicted success of treatment, and duration of therapy.
Consider liver biopsy to assist with treatment decisions. Screen for HCC with serum alfa-fetoprotein and abdominal ultrasound every 6 months in patients with cirrhosis.
Provide patient education about transmissibility of HCV, natural history of HCV infection, significance of test results and option for liver biopsy (prognosis and assistance with treatment recommendations), treatment overview and current options, teach to abstain from alcohol, refer for more intense alcohol use treatment as needed.
Provide vaccinations for hepatitis A and B if needed.
Evaluate for HCV treatment ¹ by considering patient goals (long-term considerations, concerns about transmission), history (symptomatology, last negative HCV test, likely duration of disease (to determine acute vs. chronic infection), 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). Obtain a thorough history including other medical issues, other causes of liver disease ² (autoimmune disease, seizure disorder, thyroid abnormalities, diabetes, cardiac disease, renal disease, hematologic abnormalities, pulmonary disease), and psychosocial screening.
Evaluate 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 2nd therapy. Before starting HCV treatment, consider HIV disease stability and current ART issues (i.e., side effects, adherence). Consider ART first to increase CD4+ T cell count and improve response to HCV therapy.

Note. HCV = hepatitis C virus; RNA = ribonucleic acid; PCR = polymerase chain reaction; CBC = complete blood count; PT = prothrombin time; PTT= partial thromboplastin time; ANA = antinuclear antibody panel;

HCC = hepatocellular cancer; ART = antiretroviral therapy

¹Treatment 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.

²Rule out other causes of liver disease including serum hemochromatosis, (serum iron, total iron binding capacity [TIBC]) in all patients, autoimmune hepatitis, Wilson's disease, and alfa-1 antitrypsin deficiency as individually indicated.

Goals of HIV/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
- Decrease risk of progressive liver disease, such as cirrhosis and HCC
- Decrease risk of extrahepatic diseases associated with HCV infection
- *Individuals with evidence of spontaneous clearance of HCV virus remain at a greater risk for the development of HCC and should still undergo regular screening for HCC with alfa-fetoprotein and ultrasound.*
- Current treatment guidelines lack consensus regarding the influence of factors such as HCV viral load, genotype, degree of impaired immunity from co-infection with HIV, or how the presence of fibrosis should determine who to treat and when to start treatment.

HIV/HCV Treatment Recommendations

- Studies have demonstrated an improved SVR in HIV-infected patients with HCV genotype 1 when treated with a combination of pegIFN, oral ribavirin (RBV) and a direct-acting antiviral (DAA), such as telaprevir (TPV) or boceprevir (BOC).
- DAAs should never be given as monotherapy, as resistance can develop quickly and lead to virologic failure.
- HIV-infected patients with HCV genotype 2 or 3 exhibit a 43-73% SVR with pegIFN and oral RBV.

Treatment Recommendations

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

- Low HCV viral load and CD4+ T cell counts > 500 cells/mm³ may improve response to treatment. Thus, consider initiating HCV treatment when the CD4+ T cell count is > 500 cells/mm³, or initiating ART prior to HCV treatment when the CD4+ T cell count is < 500 cells/mm³.
- Patients with insulin resistance, older age, black race, male sex, advanced fibrosis and high body mass index (BMI) have lower rates of SVR.
- HCV treatment is contraindicated in decompensated liver disease unless the patient is under the close supervision of a hepatologist.
- Adverse effects to HCV treatment, including decreased white and red blood cells, severe depression, and lactic acidosis, are more common in co-infected patients.
- Barriers to access of medications, including lack of insurance and cost of the medications, should be considered 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-drug interactions, provide adherence counseling, and warn about CD4+ T cell 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 ddI 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.
 - Telaprevir can only be safely used with one protease inhibitor (PI) regimen, boosted atazanavir, or with efavirenz, though dosing may need to be adjusted.
 - Boceprevir (BOC) cannot be used with PI regimens, or with efavirenz.
 - Use of tenofovir/emtricitabine or lamivudine or abacavir/lamivudine remains the favorable nucleoside reverse transcriptase inhibitor (NRTI) backbone.
 - Raltegravir has a demonstrated safety profile with concurrent use of TVR or BOC.
- Immune reconstitution that results from ART may result in a flare of hepatitis.
- For 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 treatment of HCV is determined by absence of Hepatitis C RNA by PCR 3 months or more post-treatment.
- Successful HCV treatment may reduce risk of current or future ART-related hepatotoxicity.

Duration of Treatment

- **Duration of treatment is dependent on HCV genotype, type of anti-HCV therapy and viral response to treatment.**
- Acute HCV infection (> 6 months duration) in individuals who do not spontaneously clear the virus within 12 weeks should be treated for ≥ 24 weeks with pegIFN with or without 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.
- Response to treatment can be determined by normalization of ALT, virologic response as demonstrated by HCV RNA, and evidence of histologic stability or improvement.
- 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).

Direct-Acting Antiretrovirals in the HIV/HCV-Infected Patient

- **Current guidelines are for HCV-monoinfection only.**
- Significant drug interactions exist between ART and DAAs.
- Optimal therapy for chronic HCV infection, genotype 1 should include peginterferon alfa and ribavirin, in addition to either boceprevir (BOC) or telaprevir (TVR).
- The only approved treatment for non-1 genotypes of HCV is the combination of peginterferon plus ribavirin.
- BOC and TVR should never be given as monotherapy for treatment of HCV infection.

- Dosing of DAAs and ART may need to be adjusted dependent on chosen regimens and responses to treatment.
- Drug interactions with ART can lead to low DAA drug concentration levels, as can non-adherence, and has the potential for treatment failure and the development of drug class resistance.

Role of the Specialist

- Whenever possible, consult, refer to, and/or co-manage with clinicians who have expertise 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.
- For patients with HCV genotype 1 infection, the combination of stage of liver fibrosis and interferon responsiveness defines the likelihood of SVR with triple therapy (peginterferon/ribavirin with either boceprevir or telaprevir). Patients with a low stage of fibrosis (METAVIR 0-2) who are sensitive to interferon (IL28B CC, 1 log₁₀ drop in HCV RNA during lead-in with peginterferon/ribavirin, or relapse after prior peginterferon/ribavirin) have a sustained virologic response approaching 90%. In contrast, patients with cirrhosis who demonstrated a null response to prior peginterferon/ribavirin have a sustained virologic response of 15%.

- The high response rate of genotypes 2 & 3 may justify offering treatment without a liver biopsy. However, knowledge of cirrhosis may still be useful for HCC surveillance decisions irrespective of the treatment decision.
- For those who defer therapy or for whom therapy is unsuccessful, a 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, is 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 with treatment of HCV/HIV co-infected patients with a history of severe depression or suicidal tendencies. Interferon has been associated with a risk of drug relapse among IDU. RBV is teratogenic in animal studies; patient or patient's partner(s) should avoid pregnancy during therapy and for 6 months after completion of therapy.

TABLE 8. 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	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

*Batts, K.P., & Ludwig J. (1995). Chronic hepatitis. An update on terminology and reporting. *American Journal of Surgical Pathology*, 19(12), 1409-1417.

Genotype 1

Recommendations for treatment-naïve patients with HCV genotype 1 consists of a direct-acting antiviral, either boceprevir (BOC) or telaprevir (TVR), in combination with peginterferon alfa (pegIFN) and ribavirin (RBV). *Recommendations are currently for HCV mono-infected individuals.*

TABLE 9A. USE OF BOCEPREVIR + PEGINTERFERON ALFA + RIBAVIRIN FOR TREATMENT OF HCV GENOTYPE 1 IN TREATMENT NAÏVE PATIENTS						
Prior to initiation of therapy	Week 1-4 (4-week lead-in therapy)	Week 4	Week 8	Week 12	Week 24	Week 48
<ul style="list-style-type: none"> • HCV genotype • HCV RNA • HIV baseline labs (CD4, HIV viral load) • Baseline CBC • Baseline CMP 	pegIFN alfa 2b + Weight-based RBV	Add BOC 800 mg TID with food + PegIFN + weight-based RBV	<p>Recheck HCV RNA If HCV RNA is undetectable at week 8, continue BOC + pegIFN + RBV for 24 weeks, total of 28 weeks with lead-in therapy.</p> <p>If HCV RNA is detectable at week 8-24, continue BOC + pegIFN + RBV for 44 weeks; a total of 48 weeks with lead-in therapy</p>	<p>Recheck HCV RNA If HCV RNA level >100 IU/mL at week 12, discontinue all treatment.</p>	<p>Recheck HCV RNA If undetectable HCV RNA at both weeks 8 and 24, may consider shortened duration of treatment (4 week lead-in with PegIFN + RBV followed by 24 weeks of BOC + PegIFN + RBV)</p> <p>If HCV RNA is detectable at week 24, discontinue treatment with all three drugs.</p>	<p>Discontinue BOC + PegIFN + RBV</p> <p>Recheck HCV RNA</p>

Note. CBC = complete blood count; CMP = comprehensive metabolic panel; pegIFN = pegylated interferon; BOC = boceprevir; TID = 3 times a day; RBV = ribavirin; RNA = ribonucleic acid
The duration of treatment using boceprevir (BOC) in treatment-naïve patients without cirrhosis is determined by response to therapy.

TABLE 9B. USE OF BOCEPREVIR + PEGINTERFERON ALFA + RIBAVIRIN FOR TREATMENT OF HCV GENOTYPE 1 IN PATIENTS WITHOUT CIRRHOSIS WHO ARE PREVIOUS PARTIAL RESPONDERS OR RELAPSE TO INTERFERON AND RIBAVIRIN THERAPY

Prior to initiation of therapy	Week 1-4 (4-week lead-in therapy)	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48
<ul style="list-style-type: none"> • HCV genotype • HCV RNA • HIV baseline labs (CD4, HIV viral load) • Baseline CBC • Baseline CMP 	PegIFN alfa 2b + Weight-based RBV	Add BOC to treatment, continue pegIFN + RBV Add BOC 800 mg TID with food + PegIFN + weight-based RBV	Recheck HCV RNA If HCV RNA is undetectable at week 8, continue BOC + pegIFN + RBV for 32 weeks, total of 36 weeks with lead-in therapy. If HCV RNA is detectable at week 8-24, continue BOC + pegIFN+RBV for 36 weeks, then continue with pegIFN + RBV for 44 weeks, for a total treatment time of 48 weeks.	Recheck HCV RNA If HCV RNA level >100 IU/mL at week 12, discontinue all treatment.	Recheck HCV RNA If undetectable HCV RNA at both weeks 8 and 24, may consider shortened duration of treatment (4 week lead-in with PegIFN+RBV followed by 24 weeks of BOC+PegIFN+RBV) If HCV RNA is detectable at week 24, discontinue treatment with all three drugs.	Recheck HCV RNA If undetectable HCV RNA at both weeks 8 and 24, discontinue treatment with BOC + pegIFN + RBV at week 32, for a total treatment time of 36 weeks.	Recheck HCV RNA Discontinue BOC + PegIFN + RBV

Note. CBC = complete blood count; CMP = comprehensive metabolic panel; pegIFN = pegylated interferon; BOC = boceprevir; TID = 3 times a day; RBV = ribavirin; RNA = ribonucleic acid

TABLE 10A. USE OF TELAPREVIR + PEGINTERFERON ALFA 2A + RIBAVIRIN FOR TREATMENT OF HCV GENOTYPE 1 IN TREATMENT NAÏVE PATIENTS

Prior to initiation of therapy	Week 1-4	Week 4	Week 12	Week 24-28	Week 48
<ul style="list-style-type: none"> • HCV genotype • HCV RNA • HIV baseline labs (CD4, HIV viral load) • Baseline CBC • Baseline CMP 	Recheck HCV RNA Initiate treatment with TVR 750 mg TID with fatty meal + pegIFN alfa 2a + weight-based RBV	Recheck HCV RNA Continue TVR 750 mg TID with food + PegIFN alfa 2a + RBV	Recheck HCV RNA If HCV RNA level is undetectable at weeks 4 and 12, may be considered for shortened duration of treatment: TVR + pegIFN + RBV for 12 weeks followed by 12 weeks of pegIFN + RBV (24 weeks in total). If HCV RNA level >1000 IU/mL, treatment should be discontinued. If HCV RNA level is <1000 IU/mL and not undetectable, continue with pegIFN + RBV for an additional 36 (48 weeks in total).	Recheck HCV RNA If HCV RNA is undetectable and patient does not have cirrhosis, discontinue treatment.	Recheck HCV RNA Discontinue PegIFN alfa 2a + RBV.

Note. CBC = complete blood count; CMP = comprehensive metabolic panel; TVR = telaprevir; pegIFN = pegylated interferon; TID = 3 times a day; RBV = ribavirin; RNA = ribonucleic acid

TABLE 10B. USE OF TELAPREVIR + PEGINTERFERON ALFA 2A + RIBAVIRIN FOR TREATMENT OF HCV GENOTYPE 1 IN PRIOR PARTIAL AND NULL RESPONDER PATIENTS

Prior to initiation of therapy	Week 1-4	Week 4	Week 12	Week 24	Week 48
<ul style="list-style-type: none"> • HCV genotype • HCV RNA • HIV baseline labs (CD4, HIV viral load) • Baseline CBC • Baseline CMP 	Recheck HCV RNA Initiate treatment with TVR 750 mg TID with fatty meal for 12 weeks + pegIFN alfa 2a + weight-based RBV	Recheck HCV RNA Continue TVR 750 mg TID with food + pegIFN alfa 2a + RBV If HCV RNA level >1000 IU/mL, treatment should be discontinued.	Recheck HCV RNA Discontinue treatment with TVR. Continue treatment with pegIFN alfa 2a + RBV If HCV RNA level >1000 IU/mL, treatment should be discontinued.	Recheck HCV RNA If HCV RNA is detectable, treatment should be discontinued.	Recheck HCV RNA Discontinue PegIFN alfa 2a + RBV.

Note. CBC = complete blood count; CMP = comprehensive metabolic panel; TVR = telaprevir; pegINF = pegylated interferon; TID = 3 times a day; RBV = ribavirin; RNA = ribonucleic acid

TABLE 11A. MEDICATION DOSING OF PEGINTERFERON IN HIV/HCV CO-INFECTED INDIVIDUALS

Strength	Dosage	Frequency	Special Considerations
<i>Vial for single use: 180 mcg/0.5 mL</i> <i>Pre-filled syringe for single use: 180 mcg/0.5 mL</i> <i>Autoinjector for single use: 180 mcg/0.5 mL or</i> <i>Autoinjector for single use: 135 mcg/0.5 mL</i>	180 mcg/0.5 mL via subcutaneous injection	weekly	Review injection site preparations and recommendations

Note. All current regimens recommended for treatment of Hepatitis C include the use of peginterferon and ribavirin.

TABLE 11B. MEDICATION DOSING OF RIBAVIRIN IN HIV/HCV CO-INFECTED INDIVIDUALS

Strength	Dosage	Frequency	Special Considerations
Copegus® 200 mg tablets	Copegus® 400 mg	Twice daily for total dose of 800 mg	Take with food, in combination with pegIFN therapy

Note. pegINF = pegylated interferon.

All current regimens recommended for treatment of Hepatitis C include the use of peginterferon and ribavirin.

Current dosing recommendations are based on HCV genotype and use of response-guided therapy (RGT).

Patients at extremes of weight may require individualized dosing. Dosing will need to be modified if severe adverse reactions or laboratory abnormalities develop and persist.

TABLE 12A. MEDICATION DOSING OF BOCEPREVIR			
Strength	Dosage	Frequency	Special Considerations
Victrelis® 200 mg capsules	Victrelis® 800 mg	TID, or every 7-9 hours, for total dose of 2400 mg	Take with food

Note. TID = 3 times a day

TABLE 12B. MEDICATION DOSING OF TELAPREVIR			
Strength	Dosage	Frequency	Special Considerations
Incivek™ 375 mg tablets	Incivek™ 750 mg	TID, or every 7-9 hours, for total dose of 2250 mg	Take with meal, recommended to contain at least 20 grams fat

Note. TID = 3 times a day

TABLE 13. 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	q4 wks
Hepatic function and basic metabolic panels	X		X	X	X	X	X	X	q4 wks
HCV RNA	X				X ¹			X ²	q12 wks
HIV RNA and CD4+ T cell profile	X				X ⁴			X ²	q12 wks
TSH	X				X			X	q12 wks
Lipids	X								q24 wks
Depression	X	X	X	X	X	X	X	X	on-going
Ophthalmologic exam	X ⁵				X			X	q3 months
PT/INR	X				X			X	q12 wks
Pregnancy Test	Perform at regular intervals if appropriate								

Note. CBC = complete blood count; RNA = ribonucleic acid; PT/INR = prothrombin time and international normalized ratio

¹Those 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 months 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).

²If undetectable HCV RNA at 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.

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

⁴Anticipate decrease in absolute cell count but stable CD4%.

⁵Interferon (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 and monitor for disturbances in vision and loss of color perception.

TABLE 14A. PEGINTERFERON (pegIFN): MANAGEMENT OF ADVERSE EFFECTS*

Side Effects	Interventions
Influenza-like symptoms	<ul style="list-style-type: none"> • NSAIDs can help relieve flu-like symptoms if administered prophylactically.
Depression Emotional lability	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Consider G-CSF 300 mcg SC weekly and titrate to maintain ANC $\geq 750/\text{mm}^3$. INF dose reduction may ultimately be required.**
Thrombocytopenia***	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Patients should be encouraged to report any changes in vision. • Refer to ophthalmologist, discontinue treatment.
Respiratory problems with pulmonary infiltrates of unknown origin	<ul style="list-style-type: none"> • 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, and counsel accordingly. • 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	<ul style="list-style-type: none"> • 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 dietician.
Diarrhea	<ul style="list-style-type: none"> • Encourage use of over-the-counter medications when appropriate. Prescribe antidiarrheal medications as needed.
Alopecia	<ul style="list-style-type: none"> • Warn patient in advance and reiterate that hair loss is reversible, most hair will grow back after treatment.
Neuropathy	<ul style="list-style-type: none"> • Warn about possible occurrence.
Hearing loss	<ul style="list-style-type: none"> • Provide patient with list of signs and symptoms. Provide clear information about contacting the provider/clinic when symptoms occur.
Thyroid dysfunction	<ul style="list-style-type: none"> • Provide patient with list of signs and symptoms. Provide clear information about contacting the provider/clinic when symptoms occur.

Note. G-CSF = granulocyte colony-stimulating factor; SC = subcutaneous; ANC = absolute neutrophil count; INF = interferon

*pegIFN 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 people with hemophilia, management should be in collaboration with hematology.

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

TABLE 14B. RIBAVIRIN (RBV) MANAGEMENT OF ADVERSE EFFECTS*

Side Effects	Interventions
Dose-dependent hemolytic anemia, associated with indirect hyperbilirubinemia and related fatigue and exercise intolerance	Hgb needs to be monitored regularly. <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.
Insomnia	Take RBV at least 3 hours before going to bed.
Rash, dry pruritic skin	Steroid cream may be used for localized rash and pruritis. Recommend skin moisturizers.
Non-cardiac chest pain Dry cough Dyspnea	Warn about possible occurrence, provide with list of signs and symptoms, and provide clear information about contacting the provider/clinic when symptoms occur.

Note. Hgb = hemoglobin; HCV = hepatitis C virus; RBV = ribavirin; SC = subcutaneous; PRN = as needed;

*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 or insemination during therapy and for 6 months after completion.

TABLE 14C. BOCEPREVIR (BOC): MANAGEMENT OF ADVERSE EFFECTS

Side Effects	Interventions
Anemia	Hgb needs to be monitored at regular intervals, at weeks 4, 8, 12. <ul style="list-style-type: none">• If Hgb is <10 g/dL, decrease dosage of BOC• If Hgb is <8.5 g/dL, discontinuation of BOC is recommended
Dysgeusia	Take with food.
Nausea	Prescribe PRN anti-nausea medications.
Fatigue	Encourage rest and energy conservation; evaluate for cause (i.e., anemia).
Hypersensitivity reaction	Example: urticaria, angioedema. Patients should be counseled about warning signs and symptoms requiring urgent evaluation. Discontinuation of BOC should be determined on a case-by-case basis.
Neutropenia	Monitor with complete blood counts at week 4, 8, 12.
Pregnancy	Pregnancy category X: Patients on BOC treatment must have a negative pregnancy test prior to the start of treatment and counseled to use at least 2 forms of contraception.

Note. Hgb = hemoglobin; BOC = boceprevir; PRN = as needed d for 6 months after completion.

TABLE 14D. TELAPREVIR (TVR): MANAGEMENT OF ADVERSE EFFECTS

Side Effects	Interventions
Anemia	<ul style="list-style-type: none"> • Hgb should be monitored at weeks 2, 4, 8, and 12 of TVR treatment. • Anemia is reversible upon the end of treatment with TVR. • Consider an erythropoiesis-stimulating agent (ESA). • Consider a dose reduction of RBV per RBV prescribing information guidelines. • If response to dose reduction of RBV is insufficient, consider discontinuation of TVR. • TVR should not be dose-reduced or restarted after discontinuation.
Anorectal signs and symptoms	<ul style="list-style-type: none"> • Counsel patients that hemorrhoids, anal pruritis, and rectal burning are common with TVR. Anyone with these symptoms should be evaluated with a rectal examination. • Consider use of oral antihistamines. • Consider use of local anesthetic. • Limit sun and heat exposure. • Avoid tight-fitting clothing. • Consider lipid-rich lotions, emollient creams, moisturizers to be applied to entire body daily for prophylactic skin care. • Consider use of topical steroids as needed.
Nausea	<ul style="list-style-type: none"> • Prescribe PRN anti-nausea medications.
Rash or skin reaction	<p>Skin reactions are most common in the first 4 weeks of treatment, although can occur at any time in the course of treatment. Patients should be counseled to report all skin reactions and be evaluated immediately.</p> <ul style="list-style-type: none"> • Consider use of emollient cream, particularly around the joints, to be applied after bathing or showering, on a daily basis. • Consider treatment of mild symptoms with oral antihistamines and topical corticosteroids. • Advise patients to wear loose-fitting clothes. • If the rash is mild and progresses, discontinuation of treatment with TVR should be considered. • If the rash continues to progress after TVR has been discontinued for 7 days, discontinuing treatment with pegIFN and RBV should be considered
Pregnancy	<ul style="list-style-type: none"> • Pregnancy category X when TVR is prescribed in combination with RBV: Patients on TVR and RBV treatment must have a negative pregnancy test prior to start of treatment and counseled to use at least 2 forms of contraception as TVR may cause unreliable drug levels of hormonal contraceptives.

Note. Hgb = hemoglobin; TVR = telaprevir; RBV = ribavirin; PRN = as needed; pegIFN = pegylated interferon

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.
 - HV 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.

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% of HCV infection in the United States is genotype 1).
- Table 15 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 14a - 14d).
 - 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). SSRI's or 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, CD4+ T cell percentage will remain relatively stable.
- General measures for managing side effects include injection timing, use of non-steroidal anti-inflammatory drugs (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.
- 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 with acquisition of other genotypes. Assess RNA periodically (every 6-12 months) for 1-5 years to exclude late relapse or reinfection.
- Risk reduction strategies include:
 - Discussion of current drug use and determination of changes the patient is willing to make, including: abstinence; treatment for substance abuse; 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 and using condoms/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, as the development of acute HAV or HBV can be life threatening when superimposed on chronic hepatitis.
- No HCV vaccine is currently available.

TABLE 15. 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 and effectiveness of ART• Improve extra-hepatic manifestations of HCV	<ul style="list-style-type: none">• Toxicities of medications• Adherence difficulties• Lack of data on effectiveness and treatment guidelines for co-infected individuals• Exacerbation of other medical conditions

Note. HCV = hepatitis C virus; ART = antiretroviral therapy

HIV & HEPATITIS E

Overview

Hepatitis E virus (HEV) has four identified genotypes. Two of the genotypes, 1 and 2, are human virus, and these are associated with modes of transmission similar to hepatitis A: fecal-oral and ingestion of contaminated water. Genotypes 1 and 2 are considered endemic. Of these, the majority of infections are caused by genotype 1 outside of Mexico and the African continent. Genotypes 3 and 4, considered autochthonous, are swine viruses and primarily infect domestic and wild pigs; however, human and other mammalian hosts have been identified.

Transmission

- Fecal-oral transmission
- Waterborne
- Consumption of undercooked pork or wild game

Diagnosis and Clinical Evaluation

The incubation period ranges from 3 to 8 weeks, and is followed by the development of symptoms, including jaundice, lasting up to several weeks and can be both an acute infection as well as chronic. Men are infected with autochthonous hepatitis E more than women, and the elderly are also more susceptible to the development of clinical features with these genotypes. Similarly, endemic hepatitis E infection is usually mild and self-limiting while autochthonous hepatitis E can be associated with significant complications including fulminant liver failure or progressive liver disease and chronic hepatitis. Patients with immunocompromising conditions, such as HIV infection, are more likely to develop chronic hepatitis E infection. Rapid progression to cirrhosis has been seen in patients with chronic immunosuppression. Extrahepatic symptoms include arthritis and pancreatitis, and hepatitis E has been associated with neurologic complications as well, although neurologic symptoms can resolve with resolution of the infection.

Tests for diagnosis of hepatitis E infection

No anti-hepatitis E virus antibody tests have FDA approval at this time. HEV RNA is detectable in stool and serum during the incubation period; it disappears from serum with resolution of illness, and persists in stool for a greater length of time, up to years. IgG anti-hepatitis E antibodies are present during initial infection and can persist for years. IgM anti-hepatitis E antibodies are present during clinical onset and disappear with resolution of hepatitis E infection, often within a year.

Treatment

There are currently no guidelines on treatment of hepatitis E. The use of antivirals such as ribavirin and peginterferon have shown favorable results in experimental trials, however neither are approved for use in the treatment of HEV and experts should be consulted prior to the initiation of treatment if hepatitis E infection is suspected.

Prevention and Patient Teaching

- Avoid undercooked pork products.
- Avoid raw shellfish, particularly for persons with immuno-compromised conditions.
- Vaccination is currently only available in China. Recombinant genotype 1 HEV vaccines offer cross-protection against multiple genotypes; a recent controlled trial indicated greater than 95% efficacy. This vaccine is not yet available in the United States.

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www.clinicalcareoptions.com and www.uptodate.com.**

RESOURCES

Mountain Plains AIDS Education and Training Center (MPAETC)

HIV & Hepatitis Resources

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.

AETC National Resource Center (NRC)

www.aids-ed.org

A central Web site for education and training materials available from AETCs around the United States.

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.

AIDS InfoNet

www.aidsinfonet.org

A project of the New Mexico AETC 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

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 healthcare providers on HIV, hepatitis, and oncology.

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Hep C Connection

www.hepc-connection.org

This is 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

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 (NCCC)

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 (NATAP)

www.natap.org

A non-profit corporation created to educate individuals about HIV and hepatitis treatments, and to advocate on 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 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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