Evaluation and Treatment of Hepatitis C and Cirrhosis

Federal Bureau of Prisons
Clinical Practice Guidelines

March 2012

What's New in this Document?

The BOP Clinical Practice Guidelines, *Stepwise Approach to the Prevention and Treatment of Hepatitis C and Cirrhosis*, distributed in March 2011, have been revised as described below. The title of the guidelines has been changed to *Evaluation and Treatment of Hepatitis C and Cirrhosis*

In May 2011, the FDA approved the first direct-acting antiviral agents for treatment of chronic Hepatitis C virus (HCV) infection, genotype 1.

- Boceprevir (Victrelis™) and telaprevir (Incivek™) are protease inhibitors (PI) that inhibit hepatitis C viral replication by preventing cleavage into mature viral forms.
- When used in combination with pegylated interferon and ribavirin as *triple therapy* (TT) for the treatment of genotype 1, these new medications achieve significantly better *sustained viral response* (SVR) rates (60–80%) than does *dual therapy* (DT) with just pegylated interferon and ribavirin alone (40–50%).

The revisions included in this updated version of the Clinical Practice Guidelines describe the use of these new medications for the treatment of persons incarcerated in the Federal Bureau of Prisons, and are summarized below. These and other changes are highlighted in yellow throughout the document.

Indications and contraindications for triple therapy include:

Indications:

- HCV genotype 1 only *and*
- Liver biopsy evidence of progressive fibrosis, i.e., stage 2 (Batts and Ludwig, periportal) or higher, including compensated cirrhosis

Those who are treatment-naïve, as well as relapsers or partial responders to prior therapy with pegylated interferon and ribavirin, may be considered.

Contraindications:

- Contraindications to pegylated interferon and ribavirin
- Co-infection with HBV or HIV
- Solid organ transplant
- Certain medications that are inducers of or metabolized by CYP3A
- Inability to adhere to a complex medication regimen, or unwillingness to consent to treatment

➡ *See information on indications, contraindications, and exclusions for triple therapy under Step 8 in Section 4. See also Appendix 6, Boceprevir/Telaprevir Drug Information.*

Selection and dosing of HCV PIs are as follows:

- Either boceprevir (BOC) or telaprevir (TVR) is used in combination with pegylated interferon and ribavirin (PR).
- The dose of BOC is 800 mg (four 200 mg capsules) orally every 8 hours (+/– 1 hour) with food.
- The dose of TVR is 750 mg (two 375 mg tablets) orally every 8 hours (+/– 1 hour) with food.
- Both BOC and TVR must be taken with food. A light snack is sufficient for BOC. However, TVR must be taken with a snack that contains at least 20 grams of fat.
- Reasons for selecting one HCV PI over another are discussed in the document.
- Either form of pegylated interferon may be used—peginterferon alfa 2A *or* alfa 2B.

➡ *See information on selecting the most appropriate HCV PI under Step 8 in Section 4. See information on dosing under Step 8 in Section 4, in Step 8 of Appendix 2, and in Appendix 6.*

Duration and monitoring of triple therapy are as follows:

- **The duration of triple therapy is determined by four variables: 1)** the history of and response to prior HCV treatment with pegylated interferon and ribavirin; **2)** the degree of liver fibrosis, specifically the presence or absence of cirrhosis; **3)** which of the two HCV PIs is used; and **4)** the on-treatment response to triple therapy.

  ➡ *See Step 9b under Section 4 for information on treatment duration for triple therapy, including rules for early discontinuation of therapy. This information is also included in Step 8 of Appendix 2 and in flowchart form in Appendices 4a and 4b.*

- **On-treatment lab monitoring of HCV PI-based regimens** is similar to that for regimens using only pegylated interferon and ribavirin, with the following exceptions.
  - HCV RNA levels are accomplished at the end of treatment weeks (TW) 4, 12, and 24 for both PI-based regimens. An additional HCV RNA level is obtained at the end of TW 8 when BOC is used.
  - Uric acid levels should be monitored when TVR is used.

  ➡ *Appendix 3, Hepatitis C Treatment Monitoring Schedule,* has been updated to reflect current recommendations.

- **Side effects:** Rates of anemia and dysgeusia are significantly higher with HCV PIs than with pegylated interferon and ribavirin alone. TVR also is associated with higher rates of anorectal *symptoms.*

  ➡ *Management of these symptoms is described under Step 9a in Section 4, in Step 9a of Appendix 2, and in Appendix 6.*

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Appendices

1. Purpose

The Federal Bureau of Prisons (BOP) Clinical Practice Guidelines on *Evaluation and Treatment of Hepatitis C and Cirrhosis* provide recommendations for the medical management of federal inmates with hepatitis C.

2. Transmission of Hepatitis C Virus

Hepatitis C virus (HCV) is a single-stranded, enveloped, RNA virus with multiple genotypes and subtypes. Genotype 1 is predominant in the United States. HCV is transmitted primarily by direct percutaneous exposures to infectious blood. Modes of transmission are summarized below in *Table 1*.

Table 1. Modes of Transmission of Hepatitis C Virus

Percutaneous Exposure to Infectious Blood (primary mode)
- Injection drug use
- Transmission of contaminated blood products (prior to July 1992)
- Tattooing with shared sharps in jails or prisons (potential mode)

Other Modes of Transmission (inefficient)
- Sexual contact (increased risk for inmates with history of STD or multiple sexual partners)
- Congenital transmission (risk of 5–6%)

Ways HCV is *not* transmitted
- Breast feeding
- Kissing, sneezing, hugging, coughing
- Food or water
- Casual contact, including sharing eating utensils or drinking glasses

Note: *Most inmates diagnosed with HCV infection have behavioral risk factors for acquiring HCV and were infected prior to incarceration. Low levels of HCV transmission between inmates have been documented via seroincidence studies and contact investigations. However, large HCV outbreaks have not been reported in the correctional setting.*

3. Acute Hepatitis C Infection

Diagnosis of Acute HCV Infection

Acute HCV infection is diagnosed when there is *circumstantial evidence* of new infection (such as recent exposure to a known HCV-infected inmate) or the presence of *clinical features* of acute hepatitis (jaundice, nausea, anorexia, and malaise), and where the other causes of hepatitis have been excluded. Acute hepatitis C rarely causes fulminant hepatic failure.

The *mean incubation period*, from transmission of HCV infection to the onset of symptoms, is 6–7 weeks (range: 2–26 weeks); however, only 20–30% of newly infected persons are actually symptomatic. Serum ALT levels increase 4–12 weeks after acute HCV infection. HCV RNA is detectable in serum within days to 8 weeks following infection. Antibodies to HCV (anti-HCV) are detectable 3 months after infection in 90% of patients. A subset of those with acute HCV infection spontaneously clear the virus. Laboratory criteria for diagnosis of acute hepatitis C are summarized below in *Table 2*.

Table 2. Laboratory Criteria for Diagnosis of Acute Hepatitis C

Confirmation of acute hepatitis C is confirmed by *all* of the following:

1) **Marked elevation in ALT** (>7 times the upper limit of normal, with or without symptoms of acute hepatitis); ***and***
2) **Negative tests for acute hepatitis A** (IgM anti-HAV) **and acute hepatitis B** (IgM anti-HBc); ***and***
3) **A positive anti-HCV screening immunoassay** (enzyme immunoassay, EIA, or chemoluminescence immunoassay, CIA) that is confirmed with *one of the following*:
   - An immunoassay with a signal to cut-off ratio predictive of a true positive for that assay; or
   - An HCV RNA assay. (HCV RNA may be detected 1–3 weeks after exposure. However, viremia may be transient post-exposure, i.e., a negative HCV RNA does not rule out acute HCV infection.)

Treatment of Acute HCV Infection

Inmates diagnosed with acute hepatitis C should be considered for antiviral therapy, in consultation with a physician who has expertise in managing hepatitis C. Treatment can be delayed for 8 to 12 weeks after acute onset of hepatitis to allow for spontaneous resolution of the infection. Patients should be considered for treatment with at least pegylated interferon. The benefits of including ribavirin in the regimen are unclear; therefore, decisions about its use should be made on a case-by-case basis. The optimal duration of a treatment regimen for acute infection is unknown. It is reasonable to treat for at least 12 weeks; however, up to a total of 24 weeks may be considered. After 12 weeks of treatment, an HCV RNA assay should be obtained to assess the response to treatment.

4. Chronic Hepatitis C Infection

Natural History of Chronic HCV Infection

Most persons infected with HCV develop chronic infection; however, a small subset of newly infected persons are able to clear the virus spontaneously. Chronic HCV infection frequently results in high levels of HCV RNA in the blood, ranging from 10^5 to 10^7 international units (IU)/mL, despite the presence of HCV antibodies. The majority of persons with chronic HCV infection are asymptomatic. Chronic HCV infection has an unpredictable course, frequently characterized by fluctuations in ALT levels that may or may not be associated with significant liver disease. Approximately one-third of persons with chronic HCV infection have no laboratory or biopsy evidence of liver disease.

A small, but significant subset of persons with chronic HCV infection develop progressive fibrosis of the liver that leads to cirrhosis. Transfusion-acquired HCV, high levels of alcohol consumption, older age at the time of infection, HIV infection, chronic HBV infection, and male gender are associated with an increased risk of disease progression. However, neither the degree of viremia ("viral load") nor the HCV genotype affect the progression of liver disease. Other factors that appear to increase the risk of cirrhosis, and decrease the response to antiviral therapy, include: hepatic steatosis, marked necroinflammation on biopsy, and certain host immunologic characteristics. Once cirrhosis develops in persons with chronic HCV infection, the risk of hepatocellular carcinoma (HCC) is about 1–4% per year. HCV accounts for one-third of the cases of HCC in the U.S. each year.

Stepwise Approach for Detecting, Evaluating, and Treating Chronic Hepatitis C

Current antiviral treatment for hepatitis C has some limitations in terms of both efficacy and toxicity. With this in mind, the BOP has developed a stepwise, systematic approach to hepatitis C detection, evaluation, and treatment. *Table 3* below lists the ten steps in this process.

Table 3. Steps for Detecting, Evaluating, and Treating Chronic Hepatitis C in the BOP

Step 1. Appropriately screen inmates for hepatitis C.
Step 2. Provide initial medical follow-up for anti-HCV positive inmates.
Step 3a. Determine if hepatitis C treatment is *not* recommended.
Step 3b. Monitor HCV-infected inmates who are *not* on treatment.
For inmates who may be eligible for hepatitis C treatment, proceed as follows:
Step 4. Obtain HCV RNA assay and HCV genotype.
Step 5. Assess liver fibrosis and need for a liver biopsy.
Step 6. Determine if treatment should be initiated.
Step 7. Conduct a pre-treatment evaluation.
Step 8. Determine appropriate treatment and obtain informed consent.
Step 9a. Manage side effects.
Step 9b. Monitor treatment response.
Step 10. Assess for sustained viral response (SVR).

Following is a discussion of Steps 1–10 for detecting, evaluating, and treating chronic hepatitis C. The actual components of each step are presented in *Appendix 2*.

Step 1. Appropriately screen inmates for hepatitis C.

Inmate Education: Appropriately trained personnel should provide newly incarcerated inmates with educational information on the transmission, natural history, and medical management of HCV infection, in accordance with BOP policy. Health education efforts should make use of the BOP peer-oriented video on infectious diseases, *Staying Alive*, as well as *Appendix 1*, *Inmate Fact Sheet on Hepatitis C Viral Infections*, and other available patient educational tools (see *Appendix 8*).

Screening Criteria: For *sentenced inmates* with hepatitis C risk factors, screening is recommended at the prevention baseline visit. In addition, all inmates with certain clinical conditions should be screened for hepatitis C, *regardless of sentencing status*. *Appendix 2–Step 1* lists the risk factors and clinical indications that should trigger screening for hepatitis C viral infection.

Screening Method: The preferred screening test for HCV infection is an immunoassay (e.g., EIA or CIA) that measures antibodies to HCV antigens.

Screening of Non-Sentenced Inmates: Unless clinically indicated, screening should ordinarily not be pursued for asymptomatic, highly mobile, non-sentenced inmates. However, non-sentenced inmates who have a history of injection drug use or other high-risk behaviors for HCV should be provided with counseling. Education should cover the risks for HCV infection, as well as behaviors that would reduce transmission of HCV infection during incarceration and upon release. Referrals to community HCV testing sites should be made when appropriate. ***Exception:*** *Long-term inmates in BOP detention facilities should be screened for HCV infection in accordance with the guidelines for sentenced inmates.*

Refusal of Testing: Sentenced inmates who have HCV risk factors—and refuse testing at the baseline visit—should be counseled about HCV testing during periodic preventive health visits.

Step 2. Provide initial medical follow-up for anti-HCV positive inmates.

Baseline Evaluation: A baseline clinician evaluation should be conducted for all inmates who are anti-HCV positive. At minimum, this evaluation should include the following:

- **Targeted history and physical examination:** Evaluate for signs and symptoms of liver disease, quantify prior alcohol consumption, and determine risk behaviors for acquiring HCV infection. Attempt to estimate and document the earliest possible date of infection, including when risk factors for exposures started and stopped, e.g., the time period in which the inmate engaged in injection drug use. Evaluate for other possible causes of liver disease, especially alcoholism, nonalcoholic steatohepatitis (NASH), iron overload, and autoimmune hepatitis. Inquire about prior treatment for HCV infection, specific medications used, dosages and duration of treatment, and outcomes, if known.
- **Laboratory tests:** Recommended baseline laboratory tests are listed in *Appendix 3*. However, until it is determined that an inmate is a potential candidate for treatment (see *Steps 3a–b*, below), *do not* obtain an HCV RNA, or an HCV genotype, or a liver biopsy.

Patient Education: Inmates diagnosed with chronic HCV infection should be counseled by a health care provider regarding the natural history of the infection, potential treatment options, and specific measures to prevent transmitting HCV infection to others (both during incarceration and upon release). Key messages about preventing HCV transmission for inmates are listed in *Appendix 1*. Sources for hepatitis C patient educational materials are listed in *Appendix 8*.

Preventive Health Measures: All inmates who are anti-HCV positive should be evaluated to assess the need for the preventive health interventions outlined in *Appendix 2–Step 2*.

Step 3a. Determine if hepatitis C treatment is *not recommended*.

Next, determine if treatment for hepatitis C is not recommended based on the following four criteria:

1. **Pegylated interferon is contraindicated.** Inmates with chronic HCV infection who are being considered for antiviral therapy should first be assessed for contraindications to interferon, as listed in *Appendix 2–Step 3a*. Inmates with contraindications to interferon cannot be treated for hepatitis C. ***Note:*** *Those with contraindications to ribavirin can be considered for peginterferon monotherapy.*
2. **The inmate will be incarcerated for an insufficient period of time for completing treatment.** Inmates who are candidates for hepatitis C treatment, but whose anticipated length of stay will not allow sufficient time to complete therapy, should *ordinarily* not be started on antiviral therapy unless continuation of treatment within the community is deemed likely. This includes inmates housed in short-term BOP detention facilities (including pre-trial and non-sentenced federal detainees), or inmates whose anticipated release date will not allow sufficient time to complete treatment.

   The potential for interruption of antiviral therapy for hepatitis C places an inmate at risk for a number of adverse outcomes, including: *treatment failure*, if the course of treatment is not completed, and *adverse effects from medications*, if the inmate does not receive the required laboratory and clinical monitoring upon release or transfer.

   Note: *Inmates entering BOP custody who are currently being treated for hepatitis C should be maintained on antiviral therapy (unless medically contraindicated). They should be evaluated and monitored in accordance with BOP guidelines. Consult with a Central Office physician if there are questions regarding continuation of therapy.*

3. **The inmate has an unstable medical or mental health condition which precludes hepatitis C treatment,** e.g., refractory HIV-infection with AIDS, uncontrolled diabetes mellitus, life-threatening COPD or CHF, or uncontrolled depression.

4. **The inmate refuses treatment.** Inmates should initially be provided with counseling about hepatitis C treatment. If an inmate then refuses the possibility of treatment, the refusal should be documented in the medical record.

➡ ***If any one of the above four criteria are present, hepatitis C treatment should not be pursued. Document in the medical record why hepatitis C treatment is not currently recommended. No further hepatitis C testing is indicated at this time, including HCV RNA testing, HCV genotyping, or liver biopsy. However, continue to monitor the inmate, as discussed in Step 3b below.***

Step 3b. Monitor HCV-infected inmates who are *not* on treatment.

HCV-infected inmates for whom treatment is *not recommended* should continue to be followed in the Chronic Care Clinic, and evaluated periodically to determine if hepatitis C treatment should be reconsidered. Monitoring recommendations are outlined in *Appendix 2–Step 3b*.

➡ ***For inmates who may be eligible for hepatitis C treatment, proceed as follows:***

Step 4. Obtain HCV RNA assay *and* HCV genotype.

HCV RNA: The detection of anti-HCV by immunoassay in a person who has risk factors for acquiring HCV infection strongly suggests prior infection. However, before initiating antiviral therapy, an HCV RNA level (viral load) is required in order to confirm chronic infection and guide therapy. If the HCV RNA level is undetectable, the individual can be considered uninfected. Possible explanations include either host clearance of viremia or a "false-positive" immunoassay result.

Notes:

(1) Strict adherence to current reference laboratory test processing guidelines for HCV RNA test samples is essential; viral RNA is unstable, and false negative tests may result from inadequate or inappropriate processing.

(2) For monitoring purposes, it is important to use the same laboratory test before and during therapy.

(3) When treating with an HCV PI-based regimen, the HCV RNA test should have a lower limit of quantitation of at least 43 IU/ml and a lower limit of detection of at least 10 IU/ml. If the HCV RNA result is below the lower limit of detection, the report should indicate further if the HCV RNA is detectable or undetectable.

(4) The RIBA supplemental test is no longer recommended for diagnosing chronic HCV infection.

HCV Genotype: *An HCV genotype must also be obtained prior to treatment initiation and should be requested in conjunction with the initial HCV RNA.* The HCV genotype significantly influences the evaluation strategy, patient counseling messages, the decision to treat, the specific medications and regimens, and the duration of therapy. Treatment response varies markedly by HCV genotype and medication regimen. Those with genotypes 2 or 3 have a 70–80% sustained viral response rate to pegylated interferon/ribavirin therapy, compared to a 40–45% response rate for genotype 1. The addition of an HCV Protease Inhibitor to pegylated interferon and ribavirin increases the sustained viral response rate in genotype 1 to 60–80%. Repeat genotype testing is not indicated, except in the rare instance when re-infection is suspected.

Step 5. Assess liver fibrosis and need for a liver biopsy.

In patients with chronic hepatitis C, liver biopsy has been the primary means for determining the stage of the liver disease and the need for treatment. In general, patients treated for HCV should have "more than portal fibrosis." General criteria for liver biopsy are outlined in *Appendix 2–Step 5*. Those with genotype 1 will ordinarily require a biopsy. *Inmates with genotype 2 or 3 usually do not need a biopsy unless they are HIV-infected or another source of liver disease is suspected.*

Calculation of APRI: Recent data indicate that the degree of liver fibrosis is correlated with the AST/Platelet Ratio Index (APRI), a simple ratio of two common lab values. Higher APRI values have been associated with higher stages of liver fibrosis on biopsy. Therefore, BOP institutions should utilize APRI values when prioritizing referral of inmates with genotype 1, 4, 5, or 6 for liver biopsies. Inmates who have an APRI of < 0.5 are lower priority for biopsy; inmates who have an APRI of ≥ 0.5 are higher priority for biopsy—with the higher the APRI, the higher the priority for biopsy. The APRI calculation is provided below in *Table 4*.

Table 4. AST/Platelet Ratio Index (APRI) Calculation

Formula: {AST ÷ lab upper limit of normal (ULN)* for AST x 100} ÷ {platelet count ÷ 1,000}	
Simple example: AST = 80 AST laboratory ULN = 40 Platelet count = 100,000	**Calculation of APRI:** {AST ÷ ULN x 100} ÷ {platelet count ÷ 1,000} {80 ÷ 40 x 100} ÷ {100,000 ÷ 1,000} 200 ÷ 100 = **2.0** = APRI
* Use "upper limit of normal (ULN)" value that is used by the laboratory that ran the AST test.	

Interpretation of Liver Biopsy Results: Histologically, fibrosis progresses along a continuum, with portal fibrosis representing an earlier stage of fibrosis and cirrhosis representing a late (or advanced) stage of fibrosis. The intermediate stages of fibrosis—periportal fibrosis and bridging fibrosis—as determined histologically, are generally recognized as the most appropriate stage for initiating treatment. These intermediate stages of fibrosis correlate with the IASL, Ludwig and Metavir Stages "2" and "3," and the Ishak stages "3" and "4." Regardless of genotype, treatment should be considered with liver biopsy results as follows: IASL, Batts & Ludwig, or Metavir ≥ Stage 2; or Ishak ≥ Stage 3.

➡ The primary scoring systems for staging hepatic fibrosis on liver biopsy are compared in *Table 5* on the next page.

Table 5. Scoring Systems for Hepatic Fibrosis (IASL Ishak, Metavir, and Batts & Ludwig)

Score	IASL	Batts & Ludwig	Metavir	Ishak
0	No fibrosis	No fibrosis	No fibrosis	No fibrosis
1	Mild fibrosis	Fibrous portal expansion	Periportal fibrotic expansion	Fibrosis expansion of some portal areas, with or without short fibrous septa
2	**Moderate fibrosis**	**Rare bridges or septae**	**Periportal septae (>1 septum)**	Fibrous expansion of most portal areas, with or without short fibrous septa
3	**Severe Fibrosis**	**Numerous bridges or septae**	**Portal-central septae**	**Fibrous expansion of most portal areas, with occasional portal-portal bridging**
4	**Cirrhosis**	**Cirrhosis**	**Cirrhosis**	**Fibrous expansion of most portal areas, with marked bridging (portal-portal and portal-central)**
5				**Marked bridging (portal-portal and portal-central) with occasional nodules (incomplete cirrhosis)**
6				**Cirrhosis, probable or definite**

Note: *The shaded areas with the* ***bolded*** *text indicate a significant liver biopsy result with a degree of fibrosis for which antiviral therapy should be considered.*

Reference: Ghany, et al. AASLD practice guidelines. Diagnosis, management and treatment of hepatitis C: an update. *Hepatology*. 2009; 49:1356-1358.

Step 6. Determine if treatment should be initiated.

Current HCV treatment options have some limitations in terms of both efficacy and toxicity. Each inmate with chronic hepatitis C should be evaluated carefully to assess the relative risks and benefits of the following: beginning therapy immediately, delaying therapy, or deferring treatment indefinitely. Prior to initiating treatment, inmates should be counseled about the potential benefits of treatment—the likelihood of achieving a sustained viral response (SVR)—as well as the potential side effects. The rationale for treatment decisions should be documented in the medical record.

Indications for Antiviral Therapy

Antiviral therapy is generally indicated for inmates with chronic hepatitis C if they have no contraindications to treatment and present with *at least one* of the following:

- **Genotype 1 and liver biopsy result** with evidence of progressive fibrosis (either IASL, Batts & Ludwig, or Metavir ≥ Stage 2; or Ishak ≥ Stage 3)
- **Genotype 2 or 3** (with no biopsy performed)
- **Genotypes 4, 5, or 6, or untypeable:** The best approach to management of these cases is not clearly defined by the medical literature. Until further data become available, the *indication* (but not necessarily the regimen) for treatment of genotypes 4, 5, or 6, or untypeable HCV should be the same as for genotype 1 as noted above.
- Various co-infections or co-morbidities, such as cirrhosis and renal disease, may affect treatment decisions and are discussed later in the document.

Special Considerations Related to Initiating Antiviral Therapy

The following co-morbidities, while not absolute contraindications, should be carefully assessed when considering whether or not to initiate antiviral treatment.

- **Mental illness:** Interferon can cause or exacerbate depression, and causes mood changes in virtually all patients. Therefore, inmates who have a history of major depression should be screened by a psychologist or a psychiatrist, and receive counseling on the risk of relapse of their depression posed by interferon treatment. For these patients, careful consideration should be given to prophylactic treatment of depression. Utilize an SSRI (or the antidepressant that was most successful in treating the patient's prior episodes of depression) for a period of three-to-six months prior to initiating interferon therapy. Similarly, other major psychiatric illnesses such as bipolar disorder, schizophrenia, and schizoaffective disorder should be well-controlled with stable doses of medication for at least six months prior to initiating interferon. Inmates with severe axis II diagnoses should be assessed by a mental health professional for their ability to comply with the frequent clinical and laboratory monitoring that is required for the safe administration of pegylated interferon and ribavirin.
- **Alcohol:** HCV-infected inmates with significant alcohol abuse histories should receive specific counseling messages. Heavy and prolonged alcohol use is an independent risk factor for the development of cirrhosis, and alcohol accelerates the progression of HCV-related fibrosis. *Hepatitis C treatment without abstinence from alcohol is unlikely to be of benefit*. The treatment response to peginterferon plus ribavirin is significantly reduced in individuals who drink more than 30 grams of alcohol per day, and perhaps with lower levels of consumption, as well.

  An inmate's unwillingness to abstain from alcohol intake while incarcerated is a potential indicator of alcoholism and should be evaluated. Effective treatment for alcoholism should be offered in prison to as many HCV-infected inmates as possible, whether or not they have been administered hepatitis C treatment or have responded to such treatment.
- **Substance abuse:** Inmates who are significant abusers of substances other than alcohol may have a number of medical issues that can affect or be affected by hepatitis C treatment. Injection drug users are at risk for HIV, HBV, endocarditis, and possible re-infection with HCV. Amphetamine and cocaine abuse may result in cardiovascular complications. Ongoing substance use in the controlled environment of prison or jail is, at best, an indicator that the inmate is not taking adequate responsibility for his or her overall health. Treatment decisions must be individualized where these issues are present.

Patient Counseling

In weighing treatment options, the following factors should be considered and discussed with the inmate:

- For those with chronic hepatitis C infection, the risk of developing cirrhosis ranges from 5% to 25%, and usually occurs over a period of 25—30 years after initial infection.
- It is difficult to predict which HCV-infected persons will develop cirrhosis *or* who will respond to treatment.
- The rate of sustained viral response (SVR) varies significantly by genotype and the medication used. Dual therapy (DT) with pegylated interferon and ribavirin achieves an SVR of 70–80% for genotypes 2 and 3, compared to only 40–45% for genotype 1. However, triple therapy for genotype 1 that uses one of the newly approved HCV Protease Inhibitors (PI)—either boceprevir or telaprevir—in addition to pegylated interferon and ribavirin achieves SVR rates of 60–80%.
- Although current antiviral therapy is usually well-tolerated, there are many—and sometimes serious—side effects to antiviral therapy.

- Close adherence to the drug regimen is essential to increasing the likelihood of "cure," as well as decreasing the risk of virologic resistance in the case of triple therapy.
- Future hepatitis C treatments may be more effective and better tolerated than those currently available. At this time, triple therapy is considered optimal for the treatment of HCV genotype 1. However, this treatment can be complex and is associated with a higher rate of side effects than treatment with pegylated interferon and ribavirin alone; newer therapies that are projected to become available within a few years could simplify the regimen and decrease the risk of virologic resistance. For these reasons, the decision to treat HCV genotype 1 infection with stage 2 fibrosis should be made on a case-by-case basis after discussion with each inmate.
- Patients must be willing to be treated and willing to conform to the treatment requirements, including abstinence from alcohol, illicit drugs, and tattooing.
- Treatment during pregnancy is generally contraindicated. Because treatment with ribavirin is known to be teratogenic, pregnancy must be avoided during treatment and for the six months after treatment is completed—in both female patients and the female partners of male patients.

Step 7. Conduct a pre-treatment evaluation.

Inmates should be evaluated by a physician and screened for other medical conditions that may complicate antiviral therapy. Lab work and tests should be obtained in accordance with the time frames enumerated in the BOP Algorithm for Treatment of Hepatitis C – Approval Form (BP-A803.060).

- **Laboratory tests:** See *Appendix 3* for list of recommended baseline laboratory tests.
- **Baseline assessment of visual acuity.**
- **Funduscopy** for inmates with diabetes or other ophthalmologic disorders.
- **Pregnancy test for all female inmates:** Ribavirin may cause fetal abnormalities. All female inmates of childbearing potential must have a pregnancy test *immediately prior to* initiating therapy and *monthly* thereafter up to at least 6 months post-treatment.
- **Cardiac risk assessment:** A basic cardiac risk assessment, performed by a clinician prior to treatment initiation, is critical because the hemolysis associated with ribavirin may precipitate angina pectoris. An electrocardiogram should be obtained in inmates with preexisting cardiac disease. Symptomatic inmates should be carefully evaluated for cardiac disease prior to initiating treatment.
- **Other patient-specific diagnostic tests** as medically indicated.
- **Mental health evaluation:** Before prescribing medication therapy, a psychiatrist or psychologist should perform a mental health evaluation: to determine if mental health treatment is warranted prior to antiviral therapy and whether ongoing mental health assessments are needed during treatment.
  - The evaluation should include an assessment of axis I and axis II diagnoses, including a comprehensive alcohol and substance abuse history and a suicide risk assessment. Interferon therapy has been associated with changes in mood and affect in most individuals. In a small percentage of patients undergoing interferon therapy, significant depression, suicide attempts, and completed suicides have resulted. A patient's history of depression or suicide attempts should prompt heightened vigilance on the part of the treating providers; however, since the absence of such a history does not appear to lessen the risk of these side effects from interferon, *all patients should be carefully monitored for changes in mood*.

- Other mental illnesses or conditions, if not treated or not in remission, may adversely affect the inmate's ability to successfully complete a course of antiviral treatment, due to issues of compliance or to an inability to tolerate even mild side effects.

- **Evaluation of inmates with compensated cirrhosis:** Prior to treatment initiation, inmates with suspected or biopsy-confirmed, compensated cirrhosis should have a liver-spleen ultrasound or abdominal CT scan, and measurements of alpha-fetoprotein. If the ultrasound result points to the possibility of portal hypertension (marked splenomegaly, ascites, retrograde flow through the portal vein), then an upper endoscopy screening for esophageal varices should be performed. CT often reveals esophageal varices, which must then be endoscopically visualized to determine size and extent. *If hepatocellular carcinoma (HCC) or decompensated cirrhosis is diagnosed, antiviral therapy is contraindicated.* (See compensated cirrhosis and decompensated cirrhosis in Definitions section.)

Step 8. Determine appropriate treatment and obtain informed consent.

Treatment of chronic HCV is complex and may require expert consultation. Regional and Central Office staff experienced in the treatment of HCV are available for such consultations as needed. If consultants from the local community are utilized, it is important to familiarize them with the BOP's approach to this condition.

Triple Therapy

Triple therapy with an HCV Protease Inhibitor (PI) such as boceprevir (Victrelis™) or telaprevir (Incivek™), in combination with pegylated interferon and ribavirin, is the preferred treatment for genotype 1 only. It is not indicated for the treatment of any other HCV genotype. HCV PIs are either contraindicated or not recommended in a number of other situations, as described below. In such cases, dual therapy for genotype 1 should be considered, unless it is contraindicated.

Indications for Triple Therapy

- HCV genotype 1 only *and*
- Liver biopsy evidence of progressive fibrosis, i.e., stage 2 (Batts and Ludwig, periportal) or higher, including compensated cirrhosis (see compensated cirrhosis in Definitions section)

Both treatment-naïve, as well as relapsers or partial responders to prior therapy with pegylated interferon and ribavirin, may be considered.

Contraindications and Exclusions for HCV PIs for Genotype 1

- Contraindications to pegylated interferon and ribavirin, including decompensated cirrhosis and pregnancy (HCV PIs should never be used as monotherapy). (See decompensated cirrhosis in Definitions section.)
- Co-infection with HBV or HIV
- Solid organ transplant
- Medications that are inducers of or metabolized by CYP3A:
  - Examples of medications that are either contraindicated, not recommended, or require dosage adjustment or close monitoring when used in combination with HCV PIs include: Certain antiarrhythmics (amiodarone, bepredil, digoxin, flecainide, lidocaine, propafenone, quinidine), macrolide antibiotics (clarithromycin, erythromycin, telithromycin), anticonvulsants (carbamazepine, phenobarbital, phenytoin), antidepressants (desipramine, trazadone), antifungals

(itraconazole, ketoconazole, posaconazole, voriconazole), calcium channel blockers (dihydropyridine and non-dihydropyridine), ergots (ergotamine, dihydroergotamine, ergonovine, methylergonovine), immunosuppressants (cyclosporine, sirolimus, tacrolimus, and some inhaled or systemic steroids), PDE_5 inhibitors (sildenafil, tadalafil, vardenafil), HIV protease inhibitors, sedative/hypnotics (alprazolam, midazolam, triazolam), statins (atorvastatin, lovastatin, simvastatin), alfuzosin, bosentan, colchicine, drospirenone, pimozide, rifabutin/rifampin, salmeterol, St. John's wort, warfarin.

- ▸ Inmates on medications that are either contraindicated or not recommended should be assessed to determine the medical necessity of the medications they are taking, and should be considered for alternative medications in the same or a different class, as clinically appropriate.

- Inability to adhere to a complex medication regimen, as demonstrated by past history of non-adherence to treatment plans or call outs, or unwillingness to consent to treatment
- Hypersensitivity to the specific HCV PI being considered, or any of its components.
- Prior treatment failure with either a boceprevir- or telaprevir-based regimen.

Selecting the Most Appropriate HCV PI for Genotype 1

Determining which HCV PI to use must be made on a case-by-case basis. The SVR rates of the HCV PIs have not been compared in head-to-head trials.

The reasons to consider boceprevir over telaprevir include, but are not limited to:

- Presence of coexisting conditions that could be exacerbated by telaprevir, e.g., dermatologic conditions (incidence of rash is increased with telaprevir), or hyperuricemia / gout (increased uric acid levels) with telaprevir.
- Metabolic conditions requiring a low-fat diet (telaprevir must be taken with a 20-gram fat snack).
- Anorectal conditions, e.g. hemorrhoids, proctitis (incidence of anorectal side effects is increased with telaprevir).
- Use of medications that are contraindicated with telaprevir, but not with boceprevir.

The reasons to consider telaprevir over boceprevir include, but are not limited to:

- Use of medications that are contraindicated with boceprevir, but not with telaprevir.
- Telaprevir might be preferred when a simpler treatment regimen is needed.

Dosing of HCV PIs for Genotype 1

Boceprevir: 800 mg (four 200 mg capsules) by mouth every 8 hours (+/- 1 hour) with a snack

Telaprevir: 750 mg (two 375 mg tablets) by mouth every 8 hours (+/- 1 hour) with a 20-gram fat snack

➡ Refer to *Appendix 2–Step 8* and *Appendix 6* for more information on dosing of HCV PIs.

➡ Dosing of pegylated interferon and *ribavirin* is the same when used as dual therapy or as triple therapy in combination with an HCV PI. Detailed drug dosages and potential side effects of pegylated interferon and ribavirin are outlined in *Appendix 2–Step 8*, and *Appendix 5*. See *Appendix 3, Hepatitis C Treatment Monitoring Schedule* for information on monitoring parameters.

Notes on dosing of HCV PIs for genotype 1:

- *HCV PIs should be prescribed and taken every 8 hours*, not TID.
- *Boceprevir or telaprevir should always be prescribed at full doses or not at all.* The doses should not be increased or decreased for any reason. They should be prescribed as noted above, or either discontinued or not prescribed at all, as determined by the clinical situation.
- *Each dose must be taken with food.* For *boceprevir*, a light snack is sufficient. *Telaprevir* must be taken with a snack that has at least 20 grams of fat. Examples of snacks that have 20 grams of fat include: a bagel with cream cheese, ½ cup of nuts or trail mix, 3 tablespoons of peanut butter, 1 cup of regular (not low fat) ice cream, 2 ounces of American or cheddar cheese, or 2 ounces of potato chips. Supplemental feeding with a snack issued by the Food Service Department may be ordered in accordance with BOP policy, or the inmate may purchase appropriate items from the commissary.
- *These medications must be prescribed and taken every 8 hours, +/- one hour.* Adherence to this regimen is necessary to achieve safe and effective outcomes. *However, the patient should be counseled on management of missed doses.* For either HCV PI, if a dose is missed, the next dose should NOT be doubled. If a *boceprevir* dose is missed, the missed dose may be taken with food so long as it is remembered more than 2 hours before the next dose; it should be skipped if there are 2 hours or less before the next dose. If a *telaprevir* dose is missed, the missed dose may be taken with a 20-gram fat snack if it is remembered more than 4 hours before the next dose, but should be skipped if there are 4 hours or less before the next dose.

Dual Therapy

Dual therapy with once-weekly pegylated interferon injections and twice-daily oral ribavirin is the standard treatment for all HCV genotypes except genotype 1. Dual therapy may also be appropriate for treatment of genotype 1 when there are contraindications or exclusions to using HCV PIs, e.g., co-infection with HBV or HIV, or use of certain medications. (Refer to the section on *Triple Therapy* above, under Step 8 in Section 4.) For persons who have contraindications to ribavirin, peginterferon can be administered as monotherapy.

➡ Ribavirin is completely ineffective as monotherapy and should never be prescribed without interferon.

- Either form of pegylated interferon, alfa 2A or alfa 2B, may be used. It is preferable to use the same form throughout the course of treatment.
- Standard dosing is detailed in *Appendix 2, Step 8*. See *Appendix 5, Interferon/Ribavirin Drug Information* for more detailed information on dosing in certain clinical circumstances, contraindications, and side effects. See *Appendix 3, Hepatitis C Treatment Monitoring Schedule* for information on monitoring parameters.

Pretreatment Consent

The medications used to treat HCV have significant potential side effects; these side effects for dual and triple therapy are outlined in *Appendix 5 and Appendix 6*, respectively, and should be discussed with the patient prior to treatment initiation. Issues unique to the HCV PIs (compared to dual therapy) should also be discussed, including: the potential for development of resistance in the event of treatment failure, and the likelihood of new medications in the near future that might entail an all-oral regimen or have fewer side effects. In cases of mono-infection with HCV genotype 1 and a lower stage of fibrosis (e.g., stage 2, predominantly periportal fibrosis), the option of postponing treatment should be presented to the inmate and discussed. The Consent to Hepatitis C Treatment form (BP-A0806) must be reviewed with and signed by the inmate *and* the attending physician, *prior to starting treatment*: The form is available on Sallyport.

Step 9a. Manage side effects.

Recommended baseline, pre-treatment, and ongoing clinical evaluations and laboratory studies are summarized in *Appendix 3*, *Hepatitis C Treatment Monitoring Schedule*. At a minimum, inmates receiving antiviral treatment should be clinically evaluated at *weeks 1, 2, and 4*, and then *monthly* thereafter. At each visit, patients should be assessed for medication adherence, side effects and potential complications. Those with compensated cirrhosis (see compensated cirrhosis in Definitions section), HIV infection, or other co-morbid conditions will require more frequent monitoring, as will those who develop significant side effects or complications during therapy. While inmates are taking interferon, psychiatry and psychology consultations should be provided, as clinically indicated.

Throughout the patient's treatment for hepatitis C, the clinician's evaluations should be directed at inquiring about the common side effects of interferon and ribavirin in order to make decisions about dose adjustments; investigate new symptoms such as chest pain, dyspnea, or visual changes; or reassure the inmate that he or she is experiencing "normal" side effects of treatment.

Assessment and management of the more frequently occurring side effects from HCV treatment are discussed below:

- **Flu-like symptoms:** Muscle aches, headaches, and low-grade fevers are experienced by over 80% of patients taking interferon. Patients should be counseled to expect these symptoms, usually about 48 hours after the weekly injection, and resolving 24–48 hours before the next injection. These symptoms usually appear after the third or fourth dose of pegylated interferon, and tend to subside after about 3 months of treatment. Acetaminophen, up to 2 grams per day, and increased fluid intake may be recommended to manage these symptoms. Flu-like symptoms can be treated prophylactically by administering 1 gram of acetaminophen 30 minutes prior to peginterferon injection. ***Nonsteroidal anti-inflammatory agents (NSAIDs) ordinarily should not be prescribed because of hepatotoxicity and the underlying liver disease.***

- **Mood changes:** Virtually all inmates on interferon will experience at least some irritability. This should be discussed at each visit to determine if other symptoms of depression are developing. A low threshold for initiating an SSRI should be maintained while inmates are taking interferon.

- **Rashes:** A variety of dermatologic conditions are associated with both the HCV infection and the medications used to treat the HCV infection, including interferon/ribavirin and the HCV PIs. New rashes during treatment are usually mild and self-limited, or respond to topical low-potency corticosteroids.

  There is an increased incidence of rash with those patients on triple therapy that includes telaprevir. Incidence of rash occurs in approximately 50% of patients using telaprevir in triple therapy, as opposed to approximately 30% in dual therapy. The rash usually develops in the first 4 weeks of triple therapy, but may occur any time during treatment. In general, the rash improves after the discontinuation of the medication, but may take weeks to fully clear. The rash may occur with or without pruritus and may range from mild to moderate to severe; however, severe or serious rashes are rare. Mild to moderate rash is defined as involving less than 50% of the body surface area. Severe rash is generalized, covers 50% or greater of the body surface, or includes the presence of vesicles, bullae, or ulcerations. Management of mild to moderate rash includes monitoring for progression/systemic symptoms and maintaining general skin care practices; oral antihistamines and/or topical steroids may be considered. *Systemic corticosteroids are NOT recommended*. **Do not reduce the dose of HCV PI.** Discontinue telaprevir if the rash progresses or becomes severe, or if systemic symptoms emerge. In this setting, pegylated interferon/ribavirin may be continued following discontinuation of telaprevir, but should be discontinued if the rash shows no improvement in 7 days. Consider oral antihistamines and/or topical steroids. **Do not restart treatment.**

- **Chest pain:** New onset of chest pain during HCV treatment should be presumed to be angina pectoris until proven otherwise. The development of anemia during treatment can precipitate angina in individuals with occult coronary artery stenosis.
- **Visual disturbances:** Ischemic retinopathy and retinal or vitreous hemorrhages can occur during interferon therapy, though rarely. The risk may be greater in diabetic patients. These inmates should be counseled to immediately report any changes in vision. A baseline retinal examination prior to treatment is recommended for diabetics and those with preexisting ophthalmologic disorders, with funduscopic examinations performed periodically and as clinically indicated during treatment.
- **Hair loss:** Alopecia areata occurs in approximately 20% of patients on HCV treatment. Inmates should be advised of this possibility, but also informed that this is self-limited after completion of treatment.
- **Thyroid dysfunction:** Approximately 4% of persons treated with interferon develop thyroid dysfunctions that may result in irreversible thyroid dysfunction—even with cessation of drug therapy. The occurrence of *hypothyroidism* usually can be managed with hormone replacement therapy while continuing interferon, on a case-by-case basis. Occurrence of *hyperthyroidism* usually necessitates discontinuation of interferon.
- **Anemia:** A common complication of antiviral therapy is anemia. Ribavirin causes a dose-related hemolysis; whereas, interferon can suppress red blood cell production. The rates of anemia nearly double when one of the HCV PIs is added to pegylated interferon and ribavirin. Patients who develop refractory anemia, progressive anemia beyond 8 weeks of treatment, or develop anemia late in the course of therapy should have a thorough evaluation for other treatable causes of anemia, such as iron deficiency anemia, gastrointestinal blood loss, and excessive menstrual blood loss. Specific strategies for managing drug-induced anemia are dependent on the degree of anemia, the presence of complicating co-morbidities such as heart disease, and the patient's virologic response to antiviral therapy. Guidance regarding drug dosage adjustments, and criteria for the use of recombinant erythropoietin, are outlined in *Appendix 2, Step 9b*. If ribavirin must be discontinued due to anemia, the HCV PI also must be discontinued. In this situation, pegylated interferon monotherapy may be continued, but efficacy rates are likely to be significantly diminished.
- **Neutropenia:** Interferon-induced bone marrow suppression may cause neutropenia. The majority of the patients who develop neutropenia while on interferon have few serious side effects. Patients with cirrhosis are at higher risk of neutropenic complications, such as sepsis, and should be followed closely. Specific strategies for neutropenia management are dependent on the degree of neutropenia, the extent of liver disease, the presence of co-morbidities that predispose to infection, and the patient's virologic response to antiviral therapy. Guidance regarding interferon dosage adjustments and criteria for the use of granulocyte colony stimulating factor are outlined in *Appendix 2, Step 9*. If pegylated interferon is discontinued due to neutropenia, the entire HCV treatment regimen, including ribavirin and the HCV PIs, must be discontinued, as well.
- **Thrombocytopenia:** Thrombocytopenia from bone marrow suppression is a potentially serious complication of interferon therapy, particularly in patients with cirrhosis who may have low platelet counts from the liver disease itself. Patients with thrombocytopenia should be monitored closely while on antiviral therapy. Interferon should be dose-adjusted or discontinued, based on the degree of thrombocytopenia, as outlined in *Appendix 2, Step 9b*. If pegylated interferon is discontinued due to thrombocytopenia, the entire HCV treatment regimen, including ribavirin and the HCV PIs, must be discontinued, as well.
- **Dysgeusia:** An altered sense of taste occurs more commonly in patients treated for HCV infection, especially with the use of HCV PIs. There are no specific recommendations for the treatment of this side effect.

- **Anorectal symptoms:** Diarrhea, anorectal discomfort, hemorrhoids, itching, and burning occur more commonly with telaprevir. General measures for itching such as topical steroids or anesthetics and/or antihistamines at bedtime, and standard anti-diarrheal measures such as fiber or loperamide, may be helpful in controlling these side effects.

Step 9b. Monitor treatment response.

Assessment of the patient's response to therapy is based on HCV RNA test results at certain intervals in the treatment process, as shown in *Table 6* below. For all patients, on-treatment HCV RNA levels should be obtained at the end of treatment weeks 4, 12, and 24, and again when the medication treatment is complete. For boceprevir-based regimens, an HCV RNA level also should be obtained at the end of treatment week 8.

Table 6. HCV Treatment Response Categories

Testing Interval	If HCV RNA test shows …	The result is considered …
End of week 4*	Undetectable HCV RNA	**RVR** – rapid viral response
End of weeks 4 & 12	Undetectable HCV RNA	**eRVR –** extended rapid viral response
End of week 12*	≥ 2 $\log_{10}$ reduction in HCV RNA	**EVR** – early viral response. EVR is also used to describe undetectable HCV RNA at TW 8 with BOC-based regimen.
End of week 12	< 2 $\log_{10}$ reduction in HCV RNA	**Null Responder**
End of week 24	≥ 2 $\log_{10}$ reduction in HCV RNA, but still detectable.	**Partial Responder**
End of recommended treatment period	Undetectable HCV RNA	**ETR** – end of treatment response (at treatment completion)
24 weeks after ETR**	Undetectable HCV RNA	**SVR** – sustained viral response (potential cure)
24 weeks after ETR	HCV RNA detectable	**Relapser**

** A viral response at week 4 and week 12 is closely correlated with treatment success.*
*** For more information on assessing patients for SVR, see Step 10 below.*

Recommended treatment duration of triple therapy for genotype 1:

The duration of triple therapy is determined by four variables: **1)** the history of and response to prior HCV treatment with pegylated interferon and ribavirin , **2)** the degree of liver fibrosis, specifically the presence or absence of cirrhosis, **3)** which of the two HCV PIs is used, and **4)** the on-treatment response to triple therapy. *Step 8 of Appendix 2*, summarizes the total weeks of therapy based on these variables.

Notes:

- Pegylated interferon and ribavirin are prescribed for the entire duration of therapy. The HCV PIs are prescribed for a shorter duration of time during the pegylated interferon and ribavirin treatment period.
- The term *treatment week* (TW) refers to the number of weeks on treatment, starting with the first day of treatment with any of the medications.
- HCV RNA tests should be obtained at the end of TWs 4, 12, 24, and at the end of treatment for a telaprevir-based regimen. An additional HCV RNA test should be obtained at the end of TW 8 for a boceprevir-based regimen.

➡ The medication regimens for triple therapy are relatively complicated. Refer to the table in *Step 8 of Appendix 2*, and the flowcharts in *Appendices 4a* and *4b*.

Boceprevir-Based Regimens

All boceprevir-based treatment regimens start with 4 weeks of dual therapy of pegylated interferon and ribavirin, and no boceprevir. This comprises TWs 1 through 4. At the beginning of TW 5, triple therapy starts with boceprevir being added to the pegylated interferon and ribavirin.

Four different treatment durations are possible—28 weeks, 36 weeks, and two different 48-week regimens—as described below:

- **28 weeks:** 4 weeks of pegylated interferon and ribavirin followed by 24 weeks of boceprevir, pegylated interferon, and ribavirin
- **36 weeks:** 4 weeks of pegylated interferon and ribavirin followed, by 32 weeks of boceprevir, pegylated interferon, and ribavirin
- **48 weeks (4+ 32 +12):** 4 weeks of pegylated interferon and ribavirin followed by 32 weeks of boceprevir, pegylated interferon, and ribavirin, followed by 12 more weeks of pegylated interferon and ribavirin. This regimen is the same as the 36-week regimen with an additional 12 weeks of pegylated interferon and ribavirin added at the end. Another way to understand this regimen is that pegylated interferon and ribavirin are prescribed for a full 48 weeks from start to finish—with boceprevir added for 32 weeks in the middle, starting after TW 4 and continuing through TW 36.
- **48 weeks (4 + 44):** 4 weeks of pegylated interferon and ribavirin, followed by 44 weeks of boceprevir, pegylated interferon, and ribavirin. This is only indicated for patients with compensated cirrhosis.

Which of these four regimens of boceprevir-based therapy to use for a given patient is determined by the patient's prior treatment history (with pegylated interferon and ribavirin) and outcome, degree of fibrosis on liver biopsy (no cirrhosis vs. compensated cirrhosis), and on-treatment response to therapy, as described below:

- **Treatment-naïve with no cirrhosis:**
  - 28-week regimen if HCV RNA is undetectable at the end of TWs 8 and 24
  - 48-week (4+32+12) regimen if HCV RNA is detectable at 8 weeks, < 100 IU/ml at 12 weeks and undetectable at 24 weeks
- **Prior relapser or partial responder with no cirrhosis:**
  - 36-week regimen if HCV RNA is undetectable at the end of TWs 8 and 24
  - 48-week (4+32+12) regimen if HCV RNA is detectable at 8 weeks, < 100 IU/ml at 12 weeks and undetectable at 24 weeks.
- **Compensated cirrhosis:**
  - 48-week (4+44) regimen.

Rules for early discontinuation of boceprevir-based regimens:

Indications for early discontinuation of boceprevir-based regimens due to treatment failure, as indicated by the HCV RNA response to treatment, include the following.

- HCV RNA ≥100 IU/ml at TW 12 ***or***
- HCV RNA detectable at TW 24 ***or***
- HCV RNA increase of > l $\log_{10}$ from nadir while on treatment

If *any* of these criteria are met, *all* therapy should be discontinued, including boceprevir, pegylated interferon, and ribavirin. Other criteria for early discontinuation of therapy include the severe adverse reactions described under *Step 9a, Management of Side Effects*.

Telaprevir-Based Regimens

The first 12-week period of all telaprevir-based regimens includes all three medications—pegylated interferon, ribavirin, and telaprevir.

After 12 weeks, telaprevir is discontinued, while pegylated interferon and ribavirin are continued for an additional 12 weeks (24 weeks total) or an additional 36 weeks (48 weeks total), as noted below.

Indications for 24 total weeks of therapy:

- Treatment-naïve or prior relapser with an undetectable on-treatment HCV RNA at both 4 and 12 weeks

Indications for 48 total weeks of therapy:

- Treatment-naïve or prior relapse with on-treatment HCV RNA detectable, but ≤ 1,000 IU/ml at 4 and 12 weeks, and undetectable at 24 weeks
- Partial responder to dual therapy with on-treatment HCV RNA ≤ 1,000 IU/ml at 4 and 12 weeks, and undetectable at 24 weeks
- Compensated cirrhosis with on-treatment HCV RNA ≤ 1,000 IU/ml at 4 and 12 weeks, and undetectable at 24 weeks (see compensated cirrhosis in Definitions section)

Rules for early discontinuation of telaprevir -based regimens:

Indications for early discontinuation of telaprevir-based regimens due to treatment failure include the following.

- HCV RNA>1000 IU/ml at TW 4 or 12 ***or***
- HCV RNA detectable at TW 24 ***or***
- HCV RNA increase of > l $\log_{10}$ from nadir while on treatment

If *any* of these criteria are met, *all* therapy should be discontinued, including telaprevir, pegylated interferon, and ribavirin. Other criteria for early discontinuation of therapy include the severe adverse reactions described under *Step 9a*, *Management of Side Effects*.

Recommended treatment duration of dual therapy with pegylated interferon and ribavirin:

➡ Refer to *Appendices 4c* and *4d* to see the following recommendations as flowcharts.

- The recommended duration of dual therapy varies by HCV genotype and on-treatment HCV RNA response.
  - **Genotypes 1, 4, 5, and 6** are treated for 48 weeks.
  - **Genotypes 2 and 3** are treated for 24 weeks.
- The optimal duration of dual therapy treatment for genotypes 4, 5, or 6, or untypeable HCV is unknown; these patients should be treated with the 48-week course recommended for genotype 1.
- Inmates who have contraindications to ribavirin, regardless of genotype, should be treated with a 48-week course of pegylated interferon alone.
- Inmates who have HIV co-infection should be treated with 48 weeks of dual therapy, regardless of genotype.
- Early discontinuation of dual therapy may be indicated, based on the documented response to treatment and the occurrence of side effects (see *Appendix 2, Step 9*, and *Appendices 4c* and *4d*).
- Failure to achieve an EVR at 12 weeks is considered treatment failure (null response). *Treatment should be discontinued.*

- If an EVR at 12 weeks is achieved, but HCV RNA is still detectable, the HCV RNA test should be repeated at 24 weeks of treatment. Detectable HCV RNA at 24 weeks is considered treatment failure. *Discontinue treatment.*
- If the patient fails to achieve an RVR at 4 weeks, but does have an EVR at 12 weeks, then 48 weeks of treatment is usually sufficient. Although it may be beneficial in such cases to extend treatment for a total of 72 weeks, that practice has not been clearly established.
- For patients who achieve an RVR at 4 weeks, but experience significant side effects:
  - **Genotypes 1, 4, 5, and 6:** 24 weeks of treatment may be sufficient. Discontinuation of therapy after at least 24 weeks of treatment can be considered on a case-by-case basis in consultation with an expert.
  - **Genotypes 2 and 3:** 16 weeks of treatment may be sufficient. Discontinuation of therapy after 16–20 weeks of therapy can be considered on a case-by-case basis in consultation with an expert.

Step 10. Assess for sustained viral response (SVR).

An HCV RNA test should be obtained 24 weeks after the treatment is completed. A sustained viral response (SVR) is defined as undetectable HCV RNA at 24 weeks after completion of the treatment. If an SVR is achieved, the infection is considered eradicated. Patients who achieve an SVR should have an HCV RNA test obtained one year following the end of their treatment. Those who have undetectable HCV RNA at this time can be discontinued from the Chronic Care Clinic (unless there are other medical problems or concerns regarding the possibility of re-infection).

Considerations Regarding Re-Treatment: Patients who do not achieve an SVR from antiviral therapy can be categorized as having a null response, partial response, or relapse, as defined in *Appendix 2, Step 9b*. Re-treatment of such prior treatment failures should be considered on a case-by-case basis with the approval of the Central Office HSD, and with consideration of the following guidance:

- For *treatment failures with non-pegylated interferon* (with or without ribavirin), re-treatment should be considered on a case-by-case basis. HCV genotype 1 cases should be considered for triple therapy with an HCV PI-based regimen. Dual therapy with pegylated interferon and ribavirin of 48 weeks duration (in those who demonstrate an on-treatment virologic response) is used for retreatment of all other genotypes.
- *Partial responders and relapsers to a regimen of pegylated interferon and ribavirin* (dual therapy) can be considered for re-treatment if they have HCV genotype 1 and are appropriate candidates for treatment with an HCV PI-based regimen. All other genotypes will ordinarily not be re-treated. Although HCV PI-based regimens are approved for treatment of prior null responders to dual therapy, the response rates are relatively low. Considering the likelihood of developing viral resistance in the majority of such cases, retreatment with an HCV PI-based regimen is not currently recommended. Cases of advanced fibrosis or cirrhosis with prior null response to pegylated interferon and ribavirin should be considered for retreatment on a case-by-case basis.
- For *treatment failures with an HCV PI-based regimen*, re-treatment also is not indicated.
- For inmates who are eligible for re-treatment, it should only be considered for those who are the most likely to benefit from therapy and who are at significant risk of disease progression.
- Consensus interferon (interferon alfacon-1) is not recommended as an alternative re-treatment for prior treatment failures with a pegylated interferon and ribavirin regimen, due to the need for daily administration, as well as low response rates.

- Long-term antiviral maintenance therapy for prior treatment failures has been found to be ineffective and should not be prescribed.

➡ ***This is the last of the steps in the Stepwise Approach for Detecting, Evaluating, and Treating Chronic Hepatitis C. Section 4, "Chronic Hepatitis C Infection," continues below.***

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Complicating Medical Conditions

Compensated and Decompensated Cirrhosis

Compensated cirrhosis is defined as: bilirubin <1.5 mg/dL; INR <1.5; albumin >3.4 g/dL; and platelet count >75,000/mm^3; as well as *no evidence of*: ascites by liver ultrasound, esophageal varices by upper endoscopy, or hepatic encephalopathy.

Decompensated cirrhosis is defined as: evidence of significant liver disease (such as ascites, encephalopathy, marked thrombocytopenia, and bleeding esophageal varices), as well as loss of liver synthetic function (e.g., albumin $\leq$ 3.4 g/dL, and INR $\geq$1.5).

Inmates with HCV-related *compensated cirrhosis* can usually be treated with a standard regimen as described in this document. However, they have a higher rate of associated side effects, lower SVR rates, and should be monitored more closely.

Inmates with hepatitis C and evidence of *decompensated cirrhosis* should be referred to a Medical Referral Center for medical management. Antiviral therapy is ordinarily contraindicated in such patients, particularly if there is evidence of ascites or hepatic encephalopathy. Inmates with an isolated lab value indicating mild impairment in hepatic synthetic function, e.g., slightly depressed albumin or elevated INR, should be considered for treatment on a case-by-case basis.

Renal Insufficiency

Persons with HCV infection have an increased risk of renal disease that may be associated with cryoglobulinemia, and histologic findings that resemble idiopathic membranoproliferative glomerulonephritis (MPGN). Clinical manifestations include hematuria, proteinuria that is often in the nephrotic range, and a variable degree of renal insufficiency. Further diagnostic evaluation should be considered, e.g., cryoglobulins or renal biopsy, in consultation with a clinician experienced in the management of these conditions. Inmates with moderate-to-severe or progressive kidney disease (e.g., nephrotic syndrome, elevated plasma creatinine concentration, new hypertension, fibrosis, or tubulointerstitial disease on biopsy) should be considered for antiviral therapy for HCV infection, even in the absence of a degree of liver disease that ordinarily warrants antiviral therapy. Specific treatment regimens should be individualized in consultation with a Central Office physician and available physician experts. Ribavirin should not be administered if the creatinine is $\geq$1.5 mg/dL or the estimated GFR is <50 mL/min. Dose adjustments should be considered if the GFR is between 51–75 mL/min. Ribavirin should not be administered to patients on dialysis. No dosage adjustments are required for the HCV PIs, boceprevir and telaprevir; however, they should not be prescribed when ribavirin is contraindicated.

Hemodialysis

The goal of treating hepatitis C in persons with end-stage renal disease is to reduce the progression of liver disease and/or to clear the HCV infection in patients who may later undergo renal transplantation. Evaluation of these patients is complicated by several factors: (1) ALT levels are more likely to be

normal or near-normal in hemodialysis patients, even in the presence of significant fibrosis; (2) the need for a liver biopsy must be balanced against the increased risk of severe bleeding; and (3) hepatitis C treatment should be considered prior to referring the inmate for transplant (in consultation with a nephrologist). Subspecialty referral is required. Those on hemodialysis must be treated with interferon monotherapy (not with ribavirin or triple therapy). See *Appendix 5* for dosing with hemodialysis.

HBV and HCV Co-Infections

Coexistent infection with both HBV and HCV is estimated to be present in 10–15% of individuals with chronic hepatitis, cirrhosis, or hepatocellular carcinoma. HCV superinfection in HBsAg carriers appears to reduce HBV DNA levels in serum and liver tissues and to increase the rate of HBsAg seroconversion. Most patients who have dual HCV and HBV infections have detectable serum HCV RNA, but undetectable or low HBV DNA levels, which indicates that HCV is the predominant cause of liver disease in these patients. However, in about one-third of patients, levels of HBV DNA and HCV RNA fluctuate over time. Liver disease in co-infected individuals is usually more severe than in patients infected by HBV alone. Patients with dual HBV and HCV infection may also have a higher rate of HCC, compared to patients infected by either virus alone, particularly those who are anti-HCV and HBeAg positive.

Antiviral therapy for inmates with HBV and HCV co-infections should be initiated with great caution, and only in consultation with a specialist, due to the uncertainty of the risks and benefits of treatment and the lack of a recommended treatment regimen. All cases that may be candidates for treatment should be reviewed with a physician with expertise in viral hepatitis treatment, and should be approved via the Central Office nonformulary review process. Currently, HCV PIs are not approved for use with HBV and HCV co-infection cases.

HIV and HCV Co-Infections

The usual approach for screening for HCV infection should be applied to HIV-infected inmates. HIV-infected person with unexplained liver disease, a CD4 + T-cell count <500 cells/mm^3, and who are anti-HCV negative should have an HCV RNA assay obtained.

Patients co-infected with HIV and HCV have a two-fold increased risk of cirrhosis compared to those with HCV infection alone; thus they are high priority among potential candidates for treatment. However, HCV treatment response rates are lower in HIV-infected patients, and they have a higher risk of serious adverse effects.

Listed below are general recommendations related to the treatment of HCV/HIV co-infection. Prior to initiating treatment, consultation with an expert is recommended.

1. **Co-infected patients whose HIV infection is controlled and who have a significant liver biopsy result** (either IASL, Batts & Ludwig, or Metavir ≥ Stage 2; or Ishak ≥ Stage 3**), regardless of genotype, should be considered for HCV antiviral therapy.**
2. **Treatment for HIV and HCV infections should *not* be initiated simultaneously.** If the inmate is a strong candidate for HIV treatment (AIDS or CD4+ T-cell count <350 cells/mm^3), he or she should be treated first with HIV antiretroviral therapy. If not, consider initiating HCV antiviral therapy prior to initiating HIV treatment. It is generally recommended that several months elapse after initiating HIV antiretroviral therapy prior to initiating HCV treatment—so that adverse effects associated with the antiretroviral therapy can be distinguished from those associated with HCV treatment.
3. **Patients should be treated with peginterferon alfa and ribavirin at doses similar to those with HCV monoinfection.**

4. **Currently, HCV PIs are not approved for use with HIV and HCV co-infection cases, due to potential drug interactions and a lack of data to support the safety and efficacy when co-administered with HIV antiretroviral agents.**

5. **The recommended standard duration of HCV treatment is 48 weeks, regardless of genotype.**

6. **Drug interactions/contraindications/adverse reactions:**

   Co-infection with HIV and HCV increases the risk for antiretroviral-induced hepatotoxicity. This is especially true for stavudine, nevirapine, full-dose ritonavir, and tipranavir boosted with a low dose of ritonavir. If possible, these antiretrovirals should not be used to treat HIV patients co-infected with HCV. Regardless of which antiretroviral therapy (ART) is used, ALT and AST should be monitored monthly with any new ART, and then every 3 months. Asymptomatic ALT elevations up to 5 times the upper limit of normal can be monitored safely and do not require discontinuation of ART. Further evaluation should be undertaken for greater increases in the ALT, which may require temporary discontinuation or changing of the ART.

   Concurrent pharmacologic treatment of both HCV and HIV increases the risk for drug-drug interactions and drug toxicities. In particular, ribavirin increases the risk for pancreatitis and lactic acidosis in patients treated with didanosine. Ribavirin also increases the risk of anemia in patients treated with zidovudine. If possible, didanosine and zidovudine should be avoided or switched to another appropriate antiretroviral medication in HIV-infected patients who are being considered for treatment of HCV infection with pegylated interferon and ribavirin.

7. **Monitor closely those co-infected inmates for whom treatment is deferred** (see *Appendix 2, Step 3b*). Calculate an APRI (see *Table 4*) every 6 months. Re-biopsy should occur within 3 years.

Latent TB and Chronic HCV Co-Infection

Inmates with latent TB infection (LTBI) and chronic HCV infection should be considered for isoniazid treatment. They should be monitored for hepatotoxicity in accordance with the same guidelines established for latent TB patients who do not have HCV infection. All inmates require screening for symptoms of hepatitis while taking isoniazid. Those inmates with baseline ALT elevations also warrant periodic monitoring of their ALT levels.

Co-infected inmates can be treated concurrently for hepatitis C and LTBI; however, it is advisable to initiate LTBI treatment first, assess if it is tolerated, and then start hepatitis C treatment six months later. If both treatments are started at the same time, and elevations of ALT occur, it is not possible to determine which is the offending agent. Isoniazid should be discontinued in inmates with marked elevations in ALT or significant signs or symptoms of hepatitis, in accordance with BOP Guidelines for the Management of Tuberculosis.

5. Management of Cirrhosis

Transplantation Issues

Liver transplantation is the treatment of choice for patients with hepatic failure from chronic HBV and HCV infections. However, the lack of available donor organs limits this option, not only for inmate populations, but also for the general population. Split-liver transplantation from living donors is a promising option that may, in the foreseeable future, expand transplantation options to patients with liver failure. Even when donor livers are available, transplantation may be unsuccessful due to high rates of re-infection and progressive liver disease in the transplanted organ.

Nevertheless, inmates with hepatic failure from viral hepatitis should be assessed for eligibility for liver transplantation on a case-by-case basis by evaluating patient-specific factors such as the following: MELD scores that help predict patient mortality, medical contraindications for transplantation, mental health stability, evidence of ongoing substance abuse, criminal history factors that may negate successful transplantation, and patient motivation (as evidenced by adherence to current treatment recommendations). Inmates who are potential candidates for liver transplantation should be advised of the limited access to donor livers and, where available, be referred to local transplant centers for evaluation. If transplantation during incarceration is not feasible, inmates should be evaluated for early release, taking into consideration public safety concerns, local correctional policies, and governing laws and regulations.

Morbidity Assessment Based on MELD Scores

The Model for End-Stage Liver Disease (MELD) predicts liver disease severity and the risk of three-month mortality using a "score" that is based on serum creatinine, serum total bilirubin, and prothrombin time (INR). In a study of patients with end-stage liver disease, who were awaiting liver transplantation, three-month mortality was closely correlated with MELD scores:

MELD < 9	mortality = 2%
MELD = 20–29	mortality = 20%
MELD = 30–39	mortality = 53%
MELD $\geq$ 40	mortality = 71%

The value of MELD as a predictor of mortality is limited by its dependency on serum creatinine, which can fluctuate with changes in fluid status. MELD is a better predictor of mortality for particular populations than for any given individual. Nevertheless, MELD provides useful information for assessing the morbidity of inmates with end-stage liver disease.

All inmates with decompensated cirrhosis should have a MELD score determined to assess their mortality risk. MELD scores should be recalculated over several weeks for inmates with shifting fluid status. The MELD score can be calculated by utilizing a calculator provided by the United Network for Organ Sharing, available at http://optn.transplant.hrsa.gov/resources/MeldPeldCalculator.asp?index=98. Data required includes: date of birth, bilirubin, creatinine, INR, and dialysis status. Inmates with MELD scores of 30 or greater should be considered for Medical Referral Center designation.

Note: *The MELD score predicts mortality, independent of clinical parameters such as hepatic encephalopathy, ascites, and variceal bleeding. These significant complications of cirrhosis, however, should also be considered in referring patients for Medical Referral Center designation.*

Preventive Measures

The following preventive measures should be considered for inmates with cirrhosis:

- **Immunize** against influenza (annually), pneumococcal pneumonia, and hepatitis A and B (unless immune).
- **Provide patient education:**
  - Eat a low-salt, low-fat, "heart healthy" diet.
  - Completely abstain from alcohol during incarceration and after release.
  - Avoid iron supplements and potentially hepatotoxic medications, such as nonsteroidal inflammatory drugs (NSAIDS).

- **Perform a baseline upper endoscopy (EGD)** to screen for esophageal varices. Once esophageal varices have developed, the annual rate of hemorrhage is 5–15%. The frequency of follow-up EGD is determined by the presence of risk factors for progression or bleeding of the varices, including decompensated cirrhosis, red wale marks on the variceal surface, and size of varices > 5 mm. Annual EGD is recommended for patients with decompensated cirrhosis, whether or not varices are present, and for those with a history of variceal hemorrhage. Biennial EGD is recommended for patients who have small varices that have not bled and who are not being treated with nonselective beta-blockers. EGD is recommended every 3 years for compensated cirrhosis with no varices. In general, routine follow-up EGD is not required for varices that have not bled if nonselective beta-blocker therapy is prescribed.

- **Nonselective beta-blocker therapy, such as propranolol or nadolol, is indicated** for prevention of variceal hemorrhage in patients with varices of any size that have not bled, with either decompensated cirrhosis or red wale marks on the varices, and for all patients with a history of variceal hemorrhage. Nonselective beta-blockers may be appropriate for patients who have varices that have not bled, but who have no other risk factors for hemorrhage. This treatment is not indicated for patients with cirrhosis who have no esophageal varices. The dose of beta-blocker should be titrated weekly to reduce the resting heart rate by 25%—without reducing the pulse to less than 55 beats/minute or the systolic blood pressure to lower than 90 mm Hg. The usual starting dose for oral propranolol is 20 mg twice each day, and for nadolol, 40 mg once daily. Once started, therapy should be continued indefinitely unless contraindicated. Nonselective beta-blocker therapy is relatively contraindicated in certain medical conditions such as asthma, peripheral vascular disease, and insulin-requiring diabetics with frequent hypoglycemic episodes.

- **Provide primary and secondary prophylaxis for spontaneous bacterial peritonitis (SBP)** with an antibiotic such as ciprofloxacin, or trimethoprim-sulfamethoxazole (TMP-SMX). Primary prophylaxis generally involves limited treatment periods in high risk patients, such as those with upper gastrointestinal hemorrhage. Secondary prophylaxis is indicated in patients with a history of one or more prior episodes of SBP. Oral medication options include: ciprofloxacin, 750 mg weekly; or TMP-SMX DS, one tablet daily.

- **Provide prophylaxis against hepatic encephalopathy, and be alert for the common factors which cause exacerbations of encephalopathy.** Lactulose is the mainstay of both treatment and prophylaxis for hepatic encephalopathy. Lactulose lowers the gut pH and converts NH_3 (ammonia) to NH_4, which is non-absorbable and thus excreted in the stool. Certain antibiotics such as neomycin and rifaximin are also sometimes prescribed to alter the gut flora and thereby decrease ammonia production. However, good, controlled studies are lacking that clearly support the use of antibiotics over lactulose; moreover, long-term use of antibiotics has the potential for bacterial overgrowth syndromes. Neomycin also has potential nephrotoxicity and ototoxicity.

  The dose of lactulose (10 grams/15mL) is patient-specific, typically starting at 15–30 mL once or twice daily until the patient is having two or three soft stools per day. If this dose does not adequately address the cognitive impairments, the dose may need to be increased, causing more frequent, semi-liquid stools.

  Lactulose enemas are the treatment of choice for somnolent patients with encephalopathy who are unresponsive to verbal and/or painful stimuli. One liter of 20% lactulose is infused per rectum every hour until the patient becomes arousable. Inmates with abnormal vital signs, low pulse oximetry, or periods of apnea should be hospitalized or placed on an inpatient unit at an MRC for this treatment.

  Common factors which exacerbate hepatic encephalopathy are:
  - Excess dietary protein intake
  - GI bleeding

- Infections (increased temperature results in dehydration)
- Sedative/hypnotic and opiate use (even at "typical" doses)
- Overzealous diuresis with loop diuretics. (Decreased potassium and decreased plasma volume result in increased ammonia levels. Titrate diuretics incrementally, and correct hypokalemia when detected.)

- **Screen for hepatocellular carcinoma (HCC).** Inmates with chronic HCV infection and cirrhosis are at increased risk for HCC. Although the optimal screening strategy is uncertain, a liver ultrasound should be considered every six months as the safest and most cost-effective approach. Screening should be conducted regardless of whether or not the inmate has been treated for hepatitis C. Serum alpha-fetoprotein screening is of limited use, since it is not usually elevated to a significant level until the tumor is at least 2 cm—which is easily detectable on ultrasound in virtually all patients. CT scanning should ordinarily not be used in lieu of ultrasound for HCC screening, due to the high radiation exposure that would be anticipated over ten or more years of biannual scans.

  HCC screening should begin when the inmate is found to have cirrhosis—whether by history, by liver biopsy, by presentation of decompensation such as bleeding esophageal varices or hepatic encephalopathy, or based on a pattern of clinical or laboratory findings. Ultrasound screening should be conducted on any HCV-infected inmate with the typical laboratory findings of cirrhosis, which include an inverted AST/ALT ratio, an albumin < 3.4, and a platelet count < 120–140K. An AST to platelet ratio index (APRI) significantly greater than 1.5 is also strongly suggestive of cirrhosis, and may be used as an independent marker to start screening for HCC (see *Table 4* for calculation).

Managing Complications and Co-Morbidities

Ascites

Of the major manifestations of decompensated cirrhosis, the most common is ascites. A diagnostic paracentesis by qualified personnel should be performed in newly presenting cases of ascites, and should include assessment of ascitic fluid cell count with differential, ascitic fluid total protein, and serum-ascites albumin gradient. A serum-ascites albumin gradient ≥ 1.1 g/dL is indicative of portal hypertension as the cause. Ascitic fluid cultures should be collected in blood culture bottles if infection is suspected, e.g., fever, abdominal pain, etc. Eighty-five percent of cases of ascites are caused by cirrhosis.

The primary treatment includes dietary sodium restriction of 2 gm/day, and a combination of oral diuretics using spironolactone and furosemide (starting at 100 mg and 40 mg, respectively) once daily in the morning. Monotherapy with spironolactone achieves less dramatic diuresis and is associated with a higher rate of hyperkalemia, but may be effective in the presence of smaller amounts of ascites or edema. If the desired weight and fluid loss is not achieved, these doses may be increased every 3 to 5 days (maintaining the same ratio) up to a maximum of 400 mg/day of spironolactone and 160 mg/day of furosemide. With this regimen, 90% of patients with ascites can achieve the goals of treatment, which include a 24-hour urinary excretion of sodium > 78 mmol/day, and diuresis of ascites and edema with a maximum rate of weight loss of 0.5 Kg/day. A greater rate of weight loss is appropriate for patients with greater amounts of edema. A spot urinary sodium/potassium ratio > 1 correlates fairly well with a 24-hour urine sodium excretion > 78 mmol/day and is easier to obtain.

Failure to achieve treatment goals should prompt an assessment of adherence to sodium restriction and diuretic therapy, the use of nonsteroidal anti-inflammatories, which interfere with diuresis, and consideration of other causes of ascites. Amiloride may be used in place of spironolactone for patients with painful gynecomastia. Although eplerenone, a selective mineralocorticoid antagonist, has a much lower incidence of gynecomastia, its role in the treatment of ascites has not been well studied. Fluid restriction is indicated for serum sodium < 120–125 mEq/L. Diuretics should be discontinued if serum

creatinine rises to > 2 mg/dL, serum sodium drops to < 120 mEq/L despite fluid restriction, or encephalopathy develops. Abstaining from alcohol and treatment for chronic hepatitis B virus infection may improve the symptoms of decompensated cirrhosis from these causes. Treatment of ascites that is refractory to these interventions may include serial paracenteses, transjugular intrahepatic portasystemic shunt (TIPS), which usually is performed by an interventional radiologist, and/or liver transplantation. TIPS is effective in reducing ascites and rates of rebleeding from esophageal varices, but may be associated with more frequent or severe episodes of encephalopathy and does not improve mortality rates. Contraindications to TIPS include: primary prevention of variceal bleeding, congestive heart failure, moderate to severe pulmonary hypertension, uncontrolled infection or sepsis, biliary obstruction, multiple hepatic cysts, hepatocellular carcinoma, hepatic vein obstruction or portal vein thrombosis, severe coagulopathy with INR > 5, or platelet count < 20,000/cm^3.

Pruritus

Pruritus in cirrhosis is thought to be due to increased bile acids from cholestasis, as well as possibly an increased production of endogenous opioids. Cholestatic pruritis may be caused by enhanced concentrations of bile salts in the systemic circulation and peripheral tissues, which is seen in patients with primary biliary cirrhosis and chronic renal failure. Intestinal anion exchange resins such as cholestyramine, colestipol, and colesevelam bind many hydrophobic bile acids in the intestine and inhibit enterohepatic reuptake of intestinal bile salts; they are effective in decreasing disease-related, enhanced concentrations that can cause cholestatic pruritis. Sertraline, at 75–100 mg daily, has been found to be effective in patients suffering from various forms of cholestasis. Naltrexone, an opioid antagonist, at 12.5–50 mg per day, may also be effective. Exogenously administered narcotics can contribute to pruritus, so the patient's need for these medications should be carefully evaluated in the context of the management of pruritus.

Depression

Inmates with cirrhosis often have comorbid depression, especially when they have decompensated cirrhosis and are struggling with ascites, wasting, and encephalopathy. Although any of the SSRIs may be effective, most require approximately 50% dose reduction to accommodate delayed hepatic metabolism. Avoid SSRIs with a long half-life, e.g., fluoxetine. Sedating antidepressants such as mirtazapine, doxepin, trazodone, and amitriptyline should be either avoided or prescribed in very low doses, due to their potential for adding to the cognitive impairments of hepatic encephalopathy.

6. Infection Control

Patient Education

During orientation to the institution and when appropriate during clinical evaluations, *all* inmates should be counseled on the importance of preventing blood exposures among themselves. They should be advised about the exposure inherent in sharing items such as toothbrushes and razors, as well as during unsafe behaviors such as injection drug use, tattooing, and sexual contact with other inmates (see *Appendix 1*, *Inmate Fact Sheet*).

Reporting

Each institution should have a surveillance system for notifiable infectious diseases, in accordance with BOP policy. Acute hepatitis C is a reportable condition in many states. Inmates with acute hepatitis C should be reported to local or state authorities where required and to the Central Office HSD. Inmates with chronic HCV infection should be reported to the local or state health authorities where required.

Containment

Inmates with acute hepatitis C and chronic HCV infection do not require isolation, but should be counseled on the specific measures necessary for preventing transmission of HCV to others—during incarceration and upon release (see *Appendix 1*). Standard infection control precautions should be used in managing these inmates (see *Infection Control Practices* below).

Infection Control Practices

Infection control practices for preventing transmission of blood borne pathogens are outlined in *Appendix 7*, including safe practices for injections and diabetes care. Each BOP institution should provide infection control training to staff who have responsibilities that involve percutaneous procedures, including practical demonstration of aseptic techniques and instruction on reporting exposures or breaches. Inmate workers should also receive infection control training that is applicable to their duties, e.g., clean-up and disinfection following a blood spill, and reporting exposures from incidents involving spray or splash of blood or accidental puncture.

Each institution should designate specific staff members to assess the facility's compliance with infection control guidelines. The assessment should include observation of relevant staff and inmate workers, and tracking use of infection control supplies.

Infection Control for Hemodialysis

- **Screening:** Inmates on hemodialysis who do not have chronic HCV infection should be screened regularly for newly acquired HCV infection. Their serum ALT levels should be measured monthly, and their anti-HCV should be measured by an immunoassay semi-annually. Hemodialysis patients who are found to have a positive anti-HCV screening immunoassay should have an HCV RNA assay performed.
- **Infection control:** Infection control measures to prevent HCV transmission during hemodialysis should be implemented in accordance with CDC guidelines. So long as these measures are conducted properly, inmates with HCV infection who are receiving dialysis do not need to be isolated from other patients or dialyzed separately on dedicated machines. Dialyzers used for inmates with HCV infection can be reused.

  The hemodialysis machine and its components can be vehicles for patient-to-patient transmission of blood borne viruses and pathogenic bacteria. Written protocols should be in place regarding sterilization, disinfection, and cleaning of medical devices and instruments. These protocols should include external surfaces and waste containers, which can be contaminated when the dialyzers are primed, when blood tubing is draped or clipped to waste containers, and when items are placed on machine surfaces. In addition to the Standard Precautions, more stringent precautions should be implemented in hemodialysis units because of the increased potential for cross-contamination. Examples of more stringent measures include restricting the use of common supplies, instruments, medications, and medication trays, and prohibiting the use of a common medication cart.

Contact Investigation

Contact investigations should be initiated for inmates with acute hepatitis C who have been incarcerated during the two-week to six-month period prior to disease onset. Inmates with acute hepatitis C should be interviewed for information regarding possible sources of exposure (see *Table 8* below). As locally required, acute hepatitis C should be reported to public health authorities.

Table 7. Contact Investigation Interview for Acute Hepatitis C

- Incarceration in BOP facility during 2-week to 6-month period prior to illness onset?
- Close contact person with confirmed or suspected hepatitis C?
- Cell-mate or dorm-mate of person with acute hepatitis?
- Injection drug use?
- Sexual partners?
- Recent hospitalization or recent dental work?
- Recent IV infusions, injections, glucometer use, or dialysis?
- Recent tattoo or body piercing? Other contact with human blood?

Post-Exposure Management

- **Emergent care:** Wounds and skin sites that have been in contact with blood or bloody body fluids should be washed with soap and water. Exposed mucous membranes should be flushed with water. *Squeezing the wound or treating with topical antiseptics is not recommended.*
- **Counseling:** Inmates with percutaneous or mucosal exposures to blood should be assessed by a qualified health care provider and counseled regarding their risk of acquiring HCV infection, the natural history of HCV infection, and the recommendations for post-exposure management.
- **Post-exposure follow-up:** No vaccine or passive immunization is available to prevent acquisition of HCV infection following an exposure. The following guidelines should be used for managing inmate exposures to HCV:
  - Whenever feasible, the source individual's blood should be tested for anti-HCV (unless that person's infection status is already known).
  - Individuals with a known hepatitis C exposure, or if status of the source individual is unknown, should be referred for a medical evaluation and follow-up. Recommended post-exposure follow-up is outlined below in *Table 8*.

    Table 8. Recommended Post-Exposure Follow-Up for Hepatitis C

    Baseline: anti-HCV & ALT

    4 Months: anti-HCV & ALT
    - If anti-HCV (+), then obtain HCV RNA.
    - If HCV RNA (+), then evaluate for treatment.

    6 months: If 4-month anti-HCV is negative, then obtain anti-HCV & ALT.
    - If anti-HCV negative, then STOP follow-up.
    - If anti-HCV (+), then obtain HCV RNA.
    - If HCV RNA (+), then evaluate for treatment.

  - The National Clinician's Post-Exposure Prophylaxis PEPline is available 24-hours for consultation on exposures to blood borne pathogens: **1-888-448-4911**.
  - Inmates with evidence of newly acquired HCV infection should be appropriately counseled and referred for further medical evaluation, including possible treatment for acute hepatitis C.
  - Acute cases of hepatitis C should be reported as required and a contact investigation initiated. See "Reporting" and "Contact Investigation" in the section on Infection Control (Section 6).

Definitions

APRI (AST Platelet Ratio Index) is a score based upon commonly available lab values that is sometimes used to assess the degree of liver fibrosis (see *Table 4* for calculation).

Absolute contraindication is a condition or factor that by itself precludes a specific intervention.

Anti-HCV is the antibody to HCV core and nonstructural proteins, detectable from several weeks to months after clinical hepatitis.

Anti-HCV screening assay is an immunoassay such as an enzyme immunoassay (EIA) or a chemiluminescence immunoassay (CIA); it is used to screen for HCV infection by measuring antibodies to HCV antigens.

Compensated cirrhosis is defined as: bilirubin <1.5 mg/dL; international normalized ratio (INR) <1.5; albumin >3.4 g/dL; and platelet count >75,000/mm^3; as well as no evidence of: ascites by liver ultrasound, esophageal varices by upper endoscopy, or hepatic encephalopathy.

Decompensated cirrhosis is defined as: evidence of significant liver disease (such as ascites, encephalopathy, marked thrombocytopenia, and bleeding esophageal varices), as well as loss of liver synthetic function (e.g., albumin $\leq$3.4 g/dL, and international normalized ratio (INR) $\geq$1.5).

Early viral response (EVR) during treatment of chronic hepatitis C is a minimum two log (2 $\log_{10}$) decrease in the level of HCV RNA (compared to pretreatment levels) after the first 12 weeks of treatment, as measured by an HCV RNA assay. This term has also been used to describe an undetectable HCV RNA level after 8 weeks of treatment with a boceprevir-based regimen.

End of treatment response (ETR) after antiviral treatment of chronic hepatitis C is the absence of detectable HCV RNA immediately after the completion of a course of treatment (usually 24 weeks for genotypes 2 and 3, and 48 weeks for genotype 1).

Extended Rapid Viral Response (eRVR) to treatment for chronic hepatitis C is defined as undetectable HCV RNA after both 4 and 12 weeks of treatment.

Hepatic steatosis, also known as "fatty liver," is the collection of excessive amounts of triglycerides and other fats inside liver cells.

Hepatitis C is an acute or chronic viral hepatitis caused by an RNA virus that is transmitted primarily by percutaneous contact with blood.

HCV is hepatitis C virus, an enveloped, single-stranded RNA virus.

MELD or Model for End-stage Liver Disease is a validated, disease severity index that uses age, creatinine, bilirubin, and prothrombin time to predict mortality.

Null Response to treatment for chronic hepatitis C is defined as less than a 2 $\log_{10}$ decrease in HCV RNA after 12 weeks of treatment.

Partial Response to treatment for chronic hepatitis C is defined as greater than or equal to a 2 $\log_{10}$ decrease in HCV RNA, but where HCV RNA is still detectable after 24 weeks of treatment.

Rapid viral response (RVR) during treatment of chronic hepatitis C is defined as undetectable HCV RNA after the first 4 weeks of treatment.

Relapse associated with the treatment for chronic hepatitis C is defined as undetectable viremia at the end of treatment, but then subsequent detection of HCV RNA virus after treatment is stopped.

Relative contraindication is a condition or factor that may preclude a specific intervention when considered in conjunction with other criteria.

RIBA (anti-HCV) is the recombinant immunoblot assay that measures antibodies to HCV antigens through immunoblot technology. RIBA is no longer routinely used to confirm HCV infection.

Standard precautions are protective measures to be used for all patient/inmate contacts in situations where infections can be transmitted by contaminated blood and body fluids. Precautions include: (1) the wearing of gloves and other personal protective equipment that provide an impervious barrier when soiling is likely; (2) procedures for protective handling of contaminated materials and equipment (e.g., using puncture-resistant devices and leak-proof protection); and (3) routine cleaning of all contaminated surfaces and equipment.

Steatosis (see *Hepatic steatosis* above)

Sustained viral response (SVR) after antiviral treatment of chronic hepatitis C is the absence of detectable HCV RNA in the serum 24 weeks after the treatment is completed; it is measured by an HCV RNA assay.

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Appendix 1. Inmate Fact Sheet on Hepatitis B and Hepatitis C

Am I at risk for infection with hepatitis B or hepatitis C?

You may be at risk for infection with hepatitis B or hepatitis C if you have ever injected drugs or had sex with an infected partner. People who received blood transfusions before 1992 may also be at risk. Talk to a health care provider about the risks of infection that affect you personally.

How can I prevent getting hepatitis B or hepatitis C while I am in prison?

- Do not have sex with other inmates, shoot drugs, or get a tattoo or body piercing.
- Do not share tooth brushes, razors, nail files or clippers, or other personal items that might have blood on them.

Why should I be tested for hepatitis B and hepatitis C?

You should be tested if you are at risk. That way, if tests show that you have hepatitis B or hepatitis C, doctors can monitor your health and decide whether you need treatment. It's also important for *you* to know if you are infected, so that you can take precautions to prevent infecting other people—including your unborn child if you or your partner become pregnant.

How do I get tested for hepatitis B and hepatitis C?

A simple blood test can determine if you are infected.

Are hepatitis B and hepatitis C dangerous to my health?

Most people with hepatitis B or hepatitis C can remain healthy. However, a small but significant number do develop serious liver disease. Treatments for hepatitis B and hepatitis C are fairly effective, and we expect that new medications in the future will work even better. Talk to a health care provider to better understand your level of risk for liver disease and to discuss your treatment plan.

How can I prevent giving hepatitis B or hepatitis C to others if I am infected?

- First, remember that you can spread this infection even if you feel fine!
- Do not shoot drugs or have sex with other inmates.
- Do not share personal items that might have your blood on them, such as tooth brushes, nail files or clippers, or razors.
- Cover your cuts and skin sores to keep your blood from contacting other people.
- If you are being released, talk to a health care provider about specific ways you can reduce the risks of spreading the infection to others. For example, in addition to the precautions you are already taking, do not donate blood, semen, or body organs.

Appendix 2. Stepwise Approach for Detecting, Evaluating, and Treating Chronic Hepatitis C

Outlined below are steps for detecting, evaluating, and treating hepatitis C in the BOP. Refer to the text in Section 4 for further information about each step.

Step 1. Appropriately screen for hepatitis C.

☐ **Assess for presence of hepatitis C risk factors:**

Presence of Certain Clinical Conditions *(regardless of sentencing status)*

- □ Chronic hemodialysis (screen ALT monthly and anti-HCV semi-annually)
- □ Elevated ALT levels of unknown etiology
- □ Evidence of extrahepatic manifestations of HCV (mixed cryoglobulinemia, mebranoproliferative glomerulonephritis, or porphyria cutanea tarda)

Presence of Hepatitis C Risk Factors *(sentenced inmates only)*

- □ Ever injected illegal drugs or shared equipment
- □ Received tattoos or body piercings while in jail or prison
- □ HIV-infected or chronic HBV infection
- □ Received a blood transfusion or organ transplant before 1992, or received clotting factor transfusion prior to 1987
- □ History of percutaneous exposure to blood
- □ Ever received hemodialysis

☐ **Screen for anti-HCV (EIA or CIA) if risk factors are present or if inmate requests a test.**

Step 2. Provide initial medical follow-up for anti-HCV positive inmates.

☐ **Take a medical history and perform a physical examination.**

☐ **Try to establish duration of HCV infection by history, e.g., time period of injection drug use**

☐ **Obtain baseline labs** (see *Appendix 3*).

☐ **Evaluate inmate for other potential causes of liver disease.**

☐ **Initiate patient counselling** (see patient education resources, *Appendix 1* and *Appendix 8*).

☐ **Initiate preventive health measures listed below:**

- **Hepatitis B vaccine:** Indicated for inmates with chronic HCV infection. For foreign-born inmates, consider prescreening for hepatitis B immunity prior to vaccination. *Inmates with evidence of liver disease should be priority candidates for hepatitis B vaccination.*
- **Hepatitis A vaccine:** Indicated for inmates with chronic HCV infection who have other evidence of liver disease. For foreign-born inmates, consider prescreening for hepatitis A immunity prior to vaccination.
- **Pneumococcal vaccine:** Offer to all HCV-infected inmates with cirrhosis.
- **Influenza vaccine:** Offer to all HCV-infected inmates annually. Inmates with cirrhosis are high priority for influenza vaccine.
- **Hepatocellular carcinoma (HCC) screening:** Data supporting specific parameters for HCC screening are lacking. For patients with both cirrhosis *and* chronic HCV infection, some experts recommend screening by liver ultrasound every six months
- **Esophageal varices screening:** Consider an upper endoscopy for any inmate with known cirrhosis, and for those with suspected cirrhosis who are not candidates for liver biopsy.

(Appendix 2 is continued on the next page.)

Appendix 2. Stepwise Approach for Detecting, Evaluating & Treating Chronic Hepatitis C *(page 2 of 8)*

Step 3a. Determine if hepatitis C treatment is *not recommended.*

Hepatitis C treatment is ***not recommended*** if any of the following four conditions are present:

(1) Contraindications to peginterferon:

- □ Severe uncontrolled psychiatric disease, particularly depression with current suicidal risk.
- □ History of solid organ transplant (renal, heart, or lung)
- □ Certain autoimmune disorders, e.g., autoimmune hepatitis
- □ Uncontrolled endocrine disorders, e.g., diabetes, thyroid disease
- □ Serious concurrent medical diseases, such as severe: hypertension, heart failure, coronary heart disease, COPD
- □ Decompensated cirrhosis (see Complicating Medical Conditions)
- □ Platelet count <75,000/mm^3 or ANC <1,500 cells/mm^3
- □ Documented nonadherence to prior therapy, or failure to complete pretreatment evaluation process
- □ Ongoing injection drug use or alcohol use
- □ Hypersensitivity to interferon

(2) Inmate will be incarcerated for an insufficient period of time to complete treatment.

(3) Inmate has an unstable medical or mental health condition which precludes antiviral therapy.

(4) Inmate refuses treatment.

If any one of the above four conditions are present, then STOP further treatment-related work-up. No further HCV testing—i.e., HCV RNA, genotype, liver biopsy—is indicated at this time. If conditions change, reconsider for hepatitis C treatment.

Step 3b. Monitor HCV-infected inmates who are *not* on treatment.

☐ **Have a plan for each inmate:** Outline the plan clearly on the Problem List/Health Summary.

☐ **Get baseline laboratory evaluations:** Obtain baseline labs as specified in *Appendix 3*.

☐ **Follow-up labs:**

- □ Every 6 months: ALT, AST, bilirubin, albumin, and INR
- □ Every year: CBC (with differential & platelets). Calculate APRI (see Table 4 for formula).
- □ Other labs as clinically indicated, e.g., A1C (diabetics); TSH and free T4 (if hyperthyroid).

☐ **Repeat liver biopsies:** The determination regarding the timing of re-biopsy (for those inmates whose treatment is deferred) should be based on subsequent increases in the AST/Platelet Ratio Index (APRI)* and/or evidence of steatosis or inflammation. Those who develop clinical evidence of liver disease should be priority candidates for re-biopsy. If the APRI < 0.5, there is a lower risk of disease progression; if the APRI > 0.5, there is a higher risk.

Note: **The following tests are generally *NOT* indicated for inmates *not* on treatment.**

- **HCV RNA and HCV genotype:** These tests are not needed unless treatment is indicated. *Do not* periodically check HCV RNA values for inmates who are not currently candidates for treatment. There is no correlation between HCV RNA levels and the risk or rate of disease progression.
- **Alpha fetoprotein:** Unless cirrhosis is known or strongly suspected, alpha fetoprotein is unnecessary because the risk for hepatocellular carcinoma in HCV infection does not begin until the development of cirrhosis.
- **Liver ultrasound or CT examinations:** Similarly, do not perform periodic liver ultrasound or CT examinations unless cirrhosis is present or there is another definitive indication.
- **Serum ammonia levels:** In a patient with known liver disease, the serum ammonia level has no prognostic value; nor can it be used for monitoring the effectiveness of medications such as lactulose. Serum ammonia levels are only useful in a delirious patient whose diagnosis is uncertain.

(Appendix 2 is continued on the next page.)

Appendix 2. Stepwise Approach for Detecting, Evaluating & Treating Chronic Hepatitis C *(page 3 of 8)*

↓ *For inmates who may be eligible for hepatitis C treatment, proceed as follows.* ↓

Step 4. Obtain HCV RNA assay and HCV genotype.

Before initiating antiviral therapy, an **HCV RNA** (viral load) is required in order to confirm chronic infection and guide therapy. If the HCV RNA level is undetectable, the individual can be considered uninfected.

The ***HCV genotype*** should be ordered in conjunction with the initial HCV RNA test. In general, the test for genotype is not repeated—unless re-infection is suspected.

Step 5. Assess liver fibrosis and need for a liver biopsy.

☐ **Determine if a liver biopsy is indicated based upon the criteria below:**

□ **HIV infection:**	High priority for liver biopsy, regardless of genotype.
□ **Other liver disease suspected:**	High priority for liver biopsy, regardless of genotype, e.g., homozygous hemochromatosis.
□ **Genotypes 1, 4, 5, 6:**	Biopsy is generally recommended. Prioritize referral of inmates for biopsy based on the AST/Platelet Ratio Index (APRI), which is calculated as follows (see example in *Table 4*): **Formula:** {AST ÷ lab upper limit of normal (ULN) for AST x 100} ÷ {platelet ct ÷ 1,000} If APRI <0.5, lower risk of progression; if APRI ≥0.5, higher risk.
□ **Genotypes 2, 3:**	Biopsy is *not needed* prior to treatment (except if HIV-infected or other type of liver disease is known or suspected). See note (*) in *Appendix 3*.
□ **Compensated cirrhosis:**	Decide about liver biopsy on a case-by-case basis, in consultation with a hepatitis C expert. Either perform a liver biopsy as soon as possible, or treat empirically *without* biopsy confirmation.
□ **Decompensated cirrhosis:**	Liver biopsy and treatment are generally not indicated (see Complicating Medical Conditions at the end of Section 4 in the text.)

Step 6. Determine if treatment should be initiated.

☐ **Identify if *any* of the following indications for antiviral therapy are present:**

- □ **Genotype 2 or 3** with no biopsy performed.
- □ **Liver biopsy reveals chronic hepatitis with significant fibrosis:** (IASL, Batts&Ludwig, or Metavir ≥2, or Ishak ≥3)—regardless of genotype (see Table 5).
- □ **Compensated liver disease** (bilirubin <1.5 mg/dL; INR <1.5; albumin >3.4 g/dL; and platelets >75,000/mm3; as well as no evidence of: ascites, esophageal varices, or hepatic encephalopathy.

☐ **Review special considerations related to treatment initiation** (i.e., mental illness, substance abuse, adherence concerns). See section on Special Considerations under Step 6 in text.)

☐ **Counsel patient regarding the pros and cons of initiating hepatitis C treatment** See section on Patient Counseling under Step 6 in text.)

☐ **Determine if patient is willing to be treated and to adhere to treatment requirements.**

☐ **Document rationale for decisions about treatment in the medical record.**

(Appendix 2 is continued on the next page.)

Appendix 2. Stepwise Approach for Detecting, Evaluating & Treating Chronic Hepatitis C *(page 4 of 8)*

Step 7. Conduct a pre-treatment evaluation.

Assure that all recommended pre-treatment evaluations have been completed within the time frames enumerated in the "Treatment Approval Form" (BOP-A803.060).

☐ **Laboratory tests:** See *Appendix 3* for list of recommended pre-treatment tests and evaluations.

- □ **Interferon—**The patient should have the following acceptable labs for treatment initiation: absolute neutrophil count >1500/cells/mm^3; platelets >75,000/mm^3.

  Note: When starting treatment with platelet counts between 75–90,000, consult first with a physician with expertise in treatment of hepatitis C.

- □ **Ribavirin—**The patient should have the following acceptable for treatment initiation: Hemoglobin >13 g/dL (men) or >12 g/dL (women); creatinine <1.5 mg/dL (or creatinine clearance >50 mL/min).

  Note: Some experts recommend that an acceptable starting hemoglobin is >12 g/dL (men) or >11 g/dL (women).

☐ **Assess for contraindications to ribavirin** *(and if present consider interferon monotherapy).*

- □ Thalassemias (sickle cell anemia) or other hemoglobinopathy.
- □ Significant cardiac disease (arrhythmias, angina, CABG, MI) in the past 12 months.
- □ Pregnancy or unwillingness to use contraception in both female patients and female partners of male patients.
- □ Renal dialysis or creatinine clearance ≤ 50 mL/min.
- □ Hypersensitivity to ribavirin

☐ **Pregnancy test:** Because ribavirin may cause fetal abnormalities, all female inmates of childbearing potential must have a pregnancy test immediately prior to initiating therapy, and monthly thereafter. Continue with monthly tests until 6 months after treatment is completed.

☐ **Cardiac risk assessment:** Prior to therapy, a cardiac risk assessment is critically important because hemolysis associated with ribavirin may precipitate angina pectoris. Also, obtain an ECG for inmates with preexisting cardiac disease.

☐ **Mental health evaluation** is critically important prior to initiating treatment due to the severe psychotropic effects of interferon.

☐ **Compensated cirrhosis:** Obtain liver-spleen ultrasound (preferred) or abdominal CT-scan, and measurements of alpha fetoprotein, prior to treatment initiation. A screening upper endoscopy is indicated if the ultrasound suggests portal hypertension.

Step 8. Determine appropriate treatment and obtain informed consent.

- **Dual Therapy:** pegylated interferon *plus* ribavirin
  - ▸ If contraindications to ribavirin exist, then the appropriate treatment is monotherapy with peginterferon. *Ribavirin should never be given as monotherapy.*
  - ▸ *Standard dosing* is outlined on the next page of Step 8. See *Appendix 5*, *Interferon/ Ribavirin Drug Information*, for information on dosing with renal failure and HIV/HCV co-infection, and when interferon is used as monotherapy.
- **Triple therapy:** pegylated interferon *plus* ribavirin *plus* HCV protease inhibitor
  - ▸ Preferred treatment for HCV genotype 1
  - ▸ See the page after next in Step 8 for *Dosing and Treatment Duration in Triple Therapy*.
- **Obtain informed consent** after reviewing potential side effects (form BP-A0806).

(Step 8 is continued on the next page.)

Appendix 2. Stepwise Approach for Detecting, Evaluating & Treating Chronic Hepatitis C *(page 5 of 8)*

Step 8. Determine appropriate treatment and obtain informed consent. *(continued)*

Dosing for antiviral therapy is complicated. The two types of pegylated inteferons are dosed differently. Moreover, the dosing of ribavirin depends on the type of peginterferon being used.

➡ ***Ribavirin should be administered on pill-line.*** *Capsules should be taken with food.*

Peginterferon alfa 2b (Peg-Intron®) and Ribavirin – STANDARD DOSING

Peg-Intron® is administered subcutaneously, once weekly. The dosing chart below is based on a recommended dose of 1.5 micrograms (mcg) per kilogram per week (regardless of HCV genotype). Peginterferon alfa 2b (Peg-Intron®) comes in four different vial strengths. Utilize the appropriate vial strength related to the patient's weight.

➡ ***Dosing for Peg-Intron® monotherapy is different.*** *See Appendix 5, Interferon/Ribavirin Drug Information.*

Body Weight (pounds)	Peginterferon alfa 2b Dosing (subcutaneously, once weekly)			Ribavirin Dosing (mg)	
	Vial Strength (microgram/0.5 mL)	Dose to Administer (1.5 mcg/kg/wk)	Volume to Administer (mL)	Every AM	Every PM
<88	50	50	0.5	400	400
88–111	80	64	0.4	400	400
112–133	80	80	0.5	400	400
134–144	120	96	0.4	400	400
145–166	120	96	0.4	400	600
167–177	120	120	0.5	400	600
178–187	120	120	0.5	600	600
188–231	150	150	0.5	600	600
> 231	150	150	0.5	600	800

Peginterferon alfa 2a (Pegasys®) and Ribavirin – STANDARD DOSING

Peginterferon alfa 2a (Pegasys®)	180 micrograms subcutaneously once weekly (regardless of weight). ➡ *Dosing for Pegasys monotherapy is the same as when it is used with ribavirin.*
Ribavirin (Rebetol®, Copegus® or generic (bio-equivalent)	**Genotype 1, 4, 5, 6 (based on patient's weight):** **<75kg (<165 lb) → total daily dose of 1000 mg administered as:** • 400 mg orally every morning • 600 mg orally every evening **≥75kg (≥165 lb) → total daily dose of 1200 mg administered as:** • 600 mg orally every morning • 600 mg orally every evening **Genotype 2 and 3 → total daily dose of 800 mg administered as:** • 400 mg orally twice daily (regardless of weight)

(Step 8 is continued on the next page.)

Appendix 2. Stepwise Approach for Detecting, Evaluating & Treating Chronic Hepatitis C *(page 6 of 8)*

Step 8. Determine appropriate treatment and obtain informed consent. *(continued)*

Boceprevir and Telaprevir — Dosing and Treatment Duration in Triple Therapy

Prior Treatment History or Degree of Fibrosis	Boceprevir-Based Regimen				Telaprevir-Based Regimen	
	Total Weeks of Therapy				Total Weeks of Therapy	
	28	36	48[1]	48[2]	24	48
Treatment Naïve & No Cirrhosis	RNA (–) at TW8 & TW24		RNA < 100 IU/ml but (+) at TW8 and (–) at TW24		RNA (–) at TW4 & TW12	RNA ≤1000 IU/ml but (+) at TW4 &/or TW12, & (–) at TW24
Relapser with Dual Therapy & No Cirrhosis		RNA (–) at TW8 & TW24	RNA < 100 IU/ml but (+) at TW8 and (–) at TW24		RNA (–) at TW4 & TW12	RNA ≤1000 IU/ml but (+) at TW4 &/or TW12, & (–) at TW24
Partial Responder with Dual Therapy & No Cirrhosis		RNA (–) at TW8 & TW24	RNA < 100 IU/ml but (+) at TW8 and (–) at TW24			RNA ≤1000 IU/ml at TW4 & TW12 & (–) at TW24
Compensated Cirrhosis				RNA < 100 IU/ml at TW8 & (–) at TW24		RNA ≤1000 IU/ml at TW 4 & TW12 & (–) at TW24

Key: **TW** = *Treatment Week*; **DT** = *Dual Therapy* with pegylated interferon and ribavirin; **TT** = *Triple Therapy* with an HCV PI + pegylated interferon and ribavirin; **(+) =** detectable HCV RNA; **(–)** = undetectable HCV RNA.

Boceprevir-Based Regimen:

The first 8 weeks of treatment are the same for all boceprevir-based regimens, as follows:

- Start therapy with a 4-week lead-in period of DT, using standard doses of pegylated interferon and ribavirin. Boceprevir (BOC) is added to the regimen after 4 full weeks of DT, and pegylated interferon and ribavirin are continued. In other words, TW 5 is the first week of TT.
- BOC dose is 800 mg (four 200 mg capsules) by mouth every 8 hours (+/-1 hr) with food /light snack.
- HCV RNA levels are obtained at the end of TWs 4, 8, 12, 24, and at the end of treatment. (–) means undetectable HCV RNA levels; (+) means detectable, but < 100 IU/ml.

Four different treatment durations are possible, as described in the above table:

- 28 weeks duration = 4 wks DT followed by 24 weeks of TT
- 36 weeks duration = 4 wks DT followed by 32 wks TT
- [1]48 weeks duration = 4 wks DT + 32 wks TT + 12 DT
- [2]48 weeks duration = 4 wks DT + 44 wks TT

Discontinue all HCV meds if any of the following occur:

- RNA ≥100 IU/ml at TW 12
- RNA detectable at TW 24
- While on treatment, HCV RNA increases by 1 $\log_{10}$ above treatment nadir

Telaprevir-Based Regimen:

- The telaprevir-based regimen starts with all 3 medications (pegylated interferon, ribavirin, and telaprevir), all of which are continued for 12 weeks. After 12 weeks, telaprevir is discontinued, while pegylated interferon and ribavirin are continued for an additional 12 weeks (24 weeks total) or an additional 36 weeks (48 weeks total).
- Telaprevir dose is 750 mg (two 375 mg tablets) by mouth every 8 hours (+/- 1 hr) with a 20-gram fat snack.
- HCV RNA levels are obtained at the end of TWs 4, 12, 24, and end of treatment. (–) means undetectable HCV RNA levels: (+) means detectable, but ≤ 1000 IU/ml.

Discontinue all HCV meds if any of the following occur:

- RNA > 1,000 IU/ml at TW 4 or TW 12
- RNA detectable at TW 24
- While on treatment, RNA increases by 1 $\log_{10}$ above treatment nadir

(Appendix 2 is continued on the next page.)

Appendix 2. Stepwise Approach for Detecting, Evaluating & Treating Chronic Hepatitis C *(page 7 of 8)*

Step 9a. Manage side effects.

☐ **Monitor side effects of treatment:**

See *Appendix 3* for treatment monitoring schedule for recommended baseline, pre-treatment, and ongoing clinical evaluations and laboratory studies. See *Guidelines for Adjusting Therapy for CBC Changes* on the page after this.

Common toxicities to assess at each clinician visit include:

☐ flu-like symptoms ☐ mood changes ☐ rashes ☐ chest pain
☐ dyspnea/cough ☐ thrombocytopenia ☐ anemia ☐ neutropenia

Step 9b. Monitor treatment response.

☐ **Monitor for treatment response based on the following virologic end-points:**

Chronic Hepatitis C Treatment Response Categories

Response		Time Frame	Result*
RVR	Rapid viral response	After 4 weeks of treatment	HCV RNA undetectable
eRVR	Extended rapid viral response	After 4 and 12 weeks of treatment	HCV RNA undetectable
EVR	Early viral response***	After 12 weeks of treatment	≥2 $\log_{10}$ HCV RNA decrease**
Null Responder		After 12 weeks of treatment	< 2$\log_{10}$ HCV RNA decrease
Partial Responder		After 24 weeks of treatment	> 2$\log_{10}$ HCV RNA decrease but still detectable
ETR	End of treatment response	At end of treatment	HCV RNA undetectable
SVR	Sustained viral response	24 wks after treatment completed	HCV RNA undetectable
Relapse		Undetectable HCV RNA at the end of treatment, but detectable sometime after treatment is stopped.	

* Throughout the course of treatment, use the same lab for HCV RNA assays so that results are comparable.
** 2 $\log_{10}$ decrease = by factor of 10^2; e.g., if baseline HCV RNA = 720,000 → then, a 2 $\log_{10}$ decrease = 7,200
*** *EVR* is also a term for an undetectable HCV RNA level after 8 wks. of treatment with a boceprevir-based regimen.

☐ **Determine the appropriate duration of therapy:**

Treatment duration is based on genotype, virologic response, and the occurrence of major side effects. See also the discussion under *Step 9b, Monitor Treatment Response*, in Section 4 of the text, and the flowcharts for triple therapy (*Appendices 4a* and *4b*) and dual therapy (*Appendices 4c* and *4d*).

➡ **Duration of triple therapy is described above in Step 8, in the table *Boceprevir and Telaprevir – Dosing and Treatment Duration in Triple Therapy*.**

- **Genotypes 1, 4, 5, 6: Standard treatment duration with dual therapy = 48 weeks**
  - If no EVR → discontinue treatment = treatment failure.
  - If EVR, but HCV RNA is still detectable at 12 weeks → repeat HCV RNA test at 24 weeks. If HCV RNA is still detectable at 24 weeks → discontinue therapy = treatment failure.
  - If significant side effects occur and RVR was achieved, can consider shortening treatment to at least 24 weeks (in consultation with an expert).
- **Genotypes 2, 3: Standard treatment duration = 24 weeks**
  - If no EVR → discontinue therapy = treatment failure.
  - If significant side effects occur and RVR was achieved → consider shortening treatment to at least 16–20 weeks (in consultation with an expert).

(Step 9 is continued is on the next page.)

Appendix 2. Stepwise Approach for Detecting, Evaluating & Treating Chronic Hepatitis C *(page 8 of 8)*

Step 9. Manage side effects and monitor treatment response. *(continued)*

Guidelines for Adjusting Therapy for CBC Changes

Hemoglobin (Hgb)

Value	*Peginterferon/Ribavirin Adjustment and Supportive Treatment*	
10–11 g/dL	☐ ***Peginterferon*** → No change. ☐ ***Ribavirin*** → ► If no or minimal symptoms, then no dose modification. ► If symptomatic, decrease ribavirin by 200 mg/day.	***Candidates for Erythropoietin:*** Rule out other causes of anemia. If anemia persists at 2 weeks after reducing ribavirin—and there is no hypertension—then consider erythropoietin, especially if the patient demonstrates a virologic response. Erythropoietin should be considered primarily for patients who are cirrhotic, post-transplant, or HIV/HCV co-infected ***Dosage:*** Epoeitin alfa 40,000 units subcutaneously weekly ***Goal:*** Hemoglobin 12 g/dL ***Note:*** If hemoglobin is <12g/dL for over 4 weeks at the reduced/adjusted dose, then discontinue ribavirin.
8.5–10 g/dL	☐ ***Peginterferon*** → ► ***Peginterferon alfa 2a*** (Pegasys) → No change. ► ***Peginterferon alfa 2b*** (Peg-Intron) → Reduce 50% (**see Note below*). ☐ ***Ribavirin*** → ↓ to 600 mg daily (200 mg AM & 400mg PM)	
< 8.5 g/dL	☐ ***Peginterferon*** → ► ***Peginterferon alfa 2a*** (Pegasys) → No change. ► ***Peginterferon alfa 2b*** (Peg-Intron) → Discontinue until resolved. ☐ ***Ribavirin*** → Discontinue until resolved.	

Note: For patients prescribed an HCV PI, if ribavirin must be discontinued according to the above parameters, the HCV PI must also be discontinued. Peginterferon monotherapy may be continued in accordance with the above parameters.

Absolute Neutrophil Count (ANC)

Value	*Peginterferon/Ribavirin Adjustment and Supportive Treatment*	
< 750	☐ ***Peginterferon*** → ► ***Peginterferon alfa 2a*** (Pegasys) → Reduce dose to 135 microgram/week (75% dose). ► ***Peginterferon alfa 2b*** (Peg-Intron) → Reduce to a 50% dose *(*see note below)* ☐ ***Ribavirin*** → No change.	
< 500	☐ ***Peginterferon*** & ***Ribavirin*** → Discontinue both until resolved.	***Granulocyte Colony Stimulating Factor (G-CSF):*** If the patient is responding to treatment and neutropenia persists despite reduced peginterferon dose, consider G-CSF (in consultation with an expert) for patients who are cirrhotic, post-transplant, or HIV/HCV co-infected. ***Dosage:*** Filgrastim 300 microgram subcutaneous daily. ***Goal:*** ANC >1500

Platelets

Value	*Peginterferon/Ribavirin Adjustment and Supportive Treatment*
< 50,000	☐ ***Peginterferon*** → ► ***Peginterferon alfa 2a*** (Pegasys) → Reduce dosage to 90 micrograms/week (50% dose) (**see note below*). ► ***Peginterferon alfa 2b*** (Peg-Intron) → Discontinue until resolved. ☐ ***Ribavirin*** → If on Peg-Intron, then discontinue ribavirin.
< 30,000	☐ ***Peginterferon*** → Discontinue until resolved. ☐ ***Ribavirin*** → Discontinue until resolved.

Note: While the manufacturer of peginterferon recommends reducing dose to 50%, recent data suggest that lowering the dose to this extent may significantly reduce the likelihood of achieving an SVR. Some experts recommend a 25% dose reduction with close monitoring of hematologic parameters.

Note: For patients prescribed an HCV PI, if peginterferon must be discontinued due to neutropenia or thrombocytopenia, the HCV PI must also be discontinued.

Step 10. Assess for sustained viral response (SVR).

An SVR is defined as undetectable HCV RNA at 24 weeks after treatment is completed. If HCV RNA is undetectable at the end of treatment, obtain an HCV RNA test 6 months later to assess for an SVR. Obtain a final HCV RNA test 12 months post-treatment. See Step 10 discussion in the text.

Appendix 3. Hepatitis C Treatment Monitoring Schedule

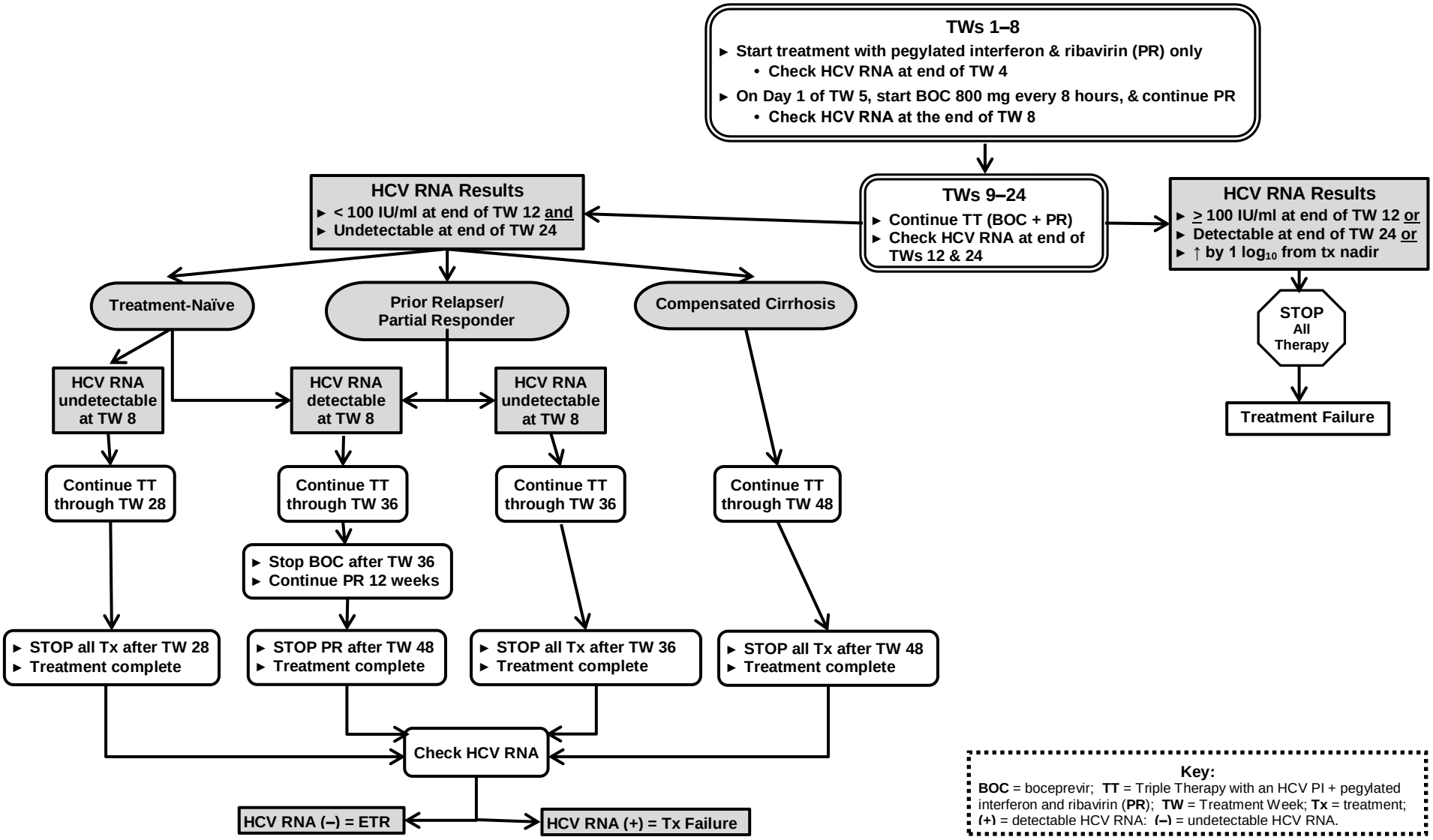
Evaluation	Baseline (anti-HCV positive)	Pre-Treatment	Ongoing Monitoring (by week of treatment)															24 wks post treatment	12 mos post treatment
			1	2	3	4	8	12	16	20	24	28	32	36	40	44	48		
Clinician evaluation	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV, HBsAg, HBsAb, Anti-HAV (IgG)	X																		
CBC + diff + platelets	X	X		X		X	*every 4-8 weeks during treatment*												
ALT & creatinine	X	X		X		X												X	X
AST, bilirubin, alkaline, phosphatase, albumin, INR	X	X	*periodically and if signs and symptoms of liver disease*																
Uric acid (telaprevir only)		X		X		X	X	X	*as clinically indicated*										
Ferritin, iron saturation, ANA*	X																		
HCV RNA**		X				X	**	X			***	*at end of treatment*						X	X
HCV genotype		X																	
Liver biopsy		*if indicated*																	
Mental health evaluation		X	*if indicated*																
Depression		X	*assess for signs and symptoms of depression at each clinician visit*																
Urine toxicology		X	*if indicated*																
Visual acuity		X																	
Funduscopic exam (if other ophthalmologic dx or diabetes)		X	*periodically and as clinically indicated*																
TSH, Free T4		X						X			X			X			X		
Triglycerides		X						X			X			X			X		
ECG (preexisting CHD)		*if indicated*	*if indicated*																
Urine pregnancy test (if childbearing potential)		X				X	X	X	X	X	X	X	X	X	X	X	X	*monthly x 6 mos*	

* Conduct further diagnostic evaluations as clinically warranted to identify other potential causes of the patient's liver disease such as hemochromatosis, Wilson's disease, or autoimmune hepatitis (e.g., serum iron, serum copper, ESR). If any of these conditions are diagnosed or are strongly suspected, a liver biopsy should be performed prior to treatment regardless of genotype.

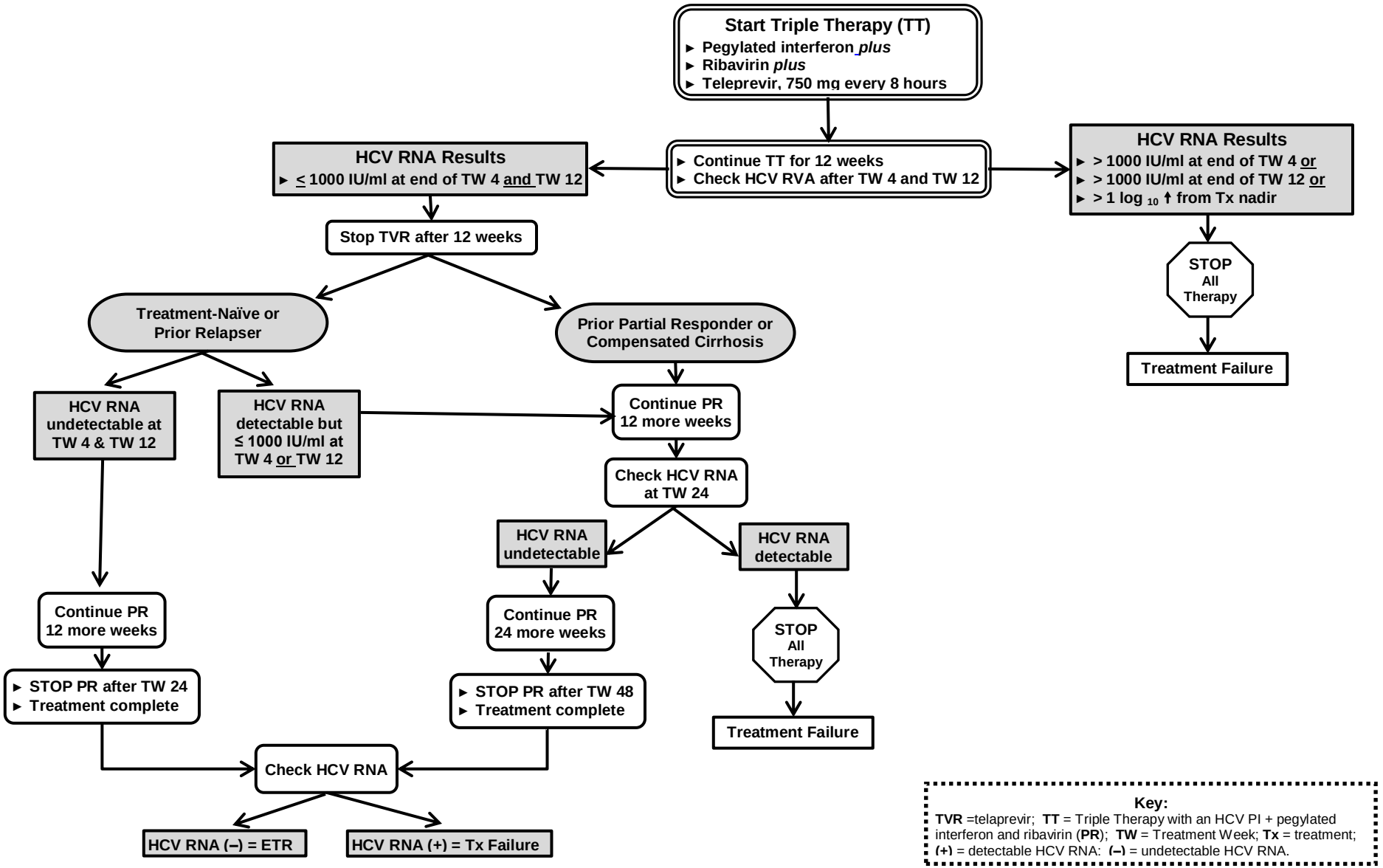
** More HCV RNA tests may be warranted during course of treatment depending upon results of previous HCV RNA assays (see *Appendices 4a, 4b, 4c,* and *4d*). If treating with boceprevir, an HCV RNA test should also be obtained at the end of treatment week 8.

*** An HCV RNA is obtained in all patients who are still on therapy at the end of 24 weeks. For some, this will be at the end of their treatment, e.g., HCV genotypes 2 and 3, and the shorter course of a telaprevir-based regimen. For all others, continuation of therapy is contingent upon an undetectable HCV RNA at the end of TW24.

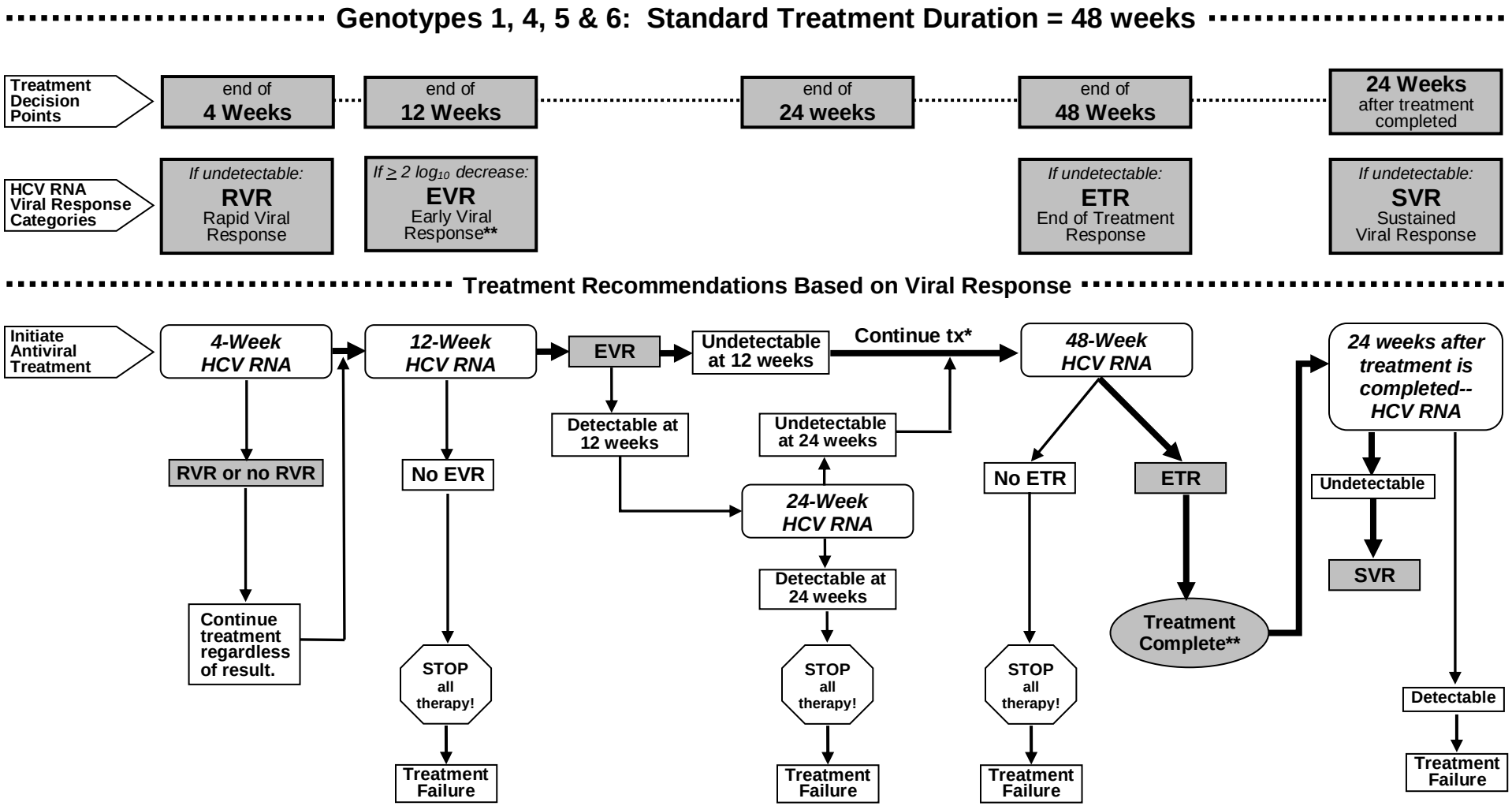
Appendix 4a. Timeline for HCV Treatment Decisions (Based on Viral Response): Genotype 1 on Triple Therapy with Boceprevir



Appendix 4b. Timeline for HCV Treatment Decisions (Based on Viral Response): Genotype 1 on Triple Therapy with Telaprevir

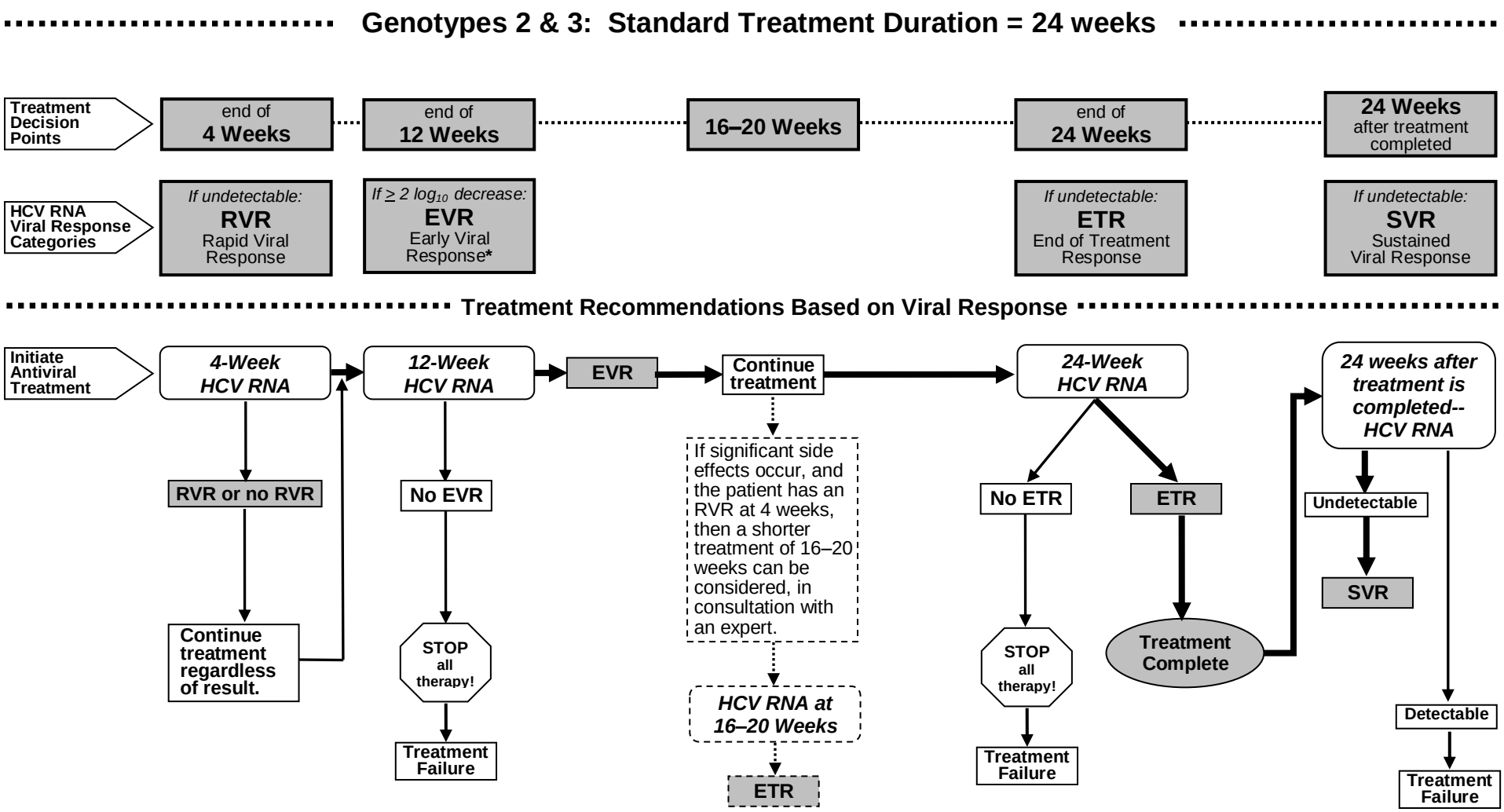


Appendix 4c. Timeline for HCV Treatment Decisions, Based on Viral Response: Genotypes 1, 4, 5, and 6 on Dual Therapy



* If significant side effects occur, and an RVR at 4 weeks was achieved, then shortening the treatment to at least 24 weeks can be considered with expert consultation.
** 2 $\log_{10}$ decrease = decrease by a factor of 10^2 (100), i.e., if baseline viral load = 720,000, then 2 log decrease = 7200.
*** If HCV RNA was detectable at 4 weeks and/or at 12 weeks, extending therapy to 72 weeks should be considered.

Appendix 4d. Timeline for HCV Treatment Decisions, Based on Viral Response: Genotypes 2 and 3 on Dual Therapy



***** 2 $\log_{10}$ decrease = decrease by a factor of 10^2 (i.e., if baseline viral load = 720,000, then 2 log decrease = 7200).

Appendix 5. Interferon/Ribavirin Drug Information

DESCRIPTION	
Peginterferon	A long-acting, synthetic interferon that is indicated for use alone or in combination with ribavirin for the treatment of chronic hepatitis C, or with ribavirin and an HCV protease inhibitor for treatment of chronic HCV genotype 1.
Ribavirin	A nucleoside analogue with antiviral activity. It is used in conjunction with peginterferon for treatment of hepatitis C. *Ribavirin should not be used alone as monotherapy for hepatitis C.*
FORMULATIONS	
Peginterferon	Two formulations are available for subcutaneous injection: ► Peginterferon alfa-2a (Pegasys®) ► Peginterferon alfa-2b (Peg-Intron®) There is no demonstrated difference in efficacy between the two formulations. However, dosing for Peg-Intron® is more complicated than for Pegasys®.
Ribavirin	Several formulations of 200 mg tablets or capsules are available for oral administration, including two brand-name versions: Copegus® and Rebetol®. The generic versions are less expensive and equivalent to the branded drugs.
STANDARD DOSING	
For standard dosing of Pegasys® and Peg-Intron®, see *Appendix 2, Step 8*.	
DOSING IN CERTAIN CLINICAL CIRCUMSTANCES	
Monotherapy with peginterferon alfa 2a (Pegasys®): 180 micrograms (mcg) subcutaneously, once weekly, regardless of weight. ***Note:*** Dosing for Pegasys® as monotherapy is the same as when it is used in conjunction with ribavirin.	
Monotherapy with peginterferon alfa 2b (Peg-Intron®): The recommended dosing of Peg-Intron® when it is used as monotherapy (without ribavirin) is 1.0 microgram/kg. See chart below.	

Body Weight (pounds)	Vial Strength (microgram/0.5 mL)	Amount to Administer (micrograms/week)	Volume to Administer (mL)
≤100	50	40	0.4
101–124	50	50	0.5
125–159	80	64	0.4
160–195	80	80	0.5
196–234	120	96	0.4
235–300	120	120	0.5
301+	150	150	0.5

Renal Dysfunction:

Peg-Intron®: In patients with moderate renal function (CrCl of 30—50 mL/min), the Peg-Intron dose should be reduced by 25%. If severe renal function impairment (CrCl 10—29 mL/min), including hemodialysis, reduce dose by 50%. If renal function decreases during treatment, discontinue treatment.

Pegasys®: In patients with impaired renal function, signs and symptoms of interferon toxicity should be closely monitored. Doses of Pegasys should be adjusted accordingly. Use with caution if CrCl <50 mL/min.

Ribavirin is not indicated in patients with a CrCl ≤50 mL/min.

Hemodialysis:

Pegasys®: Reduce dose to 135 micrograms subcutaneously, once weekly.

Peg-Intron®: Reduce dose br 50%.

Ribavirin is not indicated.

HIV/HCV Co-infection: Treat for 48 weeks, regardless of genotype. See *Section 4*.

(Appendix 5 continues on the next page.)

CONTRAINDICATIONS	
Peginterferon	► Severe uncontrolled psychiatric disease, particularly depression with current suicidal risk. ► History of solid organ transplant (renal, heart, or lung) ► Certain autoimmune disorders, e.g., autoimmune hepatitis ► Uncontrolled endocrine disorders, e.g., diabetes, thyroid disease ► Serious concurrent medical diseases such as: severe hypertension, heart failure, CHD, COPD, decompensated cirrhosis (see *definition*) ► Platelet count <75,000/mm^3 or ANC <1,500 cells/mm^3 ► Documented nonadherence to prior therapy, or failure to complete pretreatment evaluation process ► Ongoing injection drug use or alcohol use ► Hypersensitivity to interferon
Ribavirin	► Thalassemia or other hemoglobinopathy ► Significant cardiac disease (arrhythmias, angina, CABG, MI) in the past 12 months ► Pregnancy or unwillingness to use contraception in both female patients and in female partners of male patients. ► Renal dialysisSerum creatinine ≥1.5 mg/dL or creatinine clearance ≤50 mL/min ► Hemoglobin ≤12 g/dL in men or ≤11 g/dL in women ► Hypersensitivity to ribavirin
MAJOR SIDE EFFECTS	
Peginterferon	May cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.
Ribavirin	Has a primary clinical toxicity of *hemolytic anemia*. Since ribavirin-associated anemia has been known to lead to myocardial infarction, it is contraindicated in patients with significant or unstable cardiac disease. *Significant teratogenic effects* have been noted in all animal species exposed to ribavirin. Pregnancy should be prevented during therapy, and for the six months after the completion of therapy, *in both female patients and female partners of male patients.*
SIDE EFFECTS	
Peginterferon	► *Autoimmune disorders*: Can result in development or exacerbation of disorders ► *Bone marrow suppression*: Can cause severe cytopenias (see *Appendix 2, Step 9a*) ► *Cardiovascular disorders*: Hypertension, arrhythmias, and myocardial infarction ► *Cerebrovascular disorders*: Ischemic and hemorrhagic cerebrovascular events ► *Colitis*: Ulcerative and hemorrhagic/ischemic colitis, sometimes fatal ► *Dermatologic effects*: Alopecia, pruritis, and local injection site reaction ► *Endocrine disorders*: Hypo- or hyperthyroidism, hypo- or hyperglycemia & diabetes ► *Flu-like symptoms*: Fever, myalgia, fatigue, headache ► *Gastrointestinal effects*: Nausea, vomiting, diarrhea, and anorexia ► *Hypersensitivity (anaphylaxis and angioedema)*: Severe and acute ► *Infections (bacterial, fungal, and viral)*: Can be severe and sometimes fatal ► *Hepatic failure and hepatitis exacerbations with hepatic decompensation and death* ► *Neuropsychiatric symptoms*: Life threatening or fatal neuropsychiatric reactions ► *Ophthalmologic disorders*: Loss of vision, retinopathy including macular edema ► *Pancreatitis*: Sometimes fatal ► *Pulmonary disorders*: Dyspnea, pulmonary infiltrates, pneumonia, and sarcoidosis ► *Renal failure* ► *Seizures* ► *Triglyceride elevations*

("Side effects" continues on the next page of Appendix 5.)

SIDE EFFECTS *(continued from previous page)*	
Ribavirin	**Black Box Warnings:** ► **Hemolytic Anemia Warning** (primarily in the first two weeks of therapy) ► **Pregnancy Warning** (negative pregnancy test is required pre-therapy) ► **Respiratory Warning** for patients requiring assisted ventilation ► *Cardiovascular effects:* Fatal and non-fatal myocardial infarction ► *Dermatologic effects:* Alopecia, pruritis, and rashes ► *Flu-like symptoms:* Myalgia, fatigue, and headache ► *Gastrointestinal effects:* Nausea, anorexia, and vomiting ► *Hematologic:* Neutropenia and thrombocytopenia (see *Appendix 2, Step 9a*) ► *Hepatic decompensation and death* ► *Hypersensitivity—acute:* Anaphylaxis, angioedema, and bronchoconstriction ► *Pulmonary symptoms:* Dyspnea, pneumonia, and pulmonary infiltrates ► *Teratogen (significant), carthogenesis, and mutagenesis*
(End of Appendix 5)	

Appendix 6. Boceprevir/Telaprevir Drug Information

DESCRIPTION	
Boceprevir	An oral medicine that acts directly on the hepatitis C virus protease, an enzyme essential for viral replication. Boceprevir should always be taken in combination with peginterferon alfa and ribavirin. ***Boceprevir should not be used alone as monotherapy for hepatitis C.***
Telaprevir	An oral medicine that acts directly on the hepatitis C virus protease, an enzyme essential for viral replication. Telaprevir should always be taken in combination with peginterferon alfa and ribavirin. ***Telaprevir should not be used alone as monotherapy for hepatitis C.***
FORMULATIONS	
Boceprevir (Victrelis™)	Boceprevir is manufactured as 200 mg oral capsules that are packaged in daily dosage bottles of 12 capsules each. The dose for boceprevir is 800 mg (four 200 mg capsules) three times daily (every 7–9 hours), taken with food (a meal or light snack).
Telaprevir (Incivek™)	Telaprevir is manufactured as 375 mg tablets that are packaged into cartons containing a four-week supply: 4 weekly blister cards, with each card consisting of 7 daily blister strips of 6 tablets each. The dose for telaprevir is 750 mg (two 375 mg tablets) three times daily (every 7–9 hours), with each dose taken 30 minutes after eating a meal or snack that contains at least 20 grams of fat.
STANDARD DOSING	
Boceprevir	Boceprevir has been approved for administration according to a specific response-guided therapy algorithm (see *Appendix 4a*). Therapy is initiated with peginterferon and ribavirin for the first 4 weeks of treatment (peginterferon/ribavirin "lead in" period) prior to adding boceprevir. **Weeks 1-4:** ► **Peginterferon** (either *Pegasys* 180 mcg/week or *PegIntron* 1.5 mcg/kg/week) ***and*** ► **Ribavirin** (in 2 divided doses) with food: ***Weight-based ribavirin dosing with Pegasys :*** **<75kg(<165 lb):** 1000mg/day **≥75kg (≥165 lb):** 1200mg/day ***Weight-based ribavirin dosing with PegIntron:*** **<65kg (<145 lb):** 800mg/day, **65–85kg (145–177 lb):** 1000mg/day, **>85–105kg (178–231 lb):** 1200 mg/day, **>105kg (>231 lb):** 1400mg/day. Refer to *Appendix 2, Step 8* for appropriate dosing of peginterferon and ribavirin. **Beginning at Week 5:** ► **Boceprevir** 800 mg orally (4 x 200 mg capsules) every 8 hrs (+/–1 hr) with food *plus* **peginterferon** *and* **ribavirin**. **Total treatment duration** is guided by on-treatment HCV RNA response and patient characteristics, as described in boceprevir treatment algorithm (see *Appendix 4a*).

(Appendix 6 continues on the next page.)

STANDARD DOSING *(continued)*	
Telaprevir	Telaprevir is dosed 750 mg orally (2 x 375 mg tablets) every 8 hours (+/– 1hr) with food (containing a minimum of 20g of fat) for 12 weeks, ***plus:*** ► **Peginterferon** (either *Pegasys* 180 mcg/week or *PegIntron* 1.5 mcg/kg/week) ***and*** ► **Ribavirin** (in 2 divided doses) with food: ***Weight-based ribavirin dosing with Pegasys :*** **<75kg(<165 lb):** 1000mg/day **≥75kg (≥165 lb):** 1200mg/day ***Weight-based ribavirin dosing with PegIntron:*** **<65kg (<145 lb):** 800mg/day, **65–85kg (145–177 lb):** 1000mg/day, **>85–105kg (178–231 lb):** 1200 mg/day, **>105kg (>231 lb):** 1400mg/day. Refer to *Appendix 2, Step 8* for appropriate dosing of peginterferon and ribavirin. **Total treatment duration** is guided by on-treatment HCV RNA response and patient characteristics, as described in telaprevir treatment algorithm (see *Appendix 4b*).
DOSING IN CERTAIN CLINICAL CIRCUMSTANCES	
Renal Impairment: No dosage adjustment of boceprevir or telaprevir is necessary for patients with mild, moderate, or severe renal impairment; telaprevir was not studied in patients with end-stage renal disease or on hemodialysis.	
HBV/HCV Co-Infection: No safety or efficacy data are available in this population. Treatment with telaprevir or boceprevir for Hepatitis C is not indicated and has not been approved for patients co-infected with HBV.	
CONTRAINDICATIONS	
Boceprevir	► All contraindications to peginterferon alfa and ribavirin, since boceprevir must be administered with peginterferon alfa and ribavirin ► Pregnant women and men whose female partners are pregnant, because ribavirin may cause birth defects and fetal death ► Decompensated cirrhosis ► Co-infection with HBV or HIV ► Solid organ transplant recipient ► Co-administration with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, e.g., Alfuzosin, Ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine), cisapride, some statins (simvastatin, lovastatin), drosperinone, PDE5 enzyme Inhibitors (sildenafil, tadalafil), pimozide, triazolam , and orally administered midazolam ► Co-administration with drugs that strongly induce CYP3A, which may lead to lower exposure and loss of efficacy of boceprevir, e.g,. certain anticonvulsants (carbamazepine, phenobarbital, phenytoin), rifampin, and St. John's wort

(Appendix 6 continues on the next page.)

CONTRAINDICATIONS *(continued)*	
Telaprevir	► All contraindications to peginterferon alfa and ribavirin, since telaprevir must be administered with peginterferon alfa and ribavirin ► Pregnant women and men whose female partners are pregnant, because ribavirin may cause birth defects and fetal death ► Decompensated cirrhosis ► Co-infection with HBV or HIV ► Solid organ transplant recipient ► Co-administration with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, e.g., Alfuzosin, Ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine), cisapride, some statins (atorvastatin, simvastatin, lovastatin), PDE5 enzyme inhibitors (sildenafil, tadalafil), pimozide, triazolam , and orally administered midazolam ► Co-administration with drugs that strongly induce CYP3A, which may lead to lower exposure and loss of efficacy of teleprevir, e.g,. rifampin and St. John's wort
USE WITH CAUTION	
Boceprevir	The following medications may pose risk for potential interaction with boceprevir that may require close monitoring, alteration of drug dosage, or timing of administration: ► *Analgesics* (buprenorphine, methadone) ► *Antiarrhythmics* (amiodarone, bepridil, digoxin, flecainide, lidocaine, propafenone, quinidine) ► *Antibacterials* (clarithromycin, erythromycin, rifabutin, telithromycin) ► *Antidepressants* (desipramine, escitalopram, trazodone) ► *Antifungals* (itraconazole, ketoconazole, posaconazole, voriconazole) ► *Antipsychotics* (clozapine) ► *Anxiolytics/hypnotics/sedatives* (alprazolam, parenteral midazolam, zolpidem) ► *Bronchodilators* (salmeterol) ► *Calcium channel blockers* (amlodipine, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, verapamil) ► *Contraceptives/hormonal replacement* (ethinyl estradiol, norethindrone) ► *Erectile dysfunction agents* (sildenafil, tadalafil, vardenafil) ► *Gastrointestinal agents* (cimetidine, ranitidine) ► *HIV drugs* (maraviroc, delavirdine, efavirenz, etravirine, nevirapine, zidovudine, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir) ► *Immunosuppressants* (cyclosporine, sirolimus, tacrolimus) ► *Lipid-lowering agents* (atorvastatin) ► *Steroids* (budesonide, dexamethasone, fluticasone, methylprednisolone, prednisone) ► *Other drugs* (bosentan, colchicine, warfarin)

(Appendix 6 continues on the next page.)

USE WITH CAUTION *(continued)*	
Telaprevir	The following medications may pose risk for potential interaction with telaprevir that may require close monitoring, alteration of drug dosage, or timing of administration: ► *Analgesics* (buprenorphine, methadone) ► *Antiarrhythmics* (amiodarone, bepridil, digoxin, flecainide, lidocaine, propafenone, quinidine) ► *Antibacterials* (clarithromycin, erythromycin, rifabutin, telithromycin) ► *Anticonvulsants* (carbamazepine, phenobarbital, phenytoin) ► *Antidepressants* (desipramine, escitalopram, trazodone) ► *Antifungals* (itraconazole, ketoconazole, posaconazole, voriconazole) ► *Antipsychotics* (clozapine) ► *Anxiolytics/hypnotics/sedatives* (alprazolam, parenteral midazolam, zolpidem) ► *Bronchodilators* (salmeterol) ► *Calcium channel blockers* (amlodipine, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, verapamil) ► *Contraceptives/hormonal replacement* (drospirenone, ethinyl estradiol, norethindrone) ► *Erectile dysfunction agents* (sildenafil, tadalafil, vardenafil) ► *Gastrointestinal agents* (cimetidine, ranitidine) ► *HIV drugs* (maraviroc, delavirdine, efavirenz, etravirine, nevirapine, tenofovir, zidovudine, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir) ► *Immunosuppressants* (cyclosporine, sirolimus, tacrolimus) ► *Steroids* (budesonide, dexamethasone, fluticasone, methylprednisolone, prednisone) ► *Other drugs* (bosentan, colchicine, warfarin).
SIDE EFFECTS	
Boceprevir	► *Dermatologic effects:* Pruritis ► *Flu-like symptoms:* Myalgia, fatigue, and headache ► *Gastrointenstinal effects:* Dysgeusia, nausea, anorexia, and vomiting ► *Hematologic:* ► *Anemia:* The addition of boceprevir to peginterferon alfa and ribavirin (PEG/riba) is associated with an additional decrease in hemoglobin concentrations. ► *Neutropenia:* The addition of boceprevir to PEG/riba is associated with an additional decrease in neutrophil counts. Decreases in neutrophil counts may require dose reduction or discontinuation of PEG/riba. No dose adjustment should be made to boceprevir. If PEG/riba is discontinued, boceprevir should be discontinued and not restarted (see *Appendix 2, Step 9*).
Telaprevir	► *Hematologic effects:* Anemia— the addition of telaprevir to peginterferon alfa and ribavirin is associated with an additional decrease in hemoglobin concentrations (see *Appendix 2, Step 9*). ► *Dermatologic effects:* Rash with or without pruritis ► *Flu-like symptoms:* Myalgia, fatigue, headache ► *Gastrointestinal effects:* Dysgeusia, nausea, vomiting, diarrhea, and anorectal discomfort, anal pruritis, hemorrhoids
(End of Appendix 6)	

Appendix 7. Infection Control Practices for Hepatitis C

General Infection Control Practices—All Correctional Staff

Use Standard Precautions. Wear gloves when it can be reasonably anticipated that contact with blood or other body fluids (except sweat) could occur. Wash hands regularly. Immediately report any exposures to blood, including accidental needle sticks or other sharps, splashes or sprays of blood into eyes or mouth, or human bites.

General Infection Control Practices—All Health Care Staff

- Wear gloves when it can be reasonably anticipated that contact with the following could occur: blood or other potentially infectious materials, mucous membranes, non-intact skin, or potentially contaminated intact skin (e.g., skin of a patient incontinent of stool or urine).
- Remove gloves and promptly discard after contact with a patient and/or the surrounding environment (including medical equipment), using proper technique to prevent hand contamination. Follow with proper hand washing.
- Promptly contain, clean-up, and disinfect surfaces contaminated with blood.
- Regularly and appropriately use proper hand hygiene.
- Non-disposable patient care items must be cleaned, disinfected, or sterilized, as appropriate.
- Implement measures to prevent cross-contamination during patient care (e.g., dialysis, vascular access, cauterizing, dental procedures, etc.).
- Do not carry supplies and medications in pockets. Once supplies have been taken to the bedside or patient station, the non-used supplies or medications should not be used for another patient.

Safe Injection Practices

- Use sharps with engineered sharp injury protection to eliminate or minimize exposures.
- Use aseptic technique in handling medications and injection equipment to avoid microbial contamination of sterile injection equipment or infusions—including syringes, needles, and intravenous (IV) tubing.
- Health care staff should adhere to proper infection control practices during the preparation and administration of injected medications.
- Whenever possible, the CDC recommends that single-use vials be used, and that if multi-dose vials must be used, each medication vial should be restricted to a single patient and properly labeled as such.
- Do not use bags or bottles of intravenous solution as a common source supply for multiple patients.
- Never administer medications from the same syringe to more than one patient, even if the needle is changed.
- Never enter a vial with a syringe or needle that has been used for a patient if there is any possibility that the medication might be used for another patient.
- Medications should be drawn up in a designated “clean” medication area that is not adjacent to areas where potentially contaminated items are placed.
- Discard medication vials upon expiration or any time that there are concerns regarding the sterility of the medication.
- Consider a syringe or needle/cannula to be contaminated once it has been used to enter or connect to a patient’s intravenous infusion bag or administration set.

Safe Practices for Diabetes Care

- Never re-use needles, syringes, or lancets.
- Restrict use of finger stick capillary blood sampling devices to individual patients. Consider single-use lancets that permanently retract upon puncture.
- Dispose of used finger stick devices and lancets at the point of use, in a safety-approved, stationary sharps container.
- When feasible, assign glucometers to individual patients.

Appendix 8. Resources – Prevention and Treatment of Viral Hepatitis

Health Care Professionals

- **American Association for the Study of Liver Diseases**
  http://www.aasld.org/Pages/Default.aspx
- **Centers for Disease Control and Prevention**
  National Center for Infectious Diseases – Hepatitis Branch
  http://www.cdc.gov/ncidod/diseases/hepatitis/
- **MELD Score Calculator**
  http://optn.transplant.hrsa.gov/resources/MeldPeldCalculator.asp?index=98
- **National Institutes of Health**
  National Institute of Diabetes and Digestive and Kidney Diseases
  http://www.niddk.nih.gov
- **National Clinicians' Post-Exposure Prophylaxis PEPline:** (888) 448-4911
  http://www.nccc.ucsf.edu/
- **U.S. Department of Veterans Affairs National Hepatitis C Program**
  http://www.hepatitis.va.gov/

Patient Education

- **American Liver Foundation (ALF)**
  www.liverfoundation.org
- **Centers for Disease Control and Prevention (CDC)**
  www.cdc.gov/idu/hepatitis/index.htm
- **Hepatitis Foundation International (HFI)**
  www.hepfi.org
- **The National Digestive Diseases Information Clearinghouse (NDDIC)**
  http://www.digestive.niddk.nih.gov/ddiseases/pubs/hepc_ez/index.htm
- **U.S. Department of Veterans Affairs National Hepatitis C Program – For Veterans and the Public**
  www.hepatitis.va.gov/patient/index.asp