Interim Guidance for the Management of Chronic Hepatitis C Infection

Federal Bureau of Prisons
Clinical Practice Guidelines

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1. Purpose and Overview

From the time Hepatitis C virus (HCV) was first identified as a major cause for chronic hepatitis, finding a treatment that was effective, easy to administer, and relatively free from side effects has been elusive. However, starting in 2011, four new medications that act directly against HCV have been approved for treatment of this condition, and more are expected in the future. The preferred treatment regimen has changed with each of the new recently approved, direct-acting antiviral medications (DAAs)—resulting in rapidly changing clinical guidelines and treatment recommendations. While an all-oral, interferon-free regimen is currently available for certain genotypes, even newer medications are expected to become available that will be safer, simpler, and more effective. In the midst of this rapidly changing treatment landscape, the most recently published guidance on HCV treatment (*www.hcvguidelines.org*) indicates that it is reasonable to postpone treatment for cases with less advanced fibrosis, pending the expected availability of better treatments in the very near future.

The purpose of this document is to provide interim guidance for the treatment of chronic HCV infection in the federal inmate population. During this time of transition, the BOP has established treatment priorities for inmates who have a more urgent need for intervention, as described below. The recommended treatment regimens, as well as medication dosing, monitoring, and special considerations, are also discussed. The appendices cover detailed medication information, monitoring recommendations, and management of hematologic changes.

2. Priorities for Treatment

The following clinical scenarios involving chronic HCV infection should be prioritized for treatment:

- Advanced hepatic fibrosis/cirrhosis
- Liver transplant recipients
- HIV co-infection
- Comorbid medical conditions associated with HCV, e.g. cryoglobulinemia and certain types of lymphomas
- Continuity of care for newly incarcerated BOP inmates who were being treated at the time of incarceration

The degree of fibrosis may be determined in several ways: The AST-to-platelet ratio index (APRI) correlates fairly well with more advanced fibrosis/cirrhosis, having a sensitivity of 76% and specificity of 72%. The formula for calculating the APRI score is [(AST/AST ULN) x 100 / (platelet count x 10^3/µL / 1,000)]. The BOP will prioritize for treatment inmates who have an APRI score ≥ 1.0, or whose APRI score is between 0.7 and 1.0 along with other findings suggestive of advanced fibrosis (low albumin or platelets, elevated bilirubin or INR). Although a liver biopsy is no longer required unless otherwise clinically indicated, results of a prior liver biopsy may be used to meet the advanced fibrosis criteria. Abdominal imaging studies such as ultrasound or CT scan also may identify findings consistent with cirrhosis.

In addition to the above, inmates being considered for treatment of HCV should have no contraindications to any component of the treatment regimen, should not be pregnant, should have sufficient time remaining on their sentence in the BOP to complete a course of treatment, and should demonstrate a willingness and an ability to adhere to a rigorous treatment regimen and to abstain from high-risk activities while incarcerated.

3. Recommended Treatment Regimens

Note: *Current guidelines do not recommend the use of boceprevir or telaprevir when initiating treatment for HCV. However, if treatment with boceprevir or telaprevir has already been initiated, it should be continued as long as treatment criteria are met.*

The recommended treatment regimen still depends on the genotype and prior HCV treatment history, as noted below. The AASLD-IDSA preferred treatment regimen is listed; alternative regimens may be considered on a case-by-case basis.

a. HCV-1 and treatment naïve or relapser following peginterferon/ribavirin (PEG/RBV) therapy:

- *Preferred regimen:* sofosbuvir + ribavirin + peginterferon for 12 weeks
- If peginterferon is contraindicated, consider sofosbuvir + simeprevir +/- ribavirin for 12 weeks.

b. HCV-1 and non-responder (partial or null responder) to prior HCV treatment with PEG/RBV:

- Sofosbuvir + simeprevir +/- ribavirin for 12 weeks, regardless of HCV-1 subtype (a or b).

c. HCV-1 and non-responder to prior HCV treatment with PEG/RBV/HCV protease inhibitor:

- Sofosbuvir + ribavirin + peginterferon for 12 weeks

d. HCV genotypes 2 through 6, treatment naïve, relapsers, or non-responder to prior treatment with PEG/RBV:

- **HCV-2** = sofosbuvir + ribavirin for 12 weeks (extended to 16 weeks for prior non-responders with cirrhosis)
- **HCV-3** = sofosbuvir + ribavirin for 24 weeks
- **HCV-4** = sofosbuvir + ribavirin + peginterferon for 12 weeks. If peginterferon is contraindicated, sofosbuvir + ribavirin for 24 weeks is recommended.
- **HCV-5** = sofosbuvir + ribavirin + peginterferon for 12 weeks*****
- **HCV-6** = sofosbuvir + ribavirin + peginterferon for 12 weeks*****

***** *If peginterferon is contraindicated, there are no alternative regimens recommended for HCV genotype 5 or 6.*

e. Recommended medication doses for patients with compensated liver disease, normal renal function, and normal hematologic indices:

- Peginterferon alfa-2A – 180 micrograms subcut once weekly
- Peginterferon alfa-2B – consult *Appendix 1* for weight-based dosing.
- Ribavirin – According to the newest AASLD-IDSA guidance, the dose of ribavirin is based on a patient's weight for sofosbuvir- or simeprevir-based regimens. For patients ≥ 75 kg, the ribavirin dose is 600 mg by mouth twice daily. For those < 75 kg, the dose is 1000 mg/day divided in two doses, 400 mg and 600 mg. Note that the ribavirin dose recommended for sofosbuvir- or simeprevir-based regimens differs somewhat from the dose used for earlier regimens such as peginterferon + ribavirin +/– boceprevir or telaprevir. Ribavirin is recommended to be taken with food.
- Simeprevir – 150 mg by mouth once daily, with food
- Sofosbuvir – 400 mg by mouth once daily, with or without food

f. The following treatment regimens are no longer recommended for the above clinical scenarios unless completing a course of treatment that has already been started:

- Monotherapy with interferon, ribavirin, or any direct-acting antiviral agent
- Dual therapy with peginterferon and ribavirin
- Triple therapy with peginterferon, ribavirin, and either boceprevir or telaprevir

4. Monitoring

Updated guidelines have not been published on monitoring the newest medication regimens. However, the following general statements may be made:

- HCV-1a cases being considered for an alternative regimen using simeprevir in combination with peginterferon and ribavirin (without sofosbuvir) must first be tested for the NS3 Q80K polymorphism, found in BEMR as Hep C Genosure NS3/4 A Drug Resistance. Patients with the Q80K polymorphism are not candidates for this treatment regimen. A possible exception to this is an HCV-1a genotype that is being treated with a combination of simeprevir and sofosbuvir.
- Pregnancy testing is required prior to treatment with ribavirin-containing regimens, and then periodically during and after treatment.
- For all regimens, HCV viral loads need to be drawn prior to treatment and at the end of treatment, as well as either 12 or 24 weeks after treatment completion for those with undetectable end of treatment viral loads.
  - For sofosbuvir regimens, the only on-treatment viral load is drawn after 4 completed weeks of treatment, primarily to assess for adherence.
  - For simeprevir-containing regimens, viral loads need to be drawn after treatment weeks 4, 12, and 24 to assess response to treatment.
- Monitoring of interferon and/or ribavirin-containing regimens is the same as before and is included as *Appendix 5*.

5. Special Considerations

Chronic kidney disease:

- Simeprevir and sofosbuvir may be used with GFRs ≥ 30, but sofosbuvir is not recommended for GFRs < 30, and neither medication is recommended for use with hemodialysis.
- Ribavirin doses must be decreased with GFRs < 50. For GFRs 30–50, ribavirin is dosed 200 mg alternating every other day with 400 mg. For GFR < 30 including hemodialysis, the ribavirin dose is 200 mg daily.
- Pegylated interferon is dosed differently depending on which form is used. For a GFR < 30 or hemodialysis, peginterferon alfa-2A is dosed 135 micrograms/week, and peginterferon alfa-2B is dosed 1 microgram/kg/week. Regular interferon alfa dosed 3 million units three times/week is an alternative in ESRD/hemodialysis cases.

Decompensated cirrhosis or liver transplant recipients:

- Medication doses and regimens may differ from those in compensated liver disease. Such cases should be managed in consultation with an experienced clinician/specialist.
- Decompensated cirrhosis (e.g., Child-Turcotte-Pugh/CTP class B or C) is still a contraindication to interferon-containing regimens.

HIV co-infection:

- HCV medication regimens are the same for HIV co-infected patients as for HIV-negative patients.
- Antiretroviral medication changes may be necessary for patients with HIV co-infection being considered for HCV treatment, due to potential drug interactions between sofosbuvir or simeprevir and certain antiretrovirals.
  - Sofosbuvir should not be used with didanosine, zidovudine, or tipranavir.
  - Simeprevir may be used only with abacavir, tenofovir, emtricitabine, lamivudine, raltegravir, rilpivirine, maraviroc, and enfuvirtide.

Reference

AASLD, IDSA, IAS–USA. HCV testing and linkage to care. Recommendations for testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org/ Accessed May 2014.

Appendix 1: Peginterferon Drug Information

PEGINTERFERON DRUG INFORMATION

DESCRIPTION

A long-acting, synthetic interferon that enhances the antiviral immune response. Although peginterferon is approved for use as monotherapy or in combination with other antiviral medications for the treatment of chronic hepatitis C, ***current guidance recommends its use only in sofosbuvir- or simeprevir-based regimens and recommends against its use as monotherapy or as dual therapy in combination with ribavirin alone.***

FORMULATIONS

Two formulations are available for subcutaneous injection:

- Peginterferon alfa-2a (Pegasys®)
- Peginterferon alfa-2b (Peg-Intron®)

Although the two formulations are dosed differently, there is no demonstrated difference in efficacy. Note that dosing for Peg-Intron is more complicated than for Pegasys. (See *STANDARD DOSING* below.)

STANDARD DOSING

Peginterferon alfa-2a (Pegasys)

Pegasys is dosed 180 micrograms subcutaneously once weekly—regardless of weight.

Peginterferon alfa 2b (Peg-Intron)

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). Peg-Intron comes in four different vial strengths. Utilize the appropriate vial strength related to the patient's weight.

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

PEGINTERFERON DRUG INFORMATION

DOSING IN CERTAIN CLINICAL CIRCUMSTANCES

Renal Dysfunction, including hemodialysis:

- **Peginterferon alfa-2a (Pegasys):** In patients with severe impairment in renal function (CrCl < 30) including hemodialysis, a dose reduction to 135 micrograms/week is recommended.
- **Peginterferon alfa-2b (Peg-Intron):** In patients with moderate renal function impairment (CrCl of 30–50 mL/min), the Peg-Intron dose should be reduced to 1 microgram/kg/week or reduced by 25%. In severe renal function impairment (CrCl 10–29 mL/min), including hemodialysis, reduce dose by 50%.
- **Interferon alfa:** Non-pegylated interferon alfa is considered an alternative to pegylated interferon alfa in patients with severe renal function impairment (CrCl 10–29 mL/min), including hemodialysis, and is dosed 3 million units three times/week.

CONTRAINDICATIONS

- 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
- 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

MAJOR SIDE EFFECTS

May cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.

OTHER POSSIBLE SIDE EFFECTS

- *Autoimmune disorders*: Can result in development or exacerbation of disorders
- *Bone marrow suppression*: Can cause severe cytopenias
- *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*

Appendix 2: Ribavirin Drug Information

RIBAVIRIN DRUG INFORMATION

DESCRIPTION

A nucleoside analogue with antiviral activity. Ribavirin is used in conjunction with other antiviral medication for treatment of hepatitis C. ***Ribavirin should not be used alone as monotherapy for hepatitis C.***

FORMULATIONS

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 *(In combination with Simeprevir or Sofosbuvir, with or without peginterferon)*

Ribavirin dosing is based on patient's weight, regardless of genotype.
➔ ***Ribavirin should be taken with food.***

Weight <75kg (<165 lb)	Weight >75kg (>165 lb)
Total daily dose of 1000 mg administered as: • 400 mg orally every morning • 600 mg orally every evening	**Total daily dose of 1200 mg administered as:** • 600 mg orally every morning • 600 mg orally every evening

DOSING IN CERTAIN CLINICAL CIRCUMSTANCES

Renal Dysfunction, including hemodialysis: In patients with moderate renal function impairment (CrCl of 30–50 mL/min), the dose of ribavirin is 200 mg alternating with 400 mg every other day. In severe renal function impairment (CrCl 10–29 mL/min), including hemodialysis, the ribavirin dose is 200 mg/day.

CONTRAINDICATIONS

- 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.
- Hemoglobin $\leq$12 g/dL in men or $\leq$11 g/dL in women
- Hypersensitivity to ribavirin

MAJOR SIDE EFFECTS

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.*

OTHER POSSIBLE SIDE EFFECTS

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
- *Hepatic decompensation and death*
- *Hypersensitivity—acute:* Anaphylaxis, angioedema, and bronchoconstriction
- *Pulmonary symptoms:* Dyspnea, pneumonia, and pulmonary infiltrates
- *Teratogen (significant), carthogenesis, and mutagenesis*

Appendix 3. HCV Protease Inhibitor Drug Information: Simeprevir

SIMEPREVIR (OLYSIO™) DRUG INFORMATION

DESCRIPTION

Simeprevir is an oral direct-acting antiviral (DAA) agent against the Hepatitis C virus. Simeprevir is an inhibitor of the HCV NS3/4A protease, which is essential for viral replication. Simeprevir is indicated for the treatment of chronic HCV genotype 1 monoinfection as a component of a combination antiviral treatment regimen. In addition to this FDA-approved indication, the AASLD-IDSA guidance also recommends use of simeprevir as part of an alternative regimen for HCV treatment in the setting of HIV co-infection or ineligibility for peginterferon.

➜ ***Simeprevir should not be used alone as monotherapy.***

➜ Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended. Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism.

FORMULATIONS

Simeprevir is manufactured as a 150mg strength hard gelatin capsule that is packaged into 28 count bottles.

STANDARD DOSING

The dose for simeprevir is one 150mg capsule taken orally once daily with food. The type of food does not affect exposure to simeprevir. The capsule should be swallowed whole. For a missed dose within 12 hours of the usual dosing time, the patient should take the missed dose of simeprevir with food as soon as possible. If missed dose is > 12 hours past usual dosing time, skip that missed dose and resume usual dosing of simeprevir with food at the regularly scheduled time.

➜ Patients of East Asian ancestry exhibit higher simeprevir exposures. In clinical trials, higher simeprevir exposures have been associated with increased frequency of adverse reactions, including rash and photosensitivity. There are insufficient safety data to recommend an appropriate dose for patients of East Asian ancestry. The risks and benefits of simeprevir should be carefully considered prior to use in patients of East Asian ancestry.

Although simeprevir is approved for treatment of HCV genotype 1 with both peginterferon alfa and ribavirin, it has a limited role in current treatment guidance. ***For patients prescribed this regimen, consultation with an experienced clinician is recommended.***

Monitoring:
HCV RNA levels should be monitored as clinically indicated including baseline; at treatment weeks 4, 12, 24; end of treatment; and 24 weeks post-treatment completion. Use of a sensitive assay with a lower limit of quantification of at least 25 IU/mL for monitoring HCV RNA levels during treatment is recommended. Refer to the respective prescribing information for peginterferon alfa and ribavirin for baseline, on-treatment and post-treatment laboratory testing recommendations including hematology, biochemistry (including hepatic enzymes and bilirubin), and pregnancy testing.

➜ See also *Appendix 5* , *Hepatitis C Treatment Monitoring Schedule.*

DOSING IN CERTAIN CLINICAL CIRCUMSTANCES

Renal or Hepatic Impairment: There is no dose modification for toxicity or renal/hepatic insufficiency. Although the safety and efficacy of simeprevir have not been studied in HCV infected patients with a GFR < 30, renal elimination is minimal and no dosage adjustment is required for renal impairment. Simeprevir should not be used in patients on hemodialysis. Safety and efficacy of simeprevir have not been studied in HCV-infected patients with moderate or severe hepatic impairment. The combination of peginterferon and ribavirin is contraindicated in patients with moderate or severe hepatic impairment. Potential risks and benefits of simeprevir should be carefully considered prior to use in patients with moderate or severe haptic impairment.

SIMEPREVIR (OLYSIO™) DRUG INFORMATION

CONTRAINDICATIONS

- Any hypersensitivity to simeprevir or a component thereof.
- All contraindications to peginterferon alfa and ribavirin, since simeprevir must be administered with peginterferon and ribavirin
- Pregnant women and men whose female partners are pregnant, because ribavirin may cause birth defects and/or fetal death
- Concomitant usage with:
  - *Anticonvulsant* (carbamazepine, oxcarbazepine, phenobarbital, phenytoin)
  - *Antibiotics* (erythromycin, clarithromycin, telithromycin)
  - *Antifungals* (itraconazole, ketoconazole, posaconazole, fluconazole, voriconazole)
  - *Antimycobacterials* (rifampin, rifabutin, rifapentine)
  - *Corticosteroids* (systemic dexamethasone)
  - *Gastrointestinal products* (cisapride)
  - *Herbal products* (milk thistle, St. John's wort)
  - *HIV products* (All HIV Protease Inhibitors(boosted or unboosted), Any Cobicistat-containing regimen, and the following NNRTIs(efavirenz, delaviridine, etravirine, and nevirapine))

USE WITH CAUTION

Simeprevir mildly inhibits CYP1A2 activity and intestinal CYP3A4 activity, but does not affect hepatic CYP3A4 activity. Co-administration of simeprevir with drugs that are primarily metabolized by CYP3A4 may result in increased plasma concentrations of such drugs. Co-administration of simeprevir with substances that are moderate or strong inducers or inhibitors of cytochrome P450 3A (CYP3A) is not recommended as this may lead to significantly lower or higher exposure to simeprevir, respectively.

Simeprevir inhibits OATP1B1/3 and P-glycoprotein (P-gp) transporters. Co-administration of simeprevir with drugs that are substrates for OATP1B1/3 and P-gp transport may result in increased plasma concentrations of such drugs.

The following medications may pose a risk for potential interaction with simeprevir that may require close monitoring but, except those noted with *, do not require alteration of drug dosage, or timing of administration:

- *Antiarrhythmics* (digoxin, amiodarone, disopyramide, flecainide, mexiletine, propafenone, quinidine)
- *Anticoagulant* (warfarin)
- *Calcium Channel Blockers* (amlodipine, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, verapamil)
- *HMG Co-A Reductase Inhibitors* (atorvastatin*, lovastatin*, pitavastatin**, pravastatin**, rosuvastatin**, simvastatin**)
- *Immunosuppressants* (cyclosporine, sirolimus, tacrolimus)
- *Phosphodiesterase Type 5 (PDE-5) Inhibitors* (sildenafil**, tadalafil**, vardenafil**)
- *Sedatives/Anxiolytics* (oral midazolam or triazolam)

***** The interaction between simeprevir and these medications was evaluated in clinical trials and the following dose adjustment of HMG Co-A Reductase inhibitors/PDE-5 Inhibitors may be necessary:

- *Atorvastatin:* Use lowest necessary dose of atorvastatin (do not exceed 40mg)
- *Rosuvastatin:* Initiate rosuvastatin therapy with 5mg once daily; do not exceed 10mg daily
- *Simvastatin:* Titrate simvastatin dose carefully and use lowest necessary dose of simvastatin while monitoring for safety when co-administering with simeprevir.
- *Lovastatin, pitavastatin, and pravastatin:* concomitant use of simeprevir with these statins has not been studied. Titrate statin dose carefully and use lowest necessary dose of statin while monitoring for safety.
- *PDE-5 Inhibitors:* When used to treat chronic pulmonary arterial hypertension, consider starting with the lowest dose of PDE-5 inhibitor and increase as needed, with clinical monitoring as appropriate. No dose adjustment necessary if using PDE-5 for erectile dysfunction.

SIMEPREVIR (OLYSIO™) DRUG INFORMATION

SIDE EFFECTS

- ***Dermatologic effects:***
  - *Photosensitivity:* Serious photosensitivity reactions have been observed during combination therapy with simeprevir, peginterferon alfa and ribavirin. Photosensitivity may present as an exaggerated sunburn reaction, usually affecting areas exposed to light. Manifestations may include burning, erythema, exudation, blistering, and edema. Use sun protection measures and limit sun exposure. Consider discontinuation if a photosensitivity reaction occurs.
  - *Rash:* Rash occurs most frequently in the first 4 weeks of treatment with simeprevir based regimen but can occur at any time during treatment. Most rashes are mild to moderate and should be followed for possible progression of rash, including the development of mucosal signs (e.g., oral lesions, conjunctivitis) or systemic symptoms. If the rash becomes severe, discontinue simeprevir. Patients should be monitored until the rash has resolved.
  - *Pruritus*
- ***Gastrointestinal effects:*** Nausea
- ***Musculoskeletal effects:*** Myalgia
- ***Pulmonary effects:*** Dyspnea
- ***Other effects:***
  - *Hyperbilirubinemia:* Elevations in bilirubin were predominately mild to moderate in severity, and included elevation of both direct and indirect bilirubin. Elevations in bilirubin occurred early after treatment initiation, peaking by treatment week 2, and were rapidly reversible upon cessation of simeprevir. Bilirubin elevations were generally not associated with elevations in liver transaminases.

Appendix 4. HCV Polymerase Inhibitor Drug Information: Sofosbuvir

SOFOSBUVIR (SOVALDI™) DRUG INFORMATION

DESCRIPTION

Sofosbuvir is an oral direct-acting antiviral (DAA) agent against the Hepatitis C virus. Sofosbuvir is a prodrug that is metabolized to a nucleotide analogue inhibitor of the HCV NS5B RNA-dependent RNA polymerase. Sofosbuvir is indicated as one component of a combination antiviral regimen for the treatment of HCV monoinfection or co-infection with HIV.

➔ ***Sofosbuvir should not be used alone as monotherapy for hepatitis C.***

FORMULATIONS

Sofosbuvir is manufactured as a 400mg oral film coated tablet that is packaged in 28 count bottles.

STANDARD DOSING

The dose for sofosbuvir is 400mg once daily with or without food. Take a missed dose as soon as it is realized, but do not take more than one tablet daily. Sofosbuvir does not have a snack or fat content requirement. Sofosbuvir should not be used alone as monotherapy for hepatitis C and is used in combination with ribavirin and pegylated interferon or simeprevir as described below.

HCV-1 treatment regimens:

Treatment naïve or relapse post treatment with PEG/RBV

- SOF + PEG + RBV for 12 weeks
- SOF + SMV + /- RBV for 12 weeks (for interferon ineligible inmates only)

Prior non-responder to PEG/RBV treatment

- SOF + SMV + /- RBV for 12 weeks (regardless of genotype subtype (a or b)).

Prior non-responder to PEG/RBV/HCV Protease Inhibitor

- SOF + SMV + RBV for 12 weeks

Treatment naïve or prior relapse patients coinfected with HIV

- SOF + RBV + PEG for 12 weeks
- SOF + SMV + RBV for 12 weeks (for interferon ineligible inmates only)

Genotype 2 – 6 treatment regimens:

For treatment naïve, relapsers, or non-responder to prior treatment with PEG/RBV:

- HCV-2 = SOF + RBV for 12 weeks
- HCV-3 = SOF + RBV for 24 weeks
- HCV-4 = SOF + PEG + RBV for 12 weeks
- HCV-4 (interferon ineligible) = SOF + RBV for 24 weeks
- HCV-5 = SOF + PEG + RBV + for 12 weeks
- HCV-6 = SOF + PEG + RBV + for 12 weeks
- Coinfection with HIV = same as listed above for monoinfection

Refer to *Appendix 1* for dosing of peginterferon, *Appendix 2* for ribavirin, and *Appendix 3* for simeprevir.

Total treatment duration is as specified above and is **not** guided by on-treatment HCV RNA response. HCV viral loads should be drawn prior to treatment, at treatment week 4 and at 12 or 24 weeks after therapy completion.

DOSING IN CERTAIN CLINICAL CIRCUMSTANCES

Renal or Hepatic Impairment: There is no dose modification for toxicity or renal/hepatic insufficiency. Sofosbuvir should not be used in patients with GFRs less than 30 mL/min. Treatment with sofosbuvir in decompensated cirrhosis or liver transplant may differ from compensated liver disease and should be managed in consultation with an experienced clinician or consultant.

SOFOSBUVIR (SOVALDI™) DRUG INFORMATION

CONTRAINDICATIONS

- Any hypersensitivity to sofosbuvir or a component thereof.
- All contraindications to peginterferon alfa and ribavirin, since sofosbuvir must be administered ribavirin +/- peginterferon.
- Pregnant women and men whose female partners are pregnant, because ribavirin may cause birth defects and fetal death.
- HIV medications didanosine, zidovudine, and tipranavir.
- Concomitant usage with modafinil, oxcarbazepine, rifabutin, rifampin, rifapentine, or St. John's Wort.

USE WITH CAUTION

Sofosbuvir is a substrate of permeability glycoprotein (P-gp) drug transporter and breast cancer resistance protein (BCRP). ***The following medications may pose a risk for potential interaction with sofosbuvir that may require close monitoring, alteration of drug dosage, or timing of administration:***

- *Antiepileptic* (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone,
- *Antifungals* (itraconazole, ketoconazole)
- *Antihypertensives* (carvedilol, nicardipine, prazosin, propranolol, verapamil)
- *Biologics* (crizotinib, lapatinib, gefitinib, nilotinib, sunitinib, vandetanib, vemurafenib)
- *HIV drugs* (darunavir, ritonavir*, saquinavir, lopinavir, nelfinavir, saquinavir, tenofovir)
- *Immunosuppressants* (dexamethasone, doxorubicin, cyclosporine*****, tacrolimus*****, vinblastine)
- *Other drugs* (amiodarone, atorvastatin, clarithromycin, cobicistat, dipyridamole, dronadarone, eltrombopag, erythromycin, grapefruit juice, ivacaftor, lomitapide, mefloquine, nefazodone, progesterone, quinidine, quinine, ranolazine, reserpine, tamoxifen, ulipristal)

***** The interaction between SOF and these medications was evaluated in clinical trials and no adjustment of either drug should be necessary.

SIDE EFFECTS

- ***Dermatologic effects:*** Pruritus
- ***Flu-like symptoms:*** Fatigue and headache
- ***Gastrointestinal effects:*** Nausea, decreased appetite and diarrhea
- ***Hematologic effects:***
  - *Anemia:* The addition of sofosbuvir to peginterferon alfa and ribavirin (PEG/RBV) is associated with an additional decrease in hemoglobin concentrations.
  - *Neutropenia:* The addition of sofosbuvir to PEG/RBV is associated with an additional decrease in neutrophil counts. Decreases in neutrophil counts may require dose reduction or discontinuation of PEG/RBV. No dose adjustment should be made to sofosbuvir. If RBV is discontinued, sofosbuvir should be discontinued and not restarted.

Appendix 5. Hepatitis C Treatment Monitoring Schedule

Evaluation	Baseline (anti-HCV positive)	Pre-Treatment	On-Treatment Monitoring (by week of treatment)									12 or 24 wks post-treatment	12 mos post-treatment
			1	2	3	4	8	12	16	20	24		
Clinician evaluation	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*										
Ferritin, iron saturation, ANA*	X												
HCV RNA**		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 (IFN regimens)		X						X			X		
Triglycerides		X						X			X		
ECG (preexisting CHD)		*if indicated*	*if indicated*										
Urine pregnancy test (if childbearing potential)		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.

****** For treatment regimens recommended in this document, the schedule of HCV RNA testing includes a pre-treatment baseline, after 4 weeks on treatment, at the end of treatment, and again 12 to 24 weeks after completion of therapy that resulted in an undetectable end-of-treatment HCV RNA level.

Appendix 6. Management of Hematologic Changes

Note: ***For patients prescribed a Direct-Acting Antiviral (DAA) for HCV (e,g., sofosbuvir or simeprevir), if ribavirin must be discontinued due to hematologic changes, the DAA also may need to be discontinued. Consultation with an experienced clinician is recommended.***

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, HIV/HCV co-infected, or treated with a DAA. ***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.	

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, HIV/HCV co-infected, or treated with a DAA. ***Dosage:*** Filgrastim 300 microgram subcutaneous daily or less frequently. ***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.

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