Treatment of Hepatitis C with Pegylated Interferon and Ribavirin, with or without Boceprevir or Telaprevir

Federal Bureau of Prisons
Clinical Practice Guidelines

May 2014

What's New in This Document?

This document, along with the new BOP *Interim Guidance for the Management of Chronic Hepatitis C Infection*, replaces the 2012 BOP Clinical Practice Guidelines, *Evaluation and Treatment of Hepatitis C and Cirrhosis*. Please see *Section 1, Purpose and Overview,* for further explanation.

The dose and frequency of telaprevir have changed to1125 mg (three 375 mg tablets) every 12 hours +/– 2 hours. A snack should be eaten with each dose, but a 20 gm snack is no longer required.

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1. Purpose and Overview

In 2011, a new class of medications was introduced for the treatment of chronic Hepatitis C Virus (HCV) infection. The HCV protease inhibitors (PIs), boceprevir and telaprevir, in combination with peginterferon and ribavirin, demonstrated superior efficacy for the treatment of HCV genotype 1, and were integrated into the BOP Clinical Practice Guidelines. At that time, the standard treatment using peginterferon and ribavirin did not change for genotype 2 or 3. However, newer medications with improved efficacy and safety have recently been approved and have supplanted these regimens as preferred treatments for chronic HCV infection.

As a result, current AASLD-IDSA guidelines do not recommend the use of peginterferon and ribavirin—with or without boceprevir or telaprevir—when initiating treatment for HCV. For HCV patients who are already being treated with peginterferon and ribavirin, it is reasonable to continue these regimens so long as treatment goals are being met and there are no contraindications.

The purpose of this document is to provide treatment guidance for the duration of therapy using one of these regimens.

- The material is not new, but contains excerpts from the 2012 BOP Clinical Practice Guidelines on the *Evaluation and Treatment of Hepatitis C and Cirrhosis* that are most relevant to the management of these patients.
- All other cases of chronic HCV infection should be managed in accordance with the new BOP *Interim Guidance for the Management of Chronic Hepatitis C Infection*.

For patients who have started a treatment regimen of peginterferon and ribavirin—with or without boceprevir or telaprevir—the primary clinical interventions involve: *monitoring ongoing treatment*; *managing side effects*; and *determining treatment dosing, duration, and outcome*.

2. Monitoring Ongoing Treatment

Recommended baseline, pre-treatment, and ongoing clinical evaluations and laboratory studies are summarized in *Appendix 1*, *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 or new symptoms such as chest pain, dyspnea, or visual changes. Side effects should be evaluated in order to make decisions about dose adjustments, and patients should be reassured that they are experiencing the "normal" side effects of treatment. (See *Section 3*, *Managing Side Effects*, below.)
- Those with compensated cirrhosis, 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.

3. Managing Side Effects

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 three 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 the 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 four 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. 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.*

  - ***Severe rash*** is generalized, covers 50% or greater of the body surface, or includes the presence of vesicles, bullae, or ulcerations. 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. Patients 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. However—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 eight weeks of treatment) or who 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, Guidelines for Adjusting Therapy for CBC Changes*.
  - ➔ *If ribavirin must be discontinued due to anemia, the HCV PI must also 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 (G-CSF) are outlined in *Appendix 2*.
  - ➔ *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*.
  - ➔ *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.

4. Treatment Dosing, Duration, and Outcome

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.

Dosing

Dosing of Peginterferon and Ribavirin

Historically, dual therapy with once-weekly pegylated interferon injections and twice-daily oral ribavirin was the standard treatment for all HCV genotypes except genotype 1. It was also appropriate for treatment of genotype 1 when there were contraindications or exclusions to using HCV PIs such as co-infection with HBV or HIV, or use of certain medications.

➔ *Ribavirin is completely ineffective as monotherapy.*

- 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 of peginterferon and ribavirin is detailed in *Appendix 5*, which also contains more detailed information on dosing in certain clinical circumstances, contraindications, and side effects. See *Appendix 1* for information on monitoring parameters.

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: 1125 mg (three 375 mg tablets) by mouth every 12 hours (+/-–2 hours) with a snack

➔ Refer to *Appendix 3* 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 5*. See *Appendix 1* 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.* 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.
- Boceprevir must be prescribed and taken every 8 hours, +/- one hour. Telaprevir must be prescribed and taken every 12 hours +/- 2 hours. 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 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.

Duration of Treatment

Recommended Treatment Duration for 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*, 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.

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.

➔ *Appendix 3* 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 *Appendix 3* and the flowcharts in *Appendices 4a* and *4b*.

Duration of Boceprevir-Based Triple Therapy 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.

Determining which of these four regimens of boceprevir-based therapy to use for a given patient is based on 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 log10 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 *Section 3*, *Managing of Side Effects,* and *Appendix 2.*

Duration of Telaprevir-Based Triple Therapy 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

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 log10 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 *Section 3*, *Managing of Side Effects,* and *Appendix 2*.

Outcome

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 1* below. For all patients, on-treatment HCV RNA levels should be obtained at the end of treatment weeks 4, 12, and 24; at the end of treatment for treatment durations longer than 24 weeks; and again 24 weeks after completion of therapy with an end of treatment response. For boceprevir-based regimens, an HCV RNA level also should be obtained at the end of treatment week 8.

Table 1. 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*****	$\geq$ 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	$\geq$ 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.*		

References

Hepatitis C – Primary References

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Ghany MG, Strader DB, Thomas DL, Seeff LB. AASLD practice guidelines: diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009;49:1335–1374. Available at: http://www.aasld.org/practiceguidelines/Documents/Hepatitis%20C%20UPDATE.pdf

Hepatitis C – Other References

Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364:1207–1217.

Hoofnagle JH, Seeff LB. Peginterferon and ribavirin for chronic hepatitis C. *N Engl J Med*. 2006;355:2444–2451.

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McHutchison JG, Dusheiko G, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med*. 2007;357:2227–2236.

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Shiffman ML, Suter F, et al. Peginterferon alfa-2a and Ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med*. 2007;357(2):124–134.

Zeuzem S, Andreone P, Pol S, etal. Telaprevir for retreatment of HCV infection. *N Engl J Med*. 2011;364:2417–2428.

Appendix 1. 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 2. Guidelines for Adjusting Therapy for CBC Changes

<table>
<tr><th colspan="3">Hemoglobin (Hgb)</th></tr>
<tr><th>Value</th><th colspan="2">Peginterferon/Ribavirin Adjustment and Supportive Treatment</th></tr>
<tr><td>10–11 g/dL</td><td colspan="2">☐ Peginterferon → No change.
☐ Ribavirin →
► If no or minimal symptoms, then no dose modification.
► If symptomatic, decrease ribavirin by 200 mg/day.</td></tr>
<tr><td>8.5–10 g/dL</td><td colspan="2">☐ 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)</td></tr>
<tr><td>< 8.5 g/dL</td><td colspan="2">☐ Peginterferon →
► Peginterferon alfa 2a (Pegasys) → No change.
► Peginterferon alfa 2b (Peg-Intron) → Discontinue until resolved.
☐ Ribavirin → Discontinue until resolved.</td></tr>
<tr><td colspan="3">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 boceprevir or telaprevir.
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.</td></tr>
<tr><td colspan="3">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.</td></tr>
<tr><th colspan="3">Absolute Neutrophil Count (ANC)</th></tr>
<tr><th>Value</th><th colspan="2">Peginterferon/Ribavirin Adjustment and Supportive Treatment</th></tr>
<tr><td>< 750</td><td colspan="2">☐ 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.</td></tr>
<tr><td>< 500</td><td>☐ Peginterferon & Ribavirin → Discontinue both until resolved.</td><td>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 boceprevir or telaprevir..
Dosage: Filgrastim 300 microgram subcutaneous daily or less frequently.
Goal: ANC >1500</td></tr>
<tr><th colspan="3">Platelets</th></tr>
<tr><th>Value</th><th colspan="2">Peginterferon/Ribavirin Adjustment and Supportive Treatment</th></tr>
<tr><td>< 50,000</td><td colspan="2">☐ 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.</td></tr>
<tr><td>< 30,000</td><td colspan="2">☐ Peginterferon → Discontinue until resolved.
☐ Ribavirin → Discontinue until resolved.</td></tr>
<tr><td colspan="3">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.
Note: Unless the clinical condition requires urgent discontinuation of antiviral therapy, eltrombopag may be considered for regimens that include boceprevir or telaprevir.</td></tr>
</table>

Appendix 3. Dosing and Treatment Duration in Triple Therapy with Boceprevir or Telaprevir

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

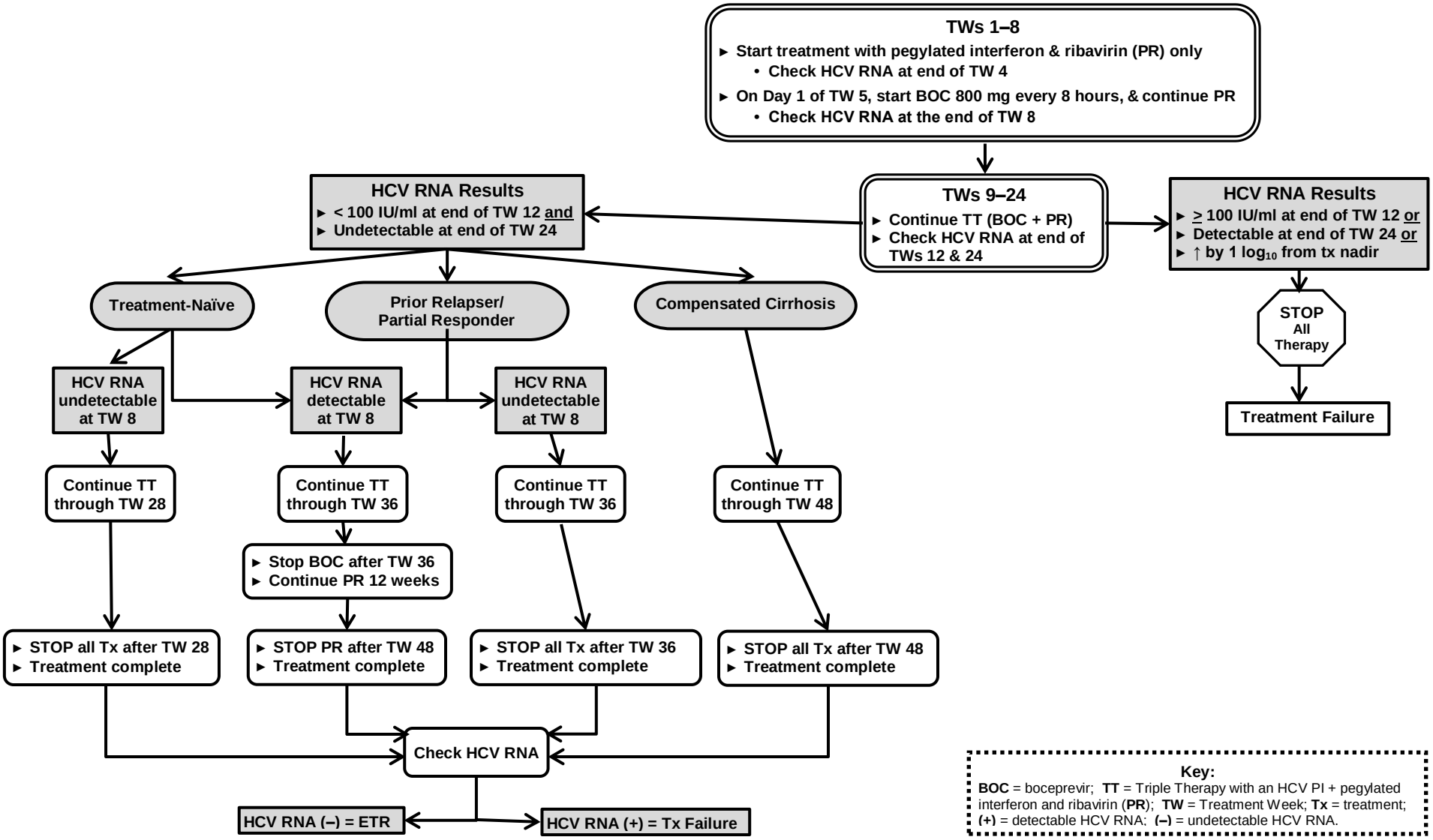
TELAPREVIR-BASED REGIMEN:

- 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.

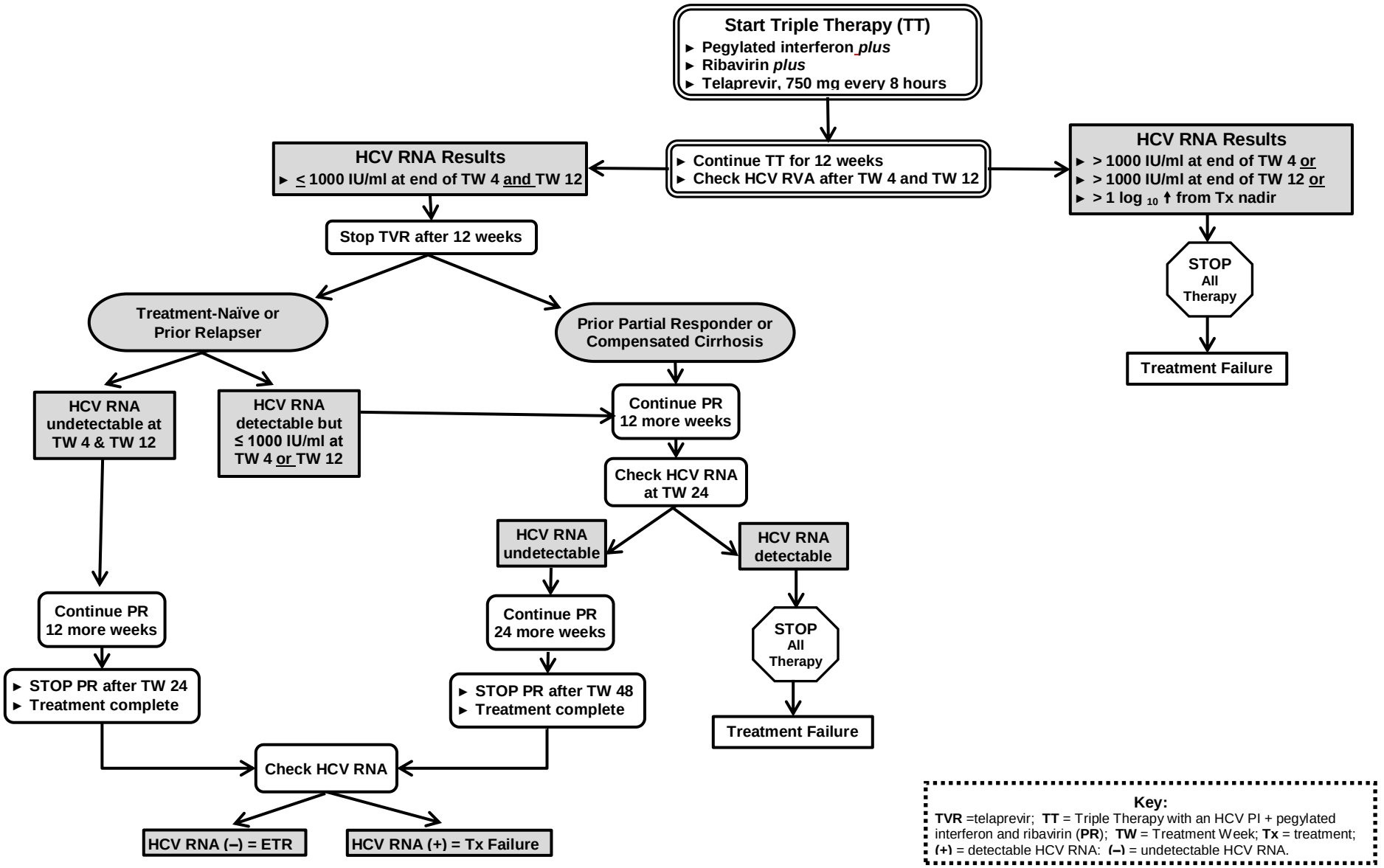
Discontinue all HCV meds if any of the following occur:

- 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

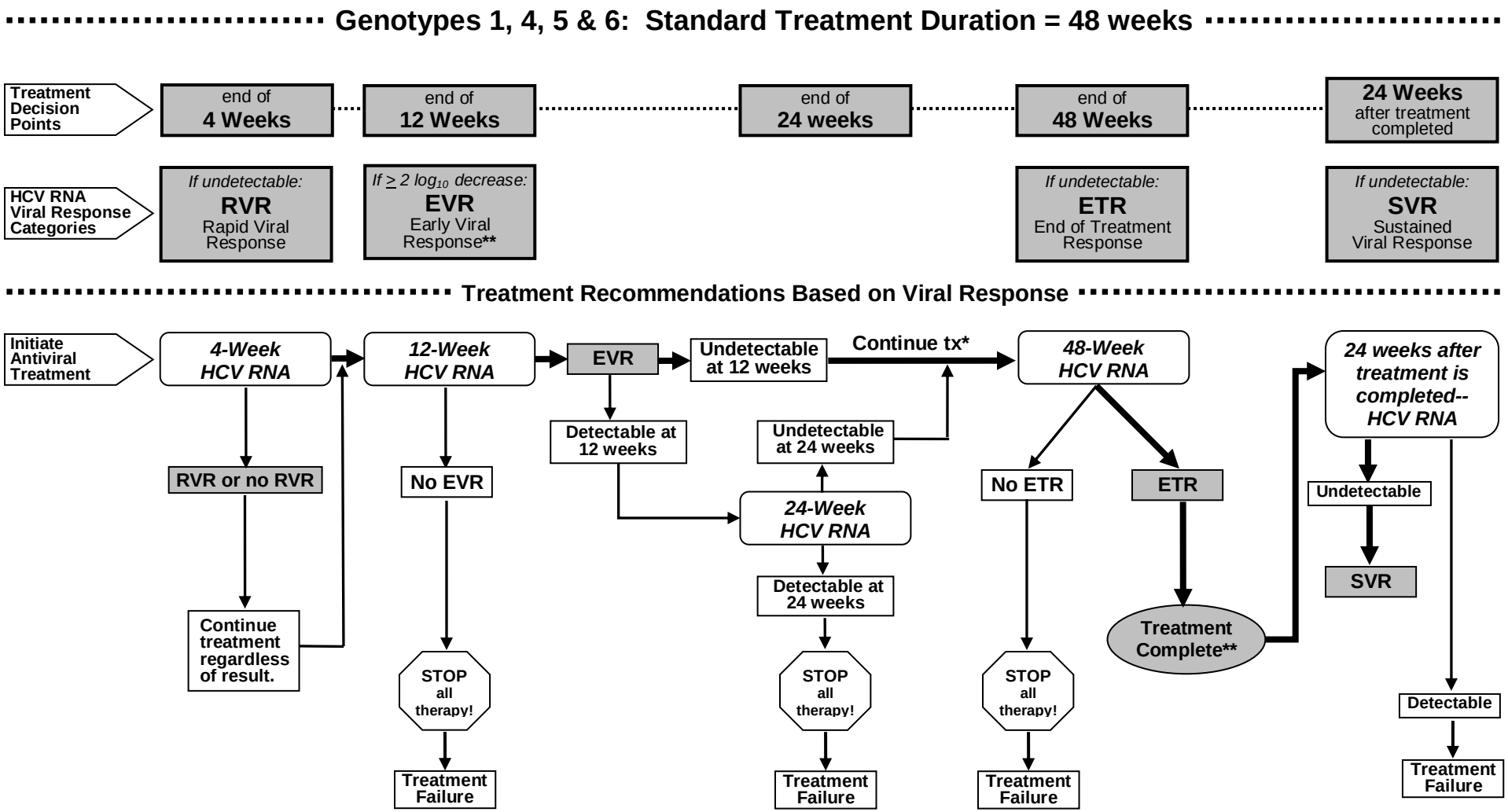
Appendix 4a. Timeline for HCV Treatment Decisions (Based on Viral Response): Genotype 1 on Triple Therapy with Boceprevir



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



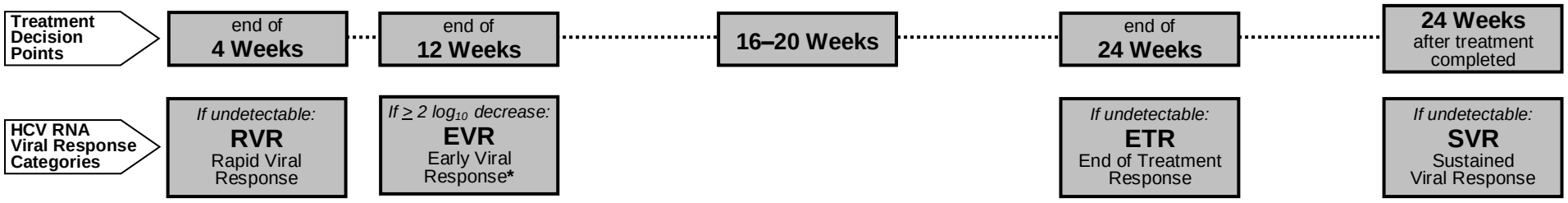
Appendix 4c. Timeline for HCV Treatment Decisions, Based on Viral Response: Genotypes 1, 4, 5, and 6 on Dual Therapy



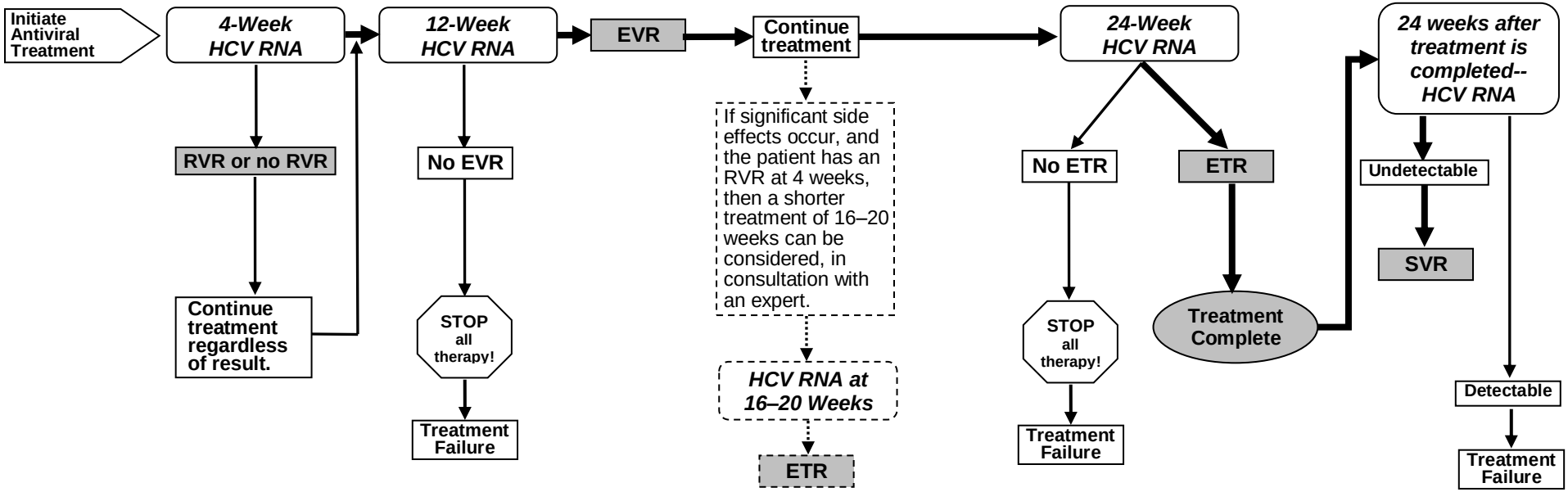
***** If significant side effects occur, and an RVR at 4 weeks was achieved, then shortening the treatment to at least 24 weeks can be considered with expert consultation.
****** 2 $\log_{10}$ decrease = decrease by a factor of 10^2 (100), i.e., if baseline viral load = 720,000, then 2 log decrease =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

Genotypes 2 & 3: Standard Treatment Duration = 24 weeks



Treatment Recommendations Based on Viral Response



***** 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

Dosing is complicated. The two types of pegylated inteferons are dosed differently. Moreover, the dosing of ribavirin depends on the type of peginterferon and the direct-acting antiviral agent being used.

Peginterferon alfa 2a (Pegasys) + Ribavirin+/- Boceprevir or Telaprevir

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)* ➔ ***Ribavirin should be taken with food.***	**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)

Peginterferon alfa 2b (Peg-Intron) + Ribavirin +/- Boceprevir or Telaprevir

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.**

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

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 by 50%.

Ribavirin is not indicated.

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

Appendix 6. Boceprevir/Telaprevir Drug Information

Note: Current AASLD-ISDA 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.

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 5* 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*).

STANDARD DOSING *(continued)*	
Telaprevir	Telaprevir is dosed 1125 mg orally (3 x 375 mg tablets) every 12 hours (+/– 2hr) with food 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 5* 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.	
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

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 telaprevir, 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)
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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 ► *Gastrointestinal 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*).
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*). ► *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