REVIEW

Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office

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Chronic hepatitis C virus (HCV) infection affects approximately 1.3% of the United States population and 4% of veterans who use Department of Veterans Affairs medical services. Chronic HCV is the primary cause of cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease requiring liver transplantation in the United States. Management of chronic HCV is aimed at halting disease progression, preventing cirrhosis decompensation, reducing the risk of HCC, and treating extrahepatic complications of the infection. As part of a comprehensive HCV management strategy, peginterferon alfa and ribavirin, along with the addition of a hepatitis C protease inhibitor therapy for many genotype 1-infected patients, are the current standard of care. Antiviral therapy should be provided to those individuals who are clinically stable, have moderate liver disease or compensated cirrhosis, and are motivated to pursue therapy. Many patients have comorbid medical and psychiatric conditions, which may affect their adherence to antiviral therapy or worsen while on antiviral therapy. To optimally manage hepatitis C and associated comorbidities, patients benefit from multidisciplinary teams that can provide HCV-specific care and treatment. Sustained virologic response is associated with "cure" of chronic HCV, and results in improved liver disease outcomes and prolonged survival.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

The prevalence of chronic hepatitis C virus (HCV) infection is approximately 1.3% in the United States population and 4% in veterans who use Department of Veterans Affairs (VA) medical services (1,2). More than 165,000 veterans with HCV currently receive care within the Veterans Health Administration, of whom more than 5,000 such patients die annually (3). The natural history of chronic HCV is variable, with cirrhosis eventually developing in 30–40% of individuals unless the virus is eradicated with therapy (4–6). Advanced liver disease due to HCV is now the leading indication for liver transplantation in the United States and Europe. In addition, hepatocellular carcinoma (HCC), a frequently lethal complication of HCV-associated cirrhosis, has increased eight-fold among HCV-infected veterans receiving VA care between 2000 and 2008 (3).

The consequences of HCV infection constitute a significant disease burden and demonstrate a need for effective medical care. Successful treatment of HCV with interferon (IFN)-based regimens can result in viral eradication, which has been associated with a reduced incidence of hepatic decompensation and HCC in addition to prolonged survival (7–9). Sustained virologic response (SVR), defined as undetectable levels of HCV RNA at least 24 weeks after completion of therapy, is the primary endpoint of successful therapy, and is associated with durable clearance of virus in more than 98% of cases (10).

All patients with chronic HCV are potential candidates for antiviral therapy. Patients most likely to benefit from antiviral treatment include those at risk for progressive liver disease and those with diminished quality of life secondary to their viral infection. Medical care providers should discuss the natural history of HCV infection, the risks and benefits of antiviral therapy, and steps that can be taken to minimize liver damage with every HCV-infected patient. It is crucial that individuals in whom treatment is deferred are re-evaluated for treatment candidacy as their comorbid conditions are effectively managed.

In 2011, the standard of care for many patients with HCV genotype 1 infection became a combination of an oral protease inhibitor (PI), boceprevir (BOC) or telaprevir (TVR), along with

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pegylated IFN (PegIFN) and ribavirin (RBV). BOC and TVR represent a new era of therapy, as they are the first commercially available hepatitis C direct-acting antiviral (DAA) agents, which directly inhibit viral replication. In clinical trials of HCV genotype 1-infected patients receiving PegIFN and RBV, combined with BOC or TVR, SVR was achieved in 63–75% of treatment-naïve patients, in 69–88% of PegIFN and RBV relapsers, and in up to 33% of PegIFN and RBV nonresponders (11–14). Triple therapy is associated with more side effects and requires closer patient follow-up than treatment with PegIFN and RBV alone. Increased hematological toxicity from triple therapy may lead to increased utilization of growth factors, which will further strain medical resources in healthcare systems. Additionally, BOC and TVR carry the risk of inducing HCV resistance mutations, and it is likely that cross-resistance to future generations of PIs will develop in some patients who do not achieve SVR (15). Extensive patient monitoring for virologic response and counseling on adherence will be necessary to minimize the development of resistant variants. With the approval of HCV PIs, providers will need to identify candidates who require immediate treatment, as well as those who can wait another 4–6 years for the likely availability of IFN-free regimens. Future IFN-free regimens may include oral second generation PIs, polymerase inhibitors, HCV nonstructural protein 5a inhibitors, and combinations of these drugs (16).

The following treatment recommendations summarize the current best practices in the management of hepatitis C, including the use of PegIFN, RBV, and BOC- or TVR-containing regimens. These recommendations are based on an extensive review of published data; the American Association for the Study of Liver Diseases Practice Guidelines: Diagnosis, Management and Treatment of Hepatitis C (2009); An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection (2011); CDC; FDA, and NIH recommendations; as well as input from thought leaders involved in the care of veterans with HCV infection (17–20). Recommendations were developed using systematic weighting and grading of the quality of evidence according to criteria used by the American Association for the Study of Liver Diseases 2009 Practice Guidelines (**Table 1**) (18). Limited data that are currently available only in abstract form also have been included when the data are derived from prospective randomized, controlled trials. Each author participated in the preparation and review of the draft recommendations, and agreed with the consensus statements reflected in the final document. Feedback from external peer reviewers was obtained. The final recommendations were reviewed and endorsed by: the VA Hepatitis C Resource Centers, the VA HCV Technical Advisory Group, the VA Gastrointestinal Field Advisory Committee, and the National Hepatitis C Program Office. Additional resources pertaining to the care of the HCV-infected patient developed by the VA Hepatitis C Resource Centers are available at www.hepatitis.va.gov.

Recommendation:
1. All patients with chronic HCV infection should be evaluated for HCV antiviral treatment. (Class IIa, Level B).

Table 1. Grading system for recommendations adapted from the AASLD Practice Guidelines for the Diagnosis, Management, and Treatment of Hepatitis C

	Description
Classification	
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation procedure/treatment is not useful/effective, and in some cases, may be harmful
Level of evidence	
Level A	Data derived from multiple RCT or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Only consensus opinion of experts, case studies, or standard-of-care

AASLD, American Association for the Study of Liver Diseases; RCT, randomized, controlled trials.

PRETREATMENT ASSESSMENTS

The 2009 American Association for the Study of Liver Diseases Practice Guidelines for the Diagnosis, Management, and Treatment of Hepatitis C describe that HCV antiviral therapy is indicated for patients with chronic HCV who are at greatest risk for progression to cirrhosis. These are patients with detectable serum HCV RNA and liver histology showing significant hepatic fibrosis (more than portal fibrosis, greater than stage 1) (18). Additional patient risk factors for increased fibrosis progression include male gender, obesity, steatosis, heavy alcohol use, age, elevated serum alanine transaminase, and greater hepatic inflammation (21–23). Pretreatment assessments are summarized in **Table 2**.

Laboratory testing

HCV antiviral therapy generally should be used only in patients with preserved liver function (serum bilirubin <1.5 mg/dl; International Normalized Ratio <1.5; albumin >3.0 g/dl; and no evidence of hepatic encephalopathy or ascites), along with adequate hematological and biochemical parameters to tolerate therapy (hemoglobin >12 g/dl; neutrophil count >1.5 k/mm^3; platelet count >75 k/mm^3; serum creatinine <1.5 mg/dl). HCV genotype should be determined, as it influences the selection of therapy and treatment duration. Baseline viral load should be measured using

Table 2. Pretreatment assessments in patients with chronic HCV infection[a]

Necessary
• Medical history, including complications of liver disease, presence of significant extrahepatic disease, and symptoms of chronic HCV that may diminish quality of life
• Psychiatric history, including past or ongoing psychiatric, and substance use disorders
• Screening for depression and alcohol use
• Biochemical markers of liver injury and assessment of hepatic function, including serum ALT, serum albumin, serum bilirubin (including direct bilirubin), and prothrombin time
• Hemoglobin, hematocrit, WBC with differential, and platelet count
• TSH
• Serum creatinine
• Serum glucose
• Uric acid (while receiving TVR)
• Serum ferritin, iron saturation, and serum ANA
• Pregnancy test (in women of childbearing age)
• HIV serology
• Serum HBsAg, antiHBc, antiHBs, antiHAV (total)
• Quantitative HCV RNA measurement
• HCV genotype
• Previous antiviral therapies and response
• ECG in patients with preexisting cardiac disease
Recommended
• Liver biopsy (if results will influence management)
• IL28B genotype (if results will influence management)
• Eye exam for retinopathy in patients with diabetes or hypertension
• Urine toxicology screen for opiates, cocaine, and amphetamines

[a]ALT, alanine transaminase; ANA, antinuclear antibodies; antiHAV, antibody to hepatitis A virus; antiHBs, antibodies to HBsAg; AntiHBc, antibody to hepatitis b core antigen; ECG, electrocardiogram; HbsAg, hepatitis B surface antigen; HCV, hepatitis C virus; TSH, thyroid-stimulating hormone; TVR, telaprevir; WBC, white blood cell.

a quantitative HCV RNA assay, so that treatment response can be assessed later (see the section "Monitoring therapy").

Liver disease staging

Liver biopsy is the best method for staging the degree of fibrosis (typically staged from 0 to 4 with the METAVIR, and 0 to 6 with the Ishak scoring system) and grading inflammation (typically graded from 0 to 4) (22,24). In most cases, patients who initiate antiviral treatment for HCV should have more than portal fibrosis (greater than stage 1). Although liver biopsy is the preferred approach, it is invasive, is subject to sampling error, and carries a risk for severe complications (24). As such, it is not required before reaching a treatment decision, and may be less useful among patients in whom the results are unlikely to alter management (18). Alternative approaches, such as liver imaging and serum fibrosis markers, can be performed instead of a liver biopsy, although with careful recognition of their limitations (25–28).

Psychiatric assessment

All patients should be evaluated for psychiatric disorders, particularly depression and suicide risk. Uncontrolled depression or active suicidal ideation is an absolute contraindication to IFN-based therapies. Patients with psychiatric disorders that are stable or in remission may receive antiviral therapy. Standardized depression scales (e.g., Beck Depression Inventory or Patient Health Questionnaire) serve as useful tools for baseline and on-treatment psychiatric assessment. Patients may require referral to a psychiatrist or mental health professional for evaluation and therapy before initiation of antiviral treatment (29).

Assessments for substance use disorders

All patients should be evaluated for current alcohol and other substance use, with validated screening instruments such as AUDIT-C or CAGE (30). The presence of current heavy alcohol use (> 14 drinks per week for men or > 7 drinks per week for women), binge alcohol use (> 4 drinks per occasion at least once a month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. Urine toxicology screens for opiates, cocaine, or amphetamines may be used to supplement patient self-report.

Alcohol and illicit drug use may affect HCV treatment adherence and response to therapy; however, on a case-by-case basis, individuals with active alcohol or substance use have been treated successfully (20). Integrated care models have demonstrated that patients who have recently become abstinent can also be treated successfully (31). Patients with past or recent substance abuse disorders often require close monitoring, and care should be coordinated with addiction specialists.

Adherence

Adherence to a treatment plan is imperative to achieve SVR and to reduce the potential for HCV resistance associated with DAA agents. Although improved SVR is achieved with the addition of BOC or TVR to PegIFN injections and oral RBV in genotype 1-infected patients, these regimens are complex, involve response-guided therapy (RGT), have a high pill burden (12–18 pills per day), confer a potential for viral resistance, and require frequent follow-up. Treatment adherence should be discussed with patients considering antiviral therapy, and the likelihood of adherence should be assessed. Evidence of prior non-adherence to medical, psychiatric, or other therapies may predict non-adherence to HCV therapy. In patients who do not comply with pretreatment evaluations, treatment initiation should be deferred and attempts to improve adherence should be made.

Evaluation for HIV co-infection

There is significant overlap in the epidemiology of and risk factors for HIV and HCV infections. Patients with a new diagnosis of HIV infection may benefit from HIV antiretroviral therapy.

HIV/HCV co-infection increases the risk of HCV-related liver damage, may influence the duration of HCV therapy and lowers the likelihood of SVR. Because of the potential clinical and public health benefits of HIV detection, all patients with HCV infection considering antiviral therapy should be offered a voluntary HIV test if the HIV status has not been established previously.

Pregnancy

RBV is potentially teratogenic (Pregnancy Category X). A pregnancy test should be obtained from women of childbearing potential before the initiation of HCV treatment, and women who are pregnant or attempting to conceive should not be treated. Pregnancy also must be avoided in the partner of an HCV-infected male patient receiving treatment. Contraception for both partners is required and should include at least one barrier method of contraception (condoms or diaphragm plus spermicide) throughout the course of HCV treatment and for 6 months after treatment cessation (32,33). Routine monthly pregnancy tests should be performed during this time, and if a patient or their partner becomes pregnant, RBV should be discontinued immediately and the pregnancy should be reported to the Ribavirin Pregnancy Registry at 1-800-593-2214 or www.ribavirinpregnancyregistry.com.

Although BOC and TVR are Pregnancy Category B agents, they must be used in combination with RBV. Due to drug–drug interactions (DDIs), oral contraceptives may be ineffective because of a decrease in their plasma levels when they are co-administered with either BOC or TVR. Thus, two alternative effective methods of contraception, such as intrauterine devices and barrier methods, should be used in at-risk patients and partners. After TVR has been discontinued for 2 weeks, oral contraceptives may be used as one of two forms of birth control (34,35).

Testing for *IL28B* genotype

Single-nucleotide polymorphisms in chromosome 19, in the region of the *IL28B* gene (which encodes IFN-λ3), are strongly associated with the probability of achieving SVR with PegIFN and RBV treatment in genotype 1-infected patients (36–38). In particular, genotype 1-infected subjects carrying the favorable CC genotype at rs12979860 have an approximately two-fold increase in SVR to PegIFN and RBV, compared with those with the less favorable CT or TT genotypes. African Americans and Hispanics have a lower frequency of the CC genotype at rs12979860, which partially explains the lower SVR in these groups (36–38). In genotype-2- or 3-infected patients, *IL28B* genotype does not appear to be strongly associated with SVR to PegIFN/RBV (39–41).

Retrospective analyses suggest that treatment-naïve, genotype 1-infected patients with *IL28B* genotype CT or TT have a higher SVR when treated with DAA-PegIFN and RBV as compared with PegIFN and RBV treatment alone. Among treatment-naïve subjects with *IL28B* CC genotype, the addition of BOC to PegIFN and RBV did not appear to improve SVR rates compared with PegIFN and RBV alone (80–82 and 78%, respectively), whereas the addition of TVR to PegIFN and RBV resulted in higher SVR rates compared with PegIFN and RBV alone (90 and 64%, respectively). Among genotype 1-infected patients who failed PegIFN and RBV treatment, SVR rate was 60–80% with retreatment involving a HCV PI-containing regimen regardless of *IL28B* genotype. However, the results of these retrospective subgroup analyses should be viewed cautiously because of the small sample size and potential differences in demographic or clinical characteristics. Prospective studies evaluating IL28B genotype and SVR with DAA-containing regimens are needed (11,12).

Testing for *IL28B* genotype before starting treatment with PegIFN/RBV±DAA agent is recommended if results might alter treatment decisions. For example, patients who are reluctant to receive treatment may be better informed of their chance of achieving an SVR if they know their IL28B genotype. After beginning treatment with PegIFN and RBV (±DAA agent), the decline in HCV RNA level during treatment (e.g., at weeks 4, 8, and 12) is more strongly associated with SVR than is *IL28B* genotype (11–14,42).

Recommendation for IL28 genotype testing:
2. IL28B genotype testing can be performed before PegIFN–RBV therapy, with or without a PI, if the information on the probability of treatment response or duration would alter treatment decisions (Class IIa, Level B).

Concomitant medical conditions

Treatment with IFN-based therapy may exacerbate the underlying autoimmune disorders. Patients with stable autoimmune thyroid disease or diabetes mellitus can generally be treated safely, but psoriasis, Crohn's disease or rheumatoid arthritis may be worsened by therapy, and should be co-managed with a specialist. HCV treatment should be administered with caution if liver histology reveals features suggestive of autoimmune hepatitis. Among patients with risk factors for retinal disease (e.g., hypertension or diabetes) or baseline visual abnormalities, a detailed eye exam should be performed before and during treatment as indicated, to identify any worsening of disease while receiving IFN (**Table 2**).

Recommendations in patients being considered for HCV therapy:
3. Patients should receive pretreatment assessments as summarized in **Table 2** *(Class I, Level B).*
4. Patients with more than portal fibrosis, including those with compensated cirrhosis, who lack contraindications, should be considered for treatment (Class I, Level B).
5. Patients should be counseled on their likelihood of achieving SVR, based upon individual factors such as body mass index, genotype, race, stage of fibrosis, and viral load before initiating therapy (Class I, Level B).

DEFINITIONS OF RESPONSE

HCV RNA decline during therapy is highly associated with the likelihood of achieving an SVR. Attaining rapid virologic response (RVR), extended RVR (eRVR), and early virologic response (EVR) can provide guidance as to the likelihood of achieving an SVR (refer to **Figure 1**) (11–15). A sensitive real-time quantitative HCV RNA PCR assay should be used to assess viral response. The assay should have a lower limit of quantification for HCV RNA

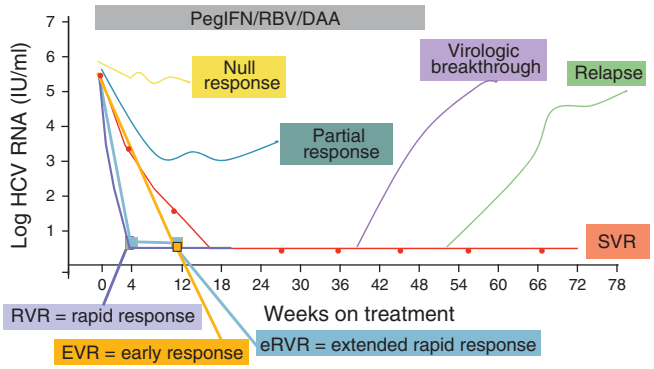

Figure 1. Patterns of virologic response related to treatment. Rapid virologic response (RVR): undetectable hepatitis C virus (HCV) RNA at week 4. Extended RVR (eRVR): HCV RNA <10–15 IU/ml at weeks 4 and 12, as defined by clinical trials with telaprevir (TVR)-based therapy (12,13). Early virologic response (EVR): ≥2 $\log_{10}$ reduction from baseline HCV RNA, but virus remains detectable (partial EVR) or is undetectable (complete EVR) at week 12. Early responders: HCV RNA <10–15 IU/ml at week 8, as definded by clinical trials with boceprevir (BOC)-based therapy (11,14). Partial response: ≥2 $\log_{10}$ reduction from baseline HCV RNA at week 12, but virus remains detectable through week 24 or treatment end. Breakthrough: undetectable HCV RNA during treatment followed by appearance of HCV RNA, despite continued treatment. End-of-treatment response (ETR): undetectable HCV RNA at the end of treatment. Sustained virologic response (SVR): undetectable HCV RNA at 24 weeks after treatment completion. Relapse: undetectable viremia during treatment and/or at the end of treatment, but subsequent viremia following treatment cessation. Non-response: detectable circulating HCV RNA throughout treatment. Null-response: <2 $\log_{10}$ reduction from baseline HCV RNA during treatment. DAA, direct-acting antiviral; PegIFN, peginterferon; RBV, ribavirin.

of ≤25 IU/ml, and a lower limit of detection of 10–15 IU/ml. The lower limit of detection of <10–15 IU/ml should be used for decision-making to determine treatment duration and RGT (34,35). Careful virological monitoring and prompt assessment of HCV RNA results are necessary to determine when treatment is futile and should be halted to avoid the emergence of resistance.

THERAPY AGAINST HEPATITIS C IN PATIENTS WITH GENOTYPE 1 INFECTION

IFN-based regimens will remain the "backbone" of HCV antiviral therapy for at least the next half decade. Either of the two pegylated IFNs, PegIFN alfa-2a (40 kD) or PegIFN alfa-2b (12 kD), administered subcutaneously once weekly in combination with oral RBV were the standard of care for treatment of HCV genotype 1 infection from 2001 to 2011, yielding overall SVR rates of 42–46% among treatment-naïve patients (43,44). SVR rates were lower in specific patient populations, such as African Americans and cirrhotics (45). Adverse events from either PegIFN alfa-2a or alfa-2b, and RBV are similar. The optimal RBV dose appears to be between 800 and 1,400 mg per day, based on weight in combination with either PegIFN product (**Table 3**) (46). The standard treatment duration of PegIFN and RBV has been 48 weeks, except in patients who are slow responders (detectable HCV RNA at 12 weeks but undetectable HCV RNA by 24 weeks into treatment), in whom extending therapy to 72 weeks may be beneficial (47,48).

Two HCV protease inhibitors, TVR and BOC, were approved by the FDA in May 2011, for use in combination with PegIFN and RBV in treatment-naïve and -experienced HCV genotype 1-infected patients with compensated liver disease. These oral agents selectively inhibit the HCV nonstructural 3/4A serine protease. Higher SVR rates are achieved in HCV genotype 1-infected patients, following the addition of TVR or BOC to PegIFN and RBV compared with PegIFN and RBV alone. The addition of an HCV PI to PegIFN and RBV represents a significant advance in the treatment of patients with HCV genotype 1.

REVIEW

Therapy for previously untreated patients with genotype 1 infection: PegIFN alfa, RBV, and TVR or BOC

Phase 3 trials have shown significantly higher SVR rates in previously untreated HCV genotype 1-infected patients following the addition of TVR or BOC to PegIFN and RBV compared with PegIFN and RBV alone; SVR 63–75% compared with 38–44%, respectively (**Table 4**). SVR was achieved in 87–97% of those who met RGT criteria for a shortened treatment duration (24–28 weeks). Approximately 44–65% of patients qualified for a shortened treatment duration if HCV RNA levels were undetectable (<10–15 IU/ml) at treatment weeks 4 and 12 with TVR-based regimens, or during treatment weeks 8–24 with BOC-based regimens. In traditionally difficult-to-treat populations, SVR was achieved in 42–62% of African Americans and 52–62% of cirrhotics with BOC- or TVR-based regimens, compared with 23–38% SVR in those receiving PegIFN and RBV alone (11,12).

The following pivotal and supplemental Phase 3 studies evaluated the safety and efficacy of BOC and TVR in combination with PegIFN and RBV (**Table 4**):

SPRINT-2 was designed to compare the efficacy of BOC/PegIFN/RBV after a 4-week PegIFN/RBV lead-in to PegIFN/RBV alone. Triple therapy for 44 weeks also was compared with a response-guided approach. PegIFN alfa-2b (1.5 mcg/kg per week) and RBV (600–1,400 mg orally daily), followed by the addition of BOC (800 mg orally every 8 h) or placebo, was studied in 1,099 treatment-naïve HCV genotype 1-infected patients, including 158 African American patients (11). The three treatment arms for randomization were: (i) PegIFN and RBV plus placebo for 48 weeks; (ii) 4 weeks of PegIFN and RBV, followed by the addition of BOC for 28 weeks of therapy in total, if HCV RNA was undetectable from treatment weeks 8 through 24; if virus was detectable at any of these timepoints, PegIFN and RBV were continued until week 48; (iii) a 4-week PegIFN and RBV lead-in, followed by the addition of BOC for 44 weeks. SVR was achieved in 38%, 63%, and 66%, respectively (11), demonstrating clear superiority in SVR with the BOC-containing regimens. Patients with bridging fibrosis or cirrhosis who received BOC/PegIFN/RBV for 44 weeks achieved higher SVR rates than those treated with triple therapy for only 24 weeks (42 vs. 34%, respectively). Higher SVR rates were also achieved in African American patients in BOC-containing arms (42–53%) compared with control (23%). In late responders who were IFN responsive (≥1.0 $\log_{10}$ decline in HCV RNA) following the 4-week lead-in with PegIFN and RBV, but had detectable HCV RNA at week 8, treatment with BOC/PegIFN/RBV for 44 weeks

Table 3. Antiviral treatment for chronic hepatitis C in adults (32–35,57,58)

Generic (Trade name)	Recommended dose	Recommended dose in renal or hepatic dysfunction
PegIFN alfa-2a (Pegasys®)	180 mcg SC once weekly	Clcr <30 ml/min: 135 mcg SC once weekly Hemodialysis: 135 mcg SC once weekly
PegIFN alfa-2b (PEG-Intron®)	1.5 mc/kg SC once weekly	Clcr 30–50 ml/min: reduce dose by 25% Clcr 10–29 ml/min: reduce dose by 50%
RBV (Copegus®, Rebetol®, Ribasphere®, RibaPak®)	*Genotype 1:* 1,000 mg (if ≤75 kg) or 1,200 mg (if >75 kg) PO daily in two divided doses, Or <65 kg: 800 mg PO daily in two divided doses 65–85 kg: 1,000 mg PO daily in two divided doses >85–105 kg: 1,200 mg PO daily in two divided doses >105 kg: 1,400 mg PO daily in two divided doses *Genotype 2 or 3:* 800 PO daily in two divided doses	Clcr 30–50 ml/min: 200 mg PO daily, alternating with 400 mg PO daily Clcr <30 ml/min: 200 mg PO daily
	PIs for treatment of HCV genotype 1	
BOC (Victrelis™)	800 mg (4×200 mg capsules) PO every 7–9 apart with food in combination with PegIFN–RBV following a 4-week lead-in with PegIFN–RBV	Dose adjustments not necessary for renal or hepatic impairment (Child-Pugh <7)
TVR (Incivek™)	750 mg (2×375 mg tablets) PO every 7–9 h with food (20 grams fat) for 12 weeks, plus PegIFN–RBV for 24 or 48 weeks	Dose adjustments not necessary for renal or hepatic impairment (Child-Pugh <7)

BOC, boceprevir; Clcr, creatinine clearance; HCV, hepatitis C virus; PegIFN, peginterferon; PI, protease inhibitor; PO, orally; RBV, ribavirin; SC, subcutaneous; TVR, telaprevir.

resulted in higher SVR than did treatment for only 24 weeks. In these patients, discontinuation of BOC at week 36, with continuation of PegIFN and RBV for another 12 weeks, was supported by modeling to limit adverse effects, and was recommended by the FDA, but this was not prospectively studied in SPRINT-2 (34).

ADVANCE compared 8 and 12 weeks of TVR/PegIFN/RBV, with subsequent PegIFN/RBV duration of 12 to 40 weeks determined by a response-guided approach to PegIFN/RBV alone for 48 weeks. TVR (750 mg orally every 8 h) or placebo was combined with PegIFN alfa 2a (180 mcg once weekly) and RBV (1,000 or 1,200 mg orally daily) in 1,088 treatment-naïve HCV genotype 1-infected patients (12). The three arms for randomization were: (i) TVR for 8 weeks plus PegIFN and RBV for 24 weeks if HCV RNA was undetectable at weeks 4 and 12 (eRVR), 48 weeks if not; (ii) TVR for 12 weeks plus PegIFN and RBV for 24 weeks if eRVR was achieved, 48 weeks if not; (iii) PegIFN and RBV plus placebo for 48 weeks. SVR was achieved in 69%, 75%, and 44%, respectively, demonstrating the clear superiority of TVR-containing regimens. SVR was significantly higher in the 12-week TVR-containing arm among cirrhotics (62%) and African American patients (62%) compared with PegIFN and RBV alone (25–33%), and lower relapse and resistance rates were seen compared with the 8-week TVR-treated arm. SVR was not significantly reduced in the 8-week TVR-containing arm compared with the 12-week arm (69 and 75%, respectively) as such, TVR may be discontinued early if it is not well tolerated without compromising SVR.

The purpose of ILLUMINATE was to define the utility of RGT in patients who achieve eRVR (49). All patients received 12 weeks of TVR/PegIFN alfa-2a/RBV (dosed as in ADVANCE), followed by 8 weeks of PegIFN and RBV. Those with eRVR were randomized at week 20 to either 4 or 28 additional weeks of PegIFN and RBV. The study included 540 treatment-naïve genotype 1-infected patients. Patient characteristics when compared with ADVANCE were as follows: more North Americans (94 vs. 60%), slightly older (51 vs. 49 years), a higher proportion of African Americans (14 vs. 9%) and cirrhotics (11 vs. 6%). Despite these differences, results were similar to ADVANCE and confirmed the efficacy of shortened treatment duration if eRVR is achieved, with 92% SVR in patients with eRVR treated for 24 weeks, and 88% in those treated for 48 weeks. SVR occurred in 72% overall, and rates were relatively high in cirrhotics (63%) and African Americans (60%).

In the Phase 3 studies, only small proportions of patients were African American (9–15%), Hispanic or Latino (10–11% in TVR trials), Asian/other (4% in BOC trials), or had bridging fibrosis or cirrhosis (6–16%). Additional prospective studies with DAA/PegIFN/RBV are needed to evaluate their efficacy and tolerability in these subgroups of patients.

Recommendations for therapy among treatment-naïve patients with genotype 1 infection:

6. PegIFN alfa and RBV, in combination with BOC (800 mg orally every 7–9 h with food) or TVR (750 mg orally every 7–9 h with 20 g of fat) is the standard of care for most treatment-naïve genotype 1-infected patients (Class I, Level A).

7. If a TVR-containing regimen is used in treatment-naïve non-cirrhotic patients who achieve eRVR, TVR should be discontinued at week 12 and PegIFN–RBV should be continued for an

Table 4. SVR rates in genotype 1-infected patients treated with PegIFN/RBV ± BOC or TVR

Study cohort, *N*	SVR to PI/PegIFN/RBV (arm 1 of trial)	SVR to PI/PegIFN/RBV (arm 2 of trial)	SVR with PegIFN/RBV
Treatment-naïve			
BOC (SPRINT-2), SVR %	63	66	38
N=1,099 (11)	BOC/PegIFN/RBV RGT	BOC/PegIFN/RBV 44 weeks	PegIFN/RBV 48 weeks
TVR (ADVANCE), SVR %	69	75	44
N=1,088 (12)	TVR for 8 weeks/PegIFN/RBV RGT	TVR for 12 weeks/PegIFN/RBV RGT	PegIFN/RBV 48 weeks
TVR (ILLUMINATE), SVR %	71	73	NA
N=540 (49)	TVR for 12 weeks/PegIFN/RBV (24 total weeks) if eRVR	TVR for 12 weeks/PegIFN/RBV (48 total weeks) if eRVR	—
Treatment-experienced			
TVR (REALIZE), SVR % overall	—	—	
N=662 (13)	NA	64–66	17
TVR for 12 weeks/PegIFN/RBV (48 weeks total)			
Prior relapsers (SVR %)	—	83–88	24
Prior partial responders (SVR %)	—	54–59	15
Prior null responders (SVR %)	—	29–33	5
BOC (RESPOND-2), SVR % overall			
N=403 (14)	59	66	21
BOC/PegIFN/RBV (48 weeks total)			
Prior relapsers (SVR %)	69	75	29
Prior partial responders (SVR %)	40	52	7

BOC, boceprevir; eRVR, extended rapid virologic response; HCV, hepatitis C virus; PegIFN, peginterferon alfa; PI, protease inhibitor; RBV, ribavirin; RGT, response-guided therapy; SVR, sustained virologic response; TVR, telaprevir.

additional 12 weeks. If HCV RNA is detectable, but <1,000 IU/ml at treatment week 4, and remains <1,000 IU/ml or becomes undetectable by week 12, TVR should be discontinued at week 12, and PegIFN and RBV can be continued for another 36 weeks (refer to **Figure 2***; Class I, Level A).*

8. If a TVR-containing regimen is used in treatment-naïve cirrhotics who achieve an HCV RNA that is undetectable or <1,000 IU/ml at treatment weeks 4 and 12, TVR should be discontinued at week 12, and PegIFN–RBV can be continued for another 36 weeks (refer to **Figure 2***; Class I, Level A).*

9. If a BOC-containing regimen is used in treatment-naïve non-cirrhotics, if HCV RNA declines by ≥1 log_{10} during the 4-week lead-in, and HCV RNA is undetectable at weeks 8–24, treatment with BOC–PegIFN–RBV for 24 weeks is sufficient. If HCV RNA is detectable at week 8, but <100 IU/ml at week 12, and negative at week 24, BOC–PegIFN–RBV should be continued until week 36, followed by PegIFN–RBV alone for 12 more weeks. If HCV RNA declines by <1 log_{10} during the lead-in, BOC–PegIFN–RBV can be continued for 44 weeks (refer to **Figure 3***; Class I, Level A).*

10. If a BOC-containing regimen is used in treatment-naïve cirrhotics, 44 weeks of BOC–PegIFN–RBV is required after the 4-week lead-in (refer to **Figure 3***; Class I, Level A).*

Therapy for patients with HCV genotpye 1, who have failed to respond, or who have relapsed to IFN-based therapy with or without ribavirin

Nonresponders or relapsers to IFN-based therapy are a growing population, many of whom are infected with genotype 1 and have advanced liver disease. Before the availability of HCV PIs, there were limited retreatment options for these patients. Retreatment strategies included PegIFN/RBV at higher doses and for longer durations, or the combination of daily consensus IFN and RBV. However, only 7–16% of nonresponders to PegIFN/RBV achieved SVR using these retreatment approaches in randomized, controlled trials (50,51). PegIFN/RBV relapsers had improved response rates compared with nonresponders, with SVR occuring in approximately 50% of patients using these re-treatment strategies (50–52).

Retreatment with PegIFN and RBV, plus BOC or TVR in patients with HCV genotype 1 has produced higher SVR rates than with PegIFN and RBV alone. As is the case with other retreatment regimens, BOC- or TVR–PegIFN/RBV therapy is more effective in relapsers than in nonresponders. With these triple therapies, SVR was achieved in 69–88% of relapsers and 29–33% of null responders, whereas SVR rates to PegIFN and RBV alone were 24–29 and 5%, respectively (13,14,34,35). The benefit of retreatment

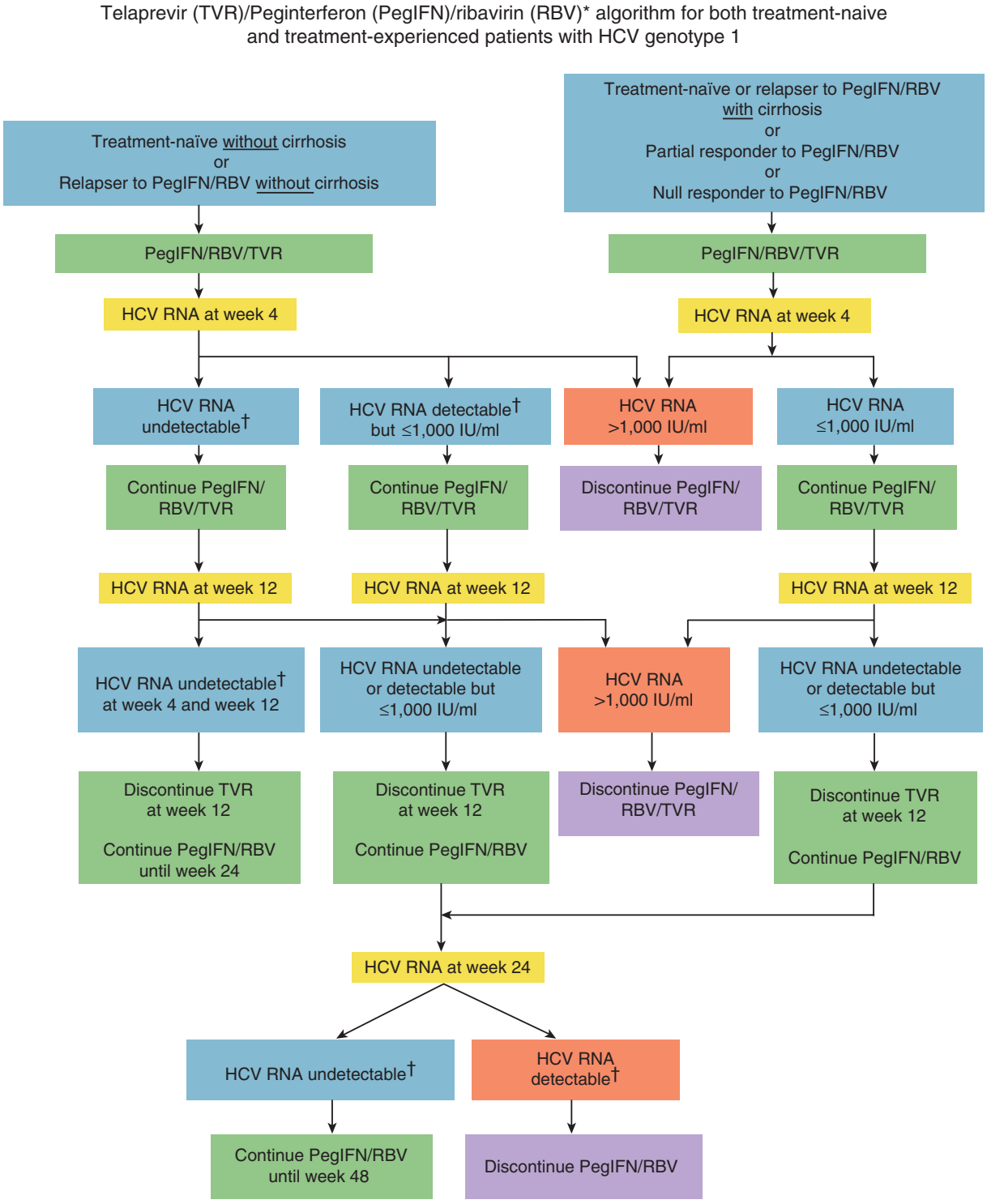

Figure 2. *PegIFN alfa-2a 180 mcg per week or PegIFN alfa-2b 1.5 mcg/kg per week. RBV (in two divided doses) with food: <75 kg: 1,000 mg per day or ≥75 kg: 1,200 mg per day; alternative weight-based RBV dosing: <65 kg: 800 mg per day, 65–85 kg: 1,000 mg per day, >85–105 kg: 1,200 mg per day, >105 kg: 1,400 mg per day. TVR 750 mg (two 375 mg tablets) orally every 8 h with food (20 g fat). †A sensitive real-time quantitative HCV RNA assay with a lower limit of detection of <10–15 IU/ml should be used for decision-making to determine treatment duration with response-guided therapy (RGT).

of prior null responders with a BOC- or TVR-containing regimen should be carefully considered. In REALIZE (discussed below), only approximately 30% of null responders achieved SVR, and viral resistance mutations developed in the majority of those who remained viremic (13). Null responders were not included in the Phase 3 BOC trial RESPOND-2, and response rates for these

Boceprevir (BOC)/Peginterferon (PegIFN)/ribavirin (RBV)* algorithm for both treatment-naive and treatment-experienced patients with HCV genotype 1

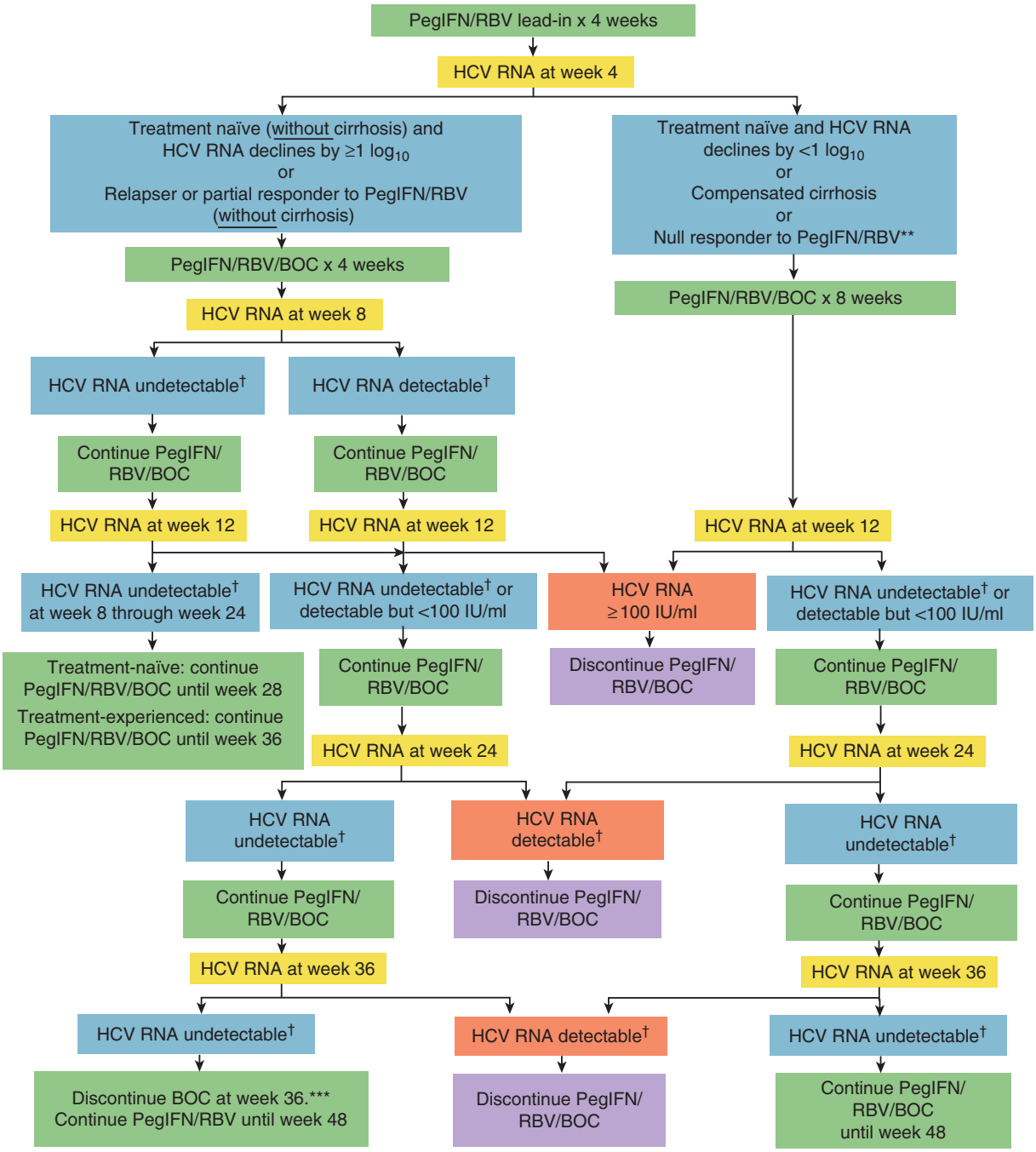

Figure 3. *PegIFN alfa-2a 180 mcg per week or alfa-2b 1.5 mcg/kg per week. RBV (in two divided doses) with food: <75 kg: 1,000 mg per day or ≥75 kg: 1,200 mg per day; alternative weight-based RBV dosing: <65 kg: 800 mg per day, 65–85 kg: 1,000 mg per day, >85–105 kg: 1,200 mg per day, >105 kg: 1,400 mg per day. BOC 800 mg (four 200 mg capsules) orally every 8 h with food. †A sensitive real-time quantitative HCV RNA assay with a lower limit of detection of <10–15 IU/ml should be used for decision-making to determine treatment duration with response-guided therapy (RGT). **BOC was not studied in null responders; this population was excluded from the Phase 3 study of patients who had previously failed treatment. Efficacy data and FDA labeling for this population is based solely on mathematical modeling. ***Discontinuation of BOC at week 36 is supported by modeling, but was not directly studied in the clinical trials. Following a 4-week lead-in with PegIFN–RBV, the addition of BOC to Peg–RBV for 44 weeks achieved higher sustained virologic response (SVR) compared with 24 weeks in late responders (detectable HCV RNA at week 8) in the registration trials.

patients were based on extrapolation. In RESPOND-2, HCV RNA decline after 4-week lead-in was a stronger predictor of SVR than was the historical treatment response.

The following pivotal Phase 3 and supplemental studies evaluated the safety and efficacy of retreatment of genotype 1 patients with BOC or TVR, in combination with PegIFN/RBV (**Table 4**):

REALIZE evaluated TVR (750 mg orally every 8 h) or placebo, in combination with PegIFN alfa-2a and RBV, in 663 patients who had previously failed PegIFN and RBV, including relapsers (53%), partial responders (19%), and null responders (27%) (13). For all patients, the total treatment duration was 12 weeks with TVR or placebo, in combination with PegIFN and RBV for 48 weeks. One of the two TVR arms used a 4-week lead-in with PegIFN and RBV before the addition of TVR, and achieved a similar SVR rate as in the arm without the lead-in (SVR 66 and 64%, respectively). Both TVR-containing arms achieved higher SVR than PegIFN and RBV alone (17%, $P<0.001$). In TVR-containing arms, SVR was achieved in a greater proportion of PegIFN and RBV relapsers (83–88%) as compared with prior partial responders (54–59%) or prior null responders (29–33%), compared with control (24%, 15%, and 5%, respectively). Prior null responders with cirrhosis had similar SVR rates with a TVR-based regimen compared with PegIFN and RBV alone (14 and 10%, respectively). In contrast, SVR rates were higher in null responders with minimal or bridging fibrosis with a TVR-based regimen compared with PegIFN and RBV alone (39–41 and 0–6%, respectively).

In a subanalysis of null responders, IFN responsiveness during the 4-week lead-in before the addition of TVR was a predictor of SVR. In patients who had <0.5 $\log_{10}$ decline and those with 0.5–1 $\log_{10}$ decline in baseline HCV RNA during the PegIFN and RBV lead-in, SVR occurred in only 6 and 20%, respectively. In those with >1 $\log_{10}$ decline during the PegIFN/RBV lead-in, SVR was achieved in 44–80% (53). The fact that the arm with a 4-week PegIFN and RBV lead-in before the addition of TVR allows IFN responsiveness to be determined raises the issue of whether this approach could be used with TVR in general.

RESPOND-2 evaluated BOC (800 mg orally every 8 h) or placebo, and PegIFN alfa-2b and RBV in 403 patients who had previously failed PegIFN and RBV, specifically prior partial responders and relapsers (14). Previous null responders were not included in the trial. Patients were randomized 1:2:2 to treatment in 3 arms: (i) PegIFN and RBV plus placebo for 48 weeks; (ii) a 4-week PegIFN and RBV lead-in, followed by the addition of BOC, with 32 weeks of triple therapy if HCV RNA was undetectable at treatment weeks 8 and 12; if virus was detectable at week 8, but undetectable at week 12, triple therapy was continued to week 32, at which time BOC was discontinued, and PegIFN and RBV were continued until week 48 (RGT arm); (iii) a 4-week PegIFN and RBV lead-in, followed by 44 weeks of BOC/PegIFN/RBV. SVR rates were significantly higher in the BOC-containing arms than in the arm receiving PegIFN and RBV (SVR 59% RGT, 66% BOC/PegIFN/RBV for 44 weeks, 21% control). PegIFN and RBV relapsers achieved higher SVR rates than prior partial responders in the BOC-treated arms (SVR 69–75 and 40–52%, respectively) and in the control arms (SVR 29% and 7%, respectively). The relapse rate was 12% in the BOC-containing arms vs. 32% for control. SVR was lower among patients with <1.0 $\log_{10}$ decline in HCV RNA than in those with >1.0 $\log_{10}$ decline in HCV RNA at treatment week 4 after a lead-in with PegIFN/RBV (SVR 33–34% BOC/PegIFN/RBV and 0% control vs. SVR 73–79% BOC/PegIFN/RBV and 25% control, respectively).

In an interim analysis of a single arm, multicenter rollover study (PROVIDE) of 48 patients who were null responders (<2 log decline in HCV RNA after 12 weeks of PegIFN and RBV without a HCV protease inhibitor) from SPRINT-2 and RESPOND-2, re-treatment using a 4-week lead-in with PegIFN–RBV followed by the addition of BOC for 44 weeks achieved SVR in 38% (54).

Recommendations for retreatment of nonresponders and relapsers with genotype 1 infection:

11. For patients who previously failed PegIFN–RBV, retreatment with BOC or TVR, and PegIFN–RBV may be considered, particularly in patients who were relapsers (Class I, Level A).

12. If a BOC-containing regimen is used for re-treatment of noncirrhotic prior partial responders or relapsers, the recommended treatment duration is 36 weeks if HCV RNA is undetectable from weeks 8 to 24. If HCV RNA is detectable at week 12, but <100 IU/ml, and is undetectable from weeks 24 to 36, BOC can be discontinued at week 36 and PegIFN–RBV can be continued for an additional 12 weeks (refer to **Figure 3***; Class I, Level B).*

13. If a BOC-containing regimen is used for re-treatment in cirrhotics, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/ml, and becomes undetectable from weeks 24 to 36 (refer to **Figure 3***; Class I, Level B).*

14. If a BOC-containing regimen is used for re-treatment of prior null responders, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/ml, and becomes undetectable from weeks 24 to 36 (refer to **Figure 3***; Class II, Level C).*

15. If a TVR-containing regimen is used for re-treatment of prior relapsers and HCV RNA is undetectable from weeks 4 and 12, TVR should be discontinued at week 12 and PegIFN–RBV should be continued for an additional 12 weeks. If HCV RNA is detectable, but <1,000 IU/ml at week 4 and/or 12, TVR can be discontinued at week 12 and PegIFN–RBV can be continued for an additional 36 weeks (refer to **Figure 2***; Class I, Level B).*

16. If a TVR-containing regimen is used for re-treatment of prior partial responders or null responders, and HCV RNA is <1,000 IU/ml at weeks 4 and 12, TVR should be discontinued at week 12 and PegIFN alfa plus RBV should be continued for an additional 36 weeks (refer to **Figure 2***; Class I, Level B).*

Issues related to triple therapy with BOC- or TVR-containing regimens

Regimen differences. Both PegIFN alfa-2a and alfa-2b have been FDA-approved for use with BOC or TVR (14,34,35,55,56). A 4-week lead-in period with PegIFN and RBV is required before the addition of BOC (**Figure 3**). Once BOC is combined with PegIFN–RBV, BOC remains part of triple therapy for the majority of the treatment duration based on RGT (**Figure 3**). TVR is administered with PegIFN and RBV for the first 12 weeks, followed by PegIFN and RBV alone, for a duration based on RGT (**Figure 2**).

Additional studies are needed to confirm whether TVR given at 1,225 mg twice daily is as effective as 750 mg every 7–9 h (55).

Drug–drug interactions. BOC and TVR are strong CYP3A4 inhibitors and CYP3A substrates. Clinicians should be careful to avoid DDIs, and should make therapeutic substitutions before starting BOC- or TVR-containing regimens (e.g., replace simvastatin with pravastatin; refer to table on "Drug–Drug Interactions" in **Supplementary Materials**) (34,35). One important DDI with HCV PIs is with oral contraceptives, which may be rendered ineffective. Two non-hormonal methods of contraception (eg., spermicide, barrier methods, intra-uterine device) should be used in women during treatment with an HCV PI and RBV, and for at least 6 months after treatment has concluded (34,35).

Dose modifications. BOC or TVR should not be dose-reduced or restarted if discontinued. On the basis of the pharmacokinetic and resistance potential of these medications, they should be either continued at full doses in combination with PegIFN and RBV, or permanently discontinued (±PegIFN and RBV) based on treatment response and tolerability. If RBV is stopped for 7 days or more in patients who are concomitantly receiving BOC or TVR, then BOC or TVR also should be permanently discontinued to avoid the potential development of HCV-resistant variants.

Pharmacological considerations. Patients should be instructed not to take a missed dose if it is within 2 h or less of the next scheduled BOC dose, or within 4 h or less of the next scheduled TVR dose (34,35). TVR and BOC should be administered with food, three times daily, 7–9 h apart. TVR must be taken with food that contains approximately 20 g of fat (e.g., bagel with cream cheese, ½ cup nuts, 3 tablespoons peanut butter, 1 cup ice-cream, 2 oz American or cheddar cheese, 2 oz potato chips, or 1½ cup trail mix). PegIFN should be refrigerated (36–46 °F) during storage (57,58). BOC should be refrigerated (36–46 °F) during storage, or stored at room temperature up to 77 °F for up to 3 months (34). TVR can be stored at room temperature between 59–86 °F (35).

Table 5. General guidelines for PegIFN–RBV dose reduction or discontinuation (32,33,57,58)

	PegIFN dose recommendation[a]
WBC	
$<1.5\times10^9$/l	PegIFN alfa-2b: reduce dose to 1 mcg/kg per week, then to 0.5 mcg/kg per week if needed
$<1.0\times10^9$/l	Discontinue PegIFN alfa-2b until resolution
ANC[b]	
$<0.75\times10^9$/l	PegIFN alfa-2a: reduce dose to 135 mcg per week PegIFN alfa-2b: reduce dose to 1 mcg/kg per week, then to 0.5 mcg/kg per week if needed
$<0.50\times10^9$/l	Discontinue PegIFN until resolution
Platelets[c]	
<50 k/mm^3	PegIFN alfa-2a: reduce dose to 90 mcg per week PegIFN alfa-2b: reduce dose to 1 mcg/kg per week, then to 0.5 mcg/kg per week if needed
<25 k/mm^3	Discontinue PegIFN until resolution
	RBV dose recommendation
Hb	
<11.0, but >10 g/dl	No change in RBV dose if patient has minimal symptoms In a symptomatic patient, consider RBV dose reduction
<10.0, but >8.5 g/dl	Decrease RBV, consider starting an erythropoietic growth factor In patients with a cardiac history, reduce RBV dose and reduce PegIFN alfa-2b dose by 50%
<8.5 g/dl	Discontinue RBV until resolution If RBV is stopped for ≥7 days or discontinued in patients who are concomitantly receiving BOC or TVR, then BOC or TVR must be permanently discontinued

ANC, absolute neutrophil count; BOC, boceprevir; GCSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HCV, hepatitis C virus; PegIFN, peginterferon; RBV, ribavirin; TVR, telaprevir; WBC, white blood cell counts.

[a]Manufacturer package insert recommendations.

[b]If dose is maintained outside of manufacturer recommendations, monitor ANC more frequently, and counsel patient on neutropenic precautions. In post-liver transplantation or HIV/HCV-coinfected patients who remain neutropenic despite dose reduction, consider starting GCSF until resolution.

[c]If dose is maintained outside of manufacturer recommendations, monitor platelet counts, and signs or symptoms of unusual bleeding or bruising more frequently.

Adverse effects

Almost all patients receiving hepatitis C antiviral therapy will experience some treatment-related adverse effects. Close monitoring is crucial throughout treatment. Poor tolerability can lead to early treatment discontinuation. Clinicians can promote adherence by counseling patients on the recognition and management of treatment-related adverse effects. Patients should be reassured that most treatment-related adverse effects can be minimized or managed.

The addition of DAA agents to PegIFN and RBV is associated with an increased incidence of adverse events, requiring discontinuation of the DAA agent in 10–21% of patients (11–14,59,60). Adverse events with increased frequency among subjects receiving a DAA agent include anemia, neutropenia (BOC), dysgeusia (altered taste), gastrointestinal upset, fatigue, rash (TVR), and perianal discomfort (TVR) (11–14). On the basis of the TVR adverse effect profile, BOC in combination with PegIFN–RBV may be more appropriate in patients with skin disorders (e.g., psoriasis) or gout.

Anemia. In clinical trials, significant anemia (hemoglobin <10 g/dl) occurred nearly twice as frequently in BOC- or TVR-treated patients than in patients receiving PegIFN and RBV alone. This led to an additional decrease in hemoglobin levels of approximately 1–1.5 g/dl, which resulted in greater RBV dose interruptions and use of growth factors. In the Phase 3 TVR trials, initial dose reduction of RBV to 600 mg daily was mandated, and use of erythropoietin generally was prohibited. In contrast, RBV dose reductions occurred in 200 mg decrements, and erythropoietin use was allowed in the Phase 3 BOC trials. On the basis of retrospective subanalyses, RBV dose reduction alone did not appear to compromise SVR rates (61–63). Initial management of HCV treatment-related anemia should consist of RBV dose reduction

Table 6. HCV PI (BOC or TVR): RGT criteria and futility rules (34,35)

	BOC–PegIFN/RBV	TVR–PegIFN/RBV
Candidates for RGT	Noncirrhotics: Treatment-naïve: 28 weeks Prior relapser/partial responder: 36 weeks	Noncirrhotics: Treatment-naïve: 24 weeks Prior relapser: 24 weeks
Criteria for RGT	HCV RNA undetectable (<10–15 IU/ml) weeks 8–24	HCV RNA undetectable (<10–15 IU/ml) weeks 4 and 12
Futility rules (stop all treatment if any of the following occur)	Week 12: HCV RNA ≥100 IU/ml Or Week 24: HCV RNA detectable Or HCV RNA rebounds at any timepoint (≥1 $\log_{10}$ increase from the nadir HCV RNA)	Week 4 or 12: HCV RNA >1,000 IU/ml Or Week 24: HCV RNA detectable Or HCV RNA rebounds at any timepoint (≥1 $\log_{10}$ increase from the nadir HCV RNA)

HCV, hepatitis C virus; PegIFN, peginterferon; PI, protease inhibitor; RBV, ribavirin; RGT, response-guided therapy; TVR, telaprevir.

in a symptomatic patient with a hemoglobin level of <10 g/dl (**Table 5**). If an erythropoiesis stimulating agent is used, the dose should be reduced or held if the baseline hemoglobin increases by >1 g/dl in any 2-week period, and if hemoglobin levels exceed 11 g/dl (32,33,64,65) based on the manufacturers' warning of risks for cardiovascular and thrombotic events.

Neutropenia. Initial management of HCV treatment-related neutropenia should consist of PegIFN dose reduction according to the manufacturer recommendations (**Table 5**) (57,58). Although the incidence of neutropenia (absolute neutrophil count (ANC) <750 per mm^3) was similar in patients treated with TVR/PegIFN/RBV and those treated with PegIFN and RBV alone (12 and 15%, respectively) (35), BOC/PegIFN/RBV was associated with an increased incidence of neutropenia. BOC-treated patients (23%) experienced grade 3 (ANC 500 to <750 per mm^3) neutropenia and 7% experienced grade 4 (ANC <500 per mm^3) compared with 13 and 4%, respectively, in those receiving PegIFN–RBV alone. BOC-treated patients required more dose reductions of PegIFN and use of a granulocyte colony-stimulating factor (34).

Rash and skin reactions. Mild-to-moderate rash occurred in more than half of patients receiving TVR, with grade 3 (severe) rash occurring in up to 7% of patients and requiring discontinuation in approximately 6% (12,13,35,59). Rash often developed within 1 month of TVR initiation, and required 4–6 weeks after TVR discontinuation to resolve. Rashes were primarily eczematous, maculopapular, or papular-lichenoid and pruritic.

Mild-to-moderate rash can be treated with oral antihistamines and/or topical corticosteroids; systemic steroids are contraindicated in combination with TVR. If rash becomes severe (>50% of body surface area), TVR should be discontinued. All HCV therapy should be discontinued immediately for any rash associated with significant systemic symptoms, including evidence of internal organ involvement (e.g., hepatitis, nephritis), facial edema, mucous membrane erosions or ulceration (e.g., conjunctivae, lips), target lesions, epidermal detachment, vesicles, or bullae. The patient should be promptly referred for urgent medical care and dermatological consultation (35). Drug Rash with Eosinophilia and Systemic Symptoms and Stevens Johnson Syndrome occurred in <1% of TVR-treated patients (35).

Anorectal signs and symptoms. Anorectal symptoms, variously described as hemorrhoids, anorectal discomfort, anal pruritus, and rectal burning, were reported by approximately 25% of patients receiving TVR (12,35). The symptoms generally were were mild to moderate in severity and rarely required treatment discontinuation. Symptomatic treatment with topical steroids or local anesthetic can be considered.

Elevated uric acid levels. Elevated uric acid levels occurred in up to 73% of patients receiving TVR, with onset during the first 2 weeks of therapy (12,13,35). In patients receiving TVR, uric acid levels should be measured at baseline, at weeks 2, 4, 8, 12, and as clinically indicated (35). Treatment with allopurinol can be considered if uric acid level is >10 mg/dl.

Elevated bilirubin levels. Elevated bilirubin levels occurred more frequently in TVR-treated patients than in those treated with PegIFN–RBV alone (41 and 28%, respectively), but were not accompanied by liver dysfunction (35). The steepest increase in bilirubin occurred during the first 1–2 weeks of TVR therapy. In patients receiving TVR, bilirubin levels should be measured at baseline, at weeks 2, 4, 8, 12, and as clinically indicated (35).

Recommendations for dose modification:

17. PegIFN alfa and RBV doses should be reduced in response to decreases in white blood cells, neutrophils, hemoglobin, or platelets, as outlined in **Table 5** *(Class I, Level A).*

18. If RBV is stopped for 7 days or more in patients who are concomitantly receiving BOC or TVR, then the PI also should be permanently discontinued (Class I, Level A).

19. HCV PIs should be either continued at full dose or discontinued (Class I, Level A).

20. Initial management of HCV treatment-related anemia should consist of RBV dose reduction in a symptomatic patient with a hemoglobin <10g/dl, or as clinically indicated. Erythropoietin may be administered in patients with symptomatic anemia related to PegIFN–RBV therapy with or without BOC/TVR

to limit anemia-related RBV dose reductions or dose discontinuations (Class II, Level C).
21. Initial management of HCV treatment-related neutropenia should consist of PegIFN dose reduction for an ANC < 750, or as clinically indicated. Granulocyte colony-stimulating factor should not be given as primary therapy to prevent PegIFN alfa dose reductions (Class I, Level C).

Monitoring therapy

Patients with a history of depression should be followed closely for recurrence of depression while receiving PegIFN therapy. Patients should also receive a clinical evaluation by a mental health professional if depression scores increase during treatment. Standardized depression screening instruments can be used to supplement the clinical exam.

Periodic laboratory monitoring of hemoglobin, hematocrit, white blood cell count with differential, platelet count, and serum alanine transaminase is necessary in all patients receiving hepatitis C antiviral therapy (refer to "Monitoring Table" in **Supplementary Materials**). Increasing the frequency of these tests is advised in patients with significant reductions in hemoglobin, white blood cell count, or platelet count, or in those who experience significant clinical adverse events.

Quantitative and/or qualitative HCV RNA assays should be performed at weeks 4, 8 (with BOC-containing regimens), 12, and 24 of treatment, at the end-of-treatment, and 24 weeks after completion of therapy. Patients receiving BOC- or TVR-containing regimens may need additional HCV RNA determinations as clinically indicated.

HCV resistance. Hepatitis C resistance is a new clinical entity with the introduction of PIs and other DAA agents. HCV resistance is defined as the selection of viral variants that have altered binding to the drug target and are less susceptible to the drug's inhibitory activity (66). HCV resistant viruses carrying amino acid changes in the nonstructural 3/4A position have been described *in vitro* and *in vivo* with BOC and TVR (67–69). Resistant viruses can develop with all genotype 1 subtypes, but are more likely to occur in patients with genotype 1a than in those with genotype 1b, when treated with BOC or TVR (70). More importantly, resistant viruses develop in most patients within 7 days of DAA use as monotherapy. Consequently, BOC and TVR should never be used without PegIFN–RBV.

Patients with poor IFN response (< 1.0 $\log_{10}$ decline in HCV RNA) to the PegIFN and RBV lead-in had lower SVR rates and higher resistance rates than IFN-sensitive patients. A good virologic response to the 4-week PegIFN and RBV lead-in, defined by a ≥ 1.0 $\log_{10}$ decline in HCV RNA, was a strong predictor of SVR. Patients without such a response had lower SVR and higher resistance rates (11,53). In patients with a < 1.0 $\log_{10}$ decline in HCV RNA during the lead-in and in prior null responders, consideration should be given as to whether the benefits of triple therapy outweigh the potential risk of developing resistance/cross-resistance to future therapies, along with determining whether the patient can wait for the availability of better treatment options.

Among patients who develop resistant viruses, the resistant variants are no longer detectable in the serum approximately 1–2 years after discontinuing BOC or TVR (66–68). However, due to limitations of current tests for resistance, it is unclear whether small numbers of resistant viruses continue to be present for prolonged periods of time. Because of the similar resistant mutations to BOC and TVR, patients who develop resistance when treated with one PI (e.g., BOC) should not be treated with the other PI (e.g., TVR), because of the high likelihood of having or developing cross resistance to the second PI.

There are no commercial assays to test for the presence of resistant viruses before or during treatment (66). The only way to suspect that a patient has developed a resistant virus is to monitor for HCV RNA rebound (> 1 $\log_{10}$ increase from the nadir HCV RNA) during treatment. Criteria for failure to respond adequately to BOC or TVR, necessitating stopping of the PI, as outlined in the package insert are given below (refer to section "Futility (stopping) rules") (34,35). Stopping rules because of failure to respond are the same for treatment-naïve and for treatment-experienced patients.

Futility (stopping) rules. Viral breakthrough with triple therapy was an infrequent event, particularly among patients who experienced eRVR with TVR-containing regimens or early response (HCV RNA < 10–15 IU/ml by treatment week 8) with BOC-containing regimens (11,12). In patients with inadequate viral suppression on therapy, stopping treatment is important to limit the development of resistance mutations.

All treatment should be stopped if any of the following occur: (i) HCV RNA level > 1,000 IU/ml at week 4 or 12 with a TVR-containing regimen, or HCV RNA level ≥ 100 IU/ml at week 12 with a BOC-containing regimen; or (ii) detectable HCV RNA levels at week 24 or at any timepoint thereafter; or (iii) HCV RNA rebounds at any timepoint (≥ 1 $\log_{10}$ increase from the nadir HCV RNA) (34,35). In addition, BOC or TVR must be discontinued permanently if RBV is stopped for longer than 7 days; PegIFN monotherapy may be continued if appropriate (refer to **Table 6**).

PegIFN and RBV (without BOC or TVR) can be continued in patients with presumed resistant viruses, although the probability of achieving an SVR is low. The stopping rules for treatment with PegIFN and RBV (< 2 $\log_{10}$ decline in HCV RNA at Week 12 and/or detectable HCV RNA at Week 24) should be applied to patients in whom the DAA is discontinued early because of resistance or intolerability.

Recommendations for treatment monitoring:
22. Patients should be monitored for treatment-related adverse effects at intervals of at least 2 weeks early in the course of therapy, and at intervals of 1–2 months during treatment as clinically indicated (Class I, Level C).
23. Patient adherence to therapy should be assessed at every visit (Class I, Level C).
24. Patients should be evaluated for depression, suicidal ideation, alcohol, and illicit drug use at each visit (Class I, Level C).
25. Patients should be counseled about avoiding pregnancy by using two forms of contraception during treatment and for 6 months

post-treatment, and pregnancy tests should be performed as indicated in (refer to "Monitoring Table" in **Supplementary Materials***). If a patient is receiving a BOC- or TVR-containing regimen, two alternative effective methods of contraception, such as intrauterine devices and barrier methods, should be used in at-risk patients and partners during and for at least 6 months after treatment (Class I, Level B).*

26. Serum markers of biochemical and virologic response should be measured, and treatment-related adverse effects monitored at intervals as outlined (refer to "Monitoring Table" in **Supplementary Materials***; Class I, Level C).*

27. In patients receiving TVR–PegIFN–RBV, all treatment should be stopped if any of the following occur: (i) HCV RNA level > 1,000 IU/ml at week 4 or 12; or (ii) detectable HCV RNA levels at week 24 or at any timepoint thereafter; or (iii) HCV RNA rebounds at any timepoint (≥1 log10 increase from the nadir HCV RNA) (Class I, Level C).

28. In patients receiving BOC–PegIFN–RBV, all treatment should be stopped if any of the following occur: (i) HCV RNA level ≥ 100 IU/ml at week 12 with a BOC-containing regimen; or (ii) detectable HCV RNA levels at week 24 or at any timepoint thereafter; or (iii) HCV RNA rebounds at any timepoint (≥ 1 $\log_{10}$ increase from the nadir HCV RNA; Class I, Level C).

29. If virologic failure occurs with a BOC- or TVR-containing regimen, the other PI must not be substituted (Class I, Level C).

GROUPS WITH SPECIAL CONSIDERATIONS FOR THERAPY

The following recommendations for each subgroup of patients have taken into account the natural history of disease, the likelihood of achieving an SVR, and the adverse effects and need for dose discontinuations with treatment. Current management of patients with genotype 2, 3 or 4 infection, end-stage renal disease and other populations are available online in **Supplementary Materials**. Refer to the **Appendix** for summary recommendations in these groups.

PegIFN–RBV therapy without a PI for HCV genotype 1-infected patients

There are some HCV genotype 1-infected patients who may be treated without an HCV PI in whom SVR rates to PegIFN–RBV alone are predicted to be very good (71). Patients who experience an RVR to the 4-week lead-in with PegIFN–RBV, those who have a low baseline HCV RNA (< 400,000 IU/ml), or those who have the IL-28B CC genotype have predicted sustained response rates to PegIFN–RBV of 60–90% (36,42,71). Treatment options for patients who were previously intolerant to therapy include PegIFN alone, or PegIFN with reduced doses of RBV (72,73). Treatment should be discontinued if there is < 2 $\log_{10}$ decline in HCV RNA at week 12 and/or if HCV RNA remains dectectable at week 24.

Recommendations for PegIFN alfa with or without RBV treatment in genotype 1 patients:

30. PegIFN alfa monotherapy may be used to treat patients with contraindications to RBV (Class I, Level A).

31. For patients who achieve RVR and have a low baseline viral load (HCV RNA < 400,000 IU/ml), 24-weeks of treatment with PegIFN–RBV may be sufficient (Class I, Level B).

Patients with minimal histological evidence of liver disease

Patients with grade 1 inflammation and minimal fibrosis are at lower risk for developing advanced liver disease in the near future, and observation without treatment may be an option. Liver biopsy may be repeated after 5 years if results would change management. Despite minimal fibrosis, HCV treatment should be provided if patients desire treatment or have extrahepatic manifestations (leukocytoclastic vasculitis, membranoproliferative glomerulonephritis, symptomatic cryoglobulinemia) (74).

Recommendations in patients with mild disease:

32. Treatment can be deferred in patients with minimal inflammation and/or minimal portal fibrosis on liver biopsy (Class I, Level B).

Patients with compensated cirrhosis

Patients with compensated HCV-related cirrhosis (Child-Pugh Class A) can be treated successfully with HCV antiviral agents, but experience higher rates of adverse events and lower SVR compared with patients with early-stage disease (11,12,43,44,75,76). The decision to treat should be individualized in these patients.

Among treatment-naïve genotype 1-infected patients with bridging fibrosis or cirrhosis treated in SPRINT-2 with BOC/PegIFN/RBV, higher SVR was achieved with 48 weeks of treatment as compared with 28 weeks of treatment (SVR 52 and 41%, respectively) or to control (SVR 38%) (11). Among treatment-naïve genotype 1-infected cirrhotics in ADVANCE treated with TVR (12 weeks)–PegIFN–RBV, SVR was achieved in 62% compared with 33% in the control arm (12). In treatment-experienced patients with advanced fibrosis (METAVIR stage 3 or 4), who were re-treated with a BOC-containing regimen in RESPOND-2, SVR occurred in 68%, although 64% of patients in the trial were prior relapsers, 36% were prior partial responders, and null responders were not included. In treatment-experienced patients with METAVIR stage 3 or 4 fibrosis, who were re-treated with a TVR-containing regimen in REALIZE, SVR rates were 84–85% in prior relapsers, 34–56% in partial responders, and 14–39% in null responders. Child-Pugh Class B or C patients (score ≥7) were excluded from the PI trials. (refer to **Supplementary Materials** for additional information on PegIFN and RBV treatment in this population).

Improvements in liver histology and clinical outcomes occur among patients with cirrhosis who achieve SVR (9,10,77–79). Despite achieving SVR, patients with cirrhosis remain at risk for developing HCC, and routine screening for HCC should continue.

Recommendations in patients with cirrhosis:

33. HCV genotype 1-infected patients with compensated cirrhosis (Child-Pugh Class < 7), adequate neutrophils (> 1.5 k/mm^3), and adequate platelet counts (> 75 k/mm^3) should be considered for treatment with BOC (for 44 weeks) or TVR (for 12 weeks) combined with PegIFN–RBV at standard doses for 48 weeks (Class I, Level B).

34. Patients with cirrhosis remain at risk for HCC and should undergo routine screening regardless of viral clearance status, in accordance with current guidelines (Class I, Level B).

African Americans

African Americans have the highest prevalence of HCV infection among the US veterans, but have lower rates of spontaneous viral clearance and lower SVR rates with all forms of IFN–RBV-based therapies than Caucasians. There is a lower prevalence of the *IL28B* CC in genotype 1-infected African Americans, which partly explains the lower SVR rates (19–28%) compared with Caucasians (39–52%) treated with PegIFN–RBV regimens (36,45,80–82). SVR rates in African Americans receiving BOC-based regimens, who were treatment-naïve (42–53%) and -experienced (53–61%) were higher than in those who received PegIFN–RBV alone (23 and 8%, respectively) (11,14). Similarly, African Americans receiving TVR-based regimens experienced higher SVR rates if they were treatment-naïve (62%) or -experienced (55%), compared with patients receiving PegIFN–RBV alone in Phase 3 trials (25 and 9%, respectively) (12,13).

Recommendation in African Americans:
35. BOC or TVR combined with PegIFN–RBV is the standard of care for genotype 1-infected African American patients (Class I, Level A).

HIV/HCV coinfection

The combination of PegIFN plus RBV remains the current standard of care for the treatment of HCV infection in HIV/HCV-coinfected patients. BOC or TVR plus PegIFN–RBV treatment in this population is under investigation. Treatment of HCV with a PI-containing regimen should be undertaken only with caution under the close supervision of a multidisciplinary team, with special attention to side effects and DDIs (83,84) (refer to **Supplementary Materials** for additional information on PegIFN and RBV treatment in this population).

Patients with a history of liver transplantation

Use of a PI with PegIFN and RBV after liver transplant has not been studied sufficiently. The only published pharmacokinetic study evaluated DDIs between TVR and either cyclosporine or tacrolimus. Cyclosporine levels were increased by 4.6-fold and tacrolimus levels by 70-fold after a single-dose administration of TVR (85). Given the significant DDIs, use of PIs with PegIFN and RBV after liver transplant should be carefully considered and only undertaken cautiously under the careful supervision of a transplant center (refer to **Supplementary Materials** for additional information on PegIFN and RBV treatment in this population).

FUTURE DIRECTIONS FOR HEPATITIS C THERAPY

Although TVR- and BOC-based regimens represent the first generation of oral DAA agents that have significantly improved SVR rates in HCV genotype 1-infected individuals, PegIFN and RBV are still required, treatment regimens are complex, adverse effects are significant, and treatment has limited efficacy in certain subgroups (e.g., nonresponders to PegIFN/RBV). Future therapies against HCV will likely yield higher SVR, lower pill burden with once or twice daily dosing, shorter treatment duration, less viral resistance, more favorable safety profiles, and broader genotype coverage (86–90). Classes of agents currently in clinical trials include: second generation HCV PIs, nucleoside/nucleotides, and non-nucleoside/non-nucleotides polymerase inhibitors, nonstructural protein 5a inhibitors, novel IFNs, and cyclophilin inhibitors. Second-generation PIs with PegIFN and RBV yield similar or better SVR rates than BOC- or TVR-based triple therapy. PegIFN lambda appears to be as effective as PegIFN alfa, but with fewer side effects, including less anemia and neutropenia. IFN-free regimens, which contain two direct acting agents (e.g., a PI and a polymerase inhibitor), with or without RBV, appear to improve SVR rates in both treatment-naïve and -experienced HCV-infected individuals (91–93). Larger studies are in progress, and FDA approval of IFN-free regimens is not expected for at least 3 years. The potency, improved dosing regimens, and continually improving efficacy of new HCV combination therapies mean that the HCV treatment field will remain dynamic for many years.

SUMMARY OF CURRENT RECOMMENDATIONS (REFER TO "APPENDIX")

The management of patients with HCV disease is evolving. In this document, we have attempted to provide a guide for the care of HCV-infected patients rather than to dictate absolute rules for practice. Treatment should be provided to those individuals who meet criteria for treatment and who are at greatest risk for progressive liver disease. Many of these patients will have relative contraindications to treatment, often because of concomitant psychiatric disease or other comorbid conditions. Close collaboration is necessary with specialists, including psychiatrists and substance abuse providers, to manage these comorbid conditions that represent barriers to the initiation of HCV antiviral therapy. Given the potential adverse events associated with antiviral therapy, patients should be counseled on their likelihood of achieving SVR (based upon individual factors such as body mass index, genotype, race, stage of fibrosis, and viral load) before initiating therapy.

CONFLICT OF INTEREST

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REVIEW

APPENDIX

SUMMARY OF RECOMMENDATIONS

Recommendation:
1. All patients with chronic HCV infection should be evaluated for HCV antiviral treatment. (Class IIa, Level B)

Recommendation for IL28 genotype testing:
2 IL28B genotype testing can be performed before PegIFN–RBV therapy with or without a PI, if the information on the probability of treatment response or duration would alter treatment decisions (Class IIa, Level B).

Recommendations in patients being considered for HCV therapy:
*3. Patients should receive pretreatment assessments as summarized in **Table 2** (Class I, Level B).*
4. Patients with more than portal fibrosis, including those with compensated cirrhosis, who lack contraindications, should be considered for treatment (Class I, Level B).
5. Patients should be counseled on their likelihood of achieving SVR, based upon individual factors such as body mass index, genotype, race, stage of fibrosis, and viral load before initiating therapy (Class I, Level B).

Recommendations for therapy for treatment-naïve patients with genotype 1 infection:
6. PegIFN alfa and RBV, in combination with BOC (800 mg orally every 7–9 h with food) or TVR (750 mg orally every 7–9 h with 20 g of fat), is the standard of care for most treatment-naïve genotype 1-infected patients (Class I, Level A).
*7. If a TVR-containing regimen is used in treatment-naïve noncirrhotic patients who achieve eRVR, TVR should be discontinued at week 12 and PegIFN–RBV should be continued for an additional 12 weeks. If HCV RNA is detectable, but < 1,000 IU/ml at treatment week 4, and remains < 1,000 IU/ml or becomes undetectable by week 12, TVR should be discontinued at week 12, and PegIFN and RBV can be continued for another 36 weeks (refer to **Figure 2**; Class I, Level A).*
*8. If a TVR-containing regimen is used in treatment-naïve cirrhotics who achieve an HCV RNA that is undetectable or < 1,000 IU/ml at treatment weeks 4 and 12, TVR should be discontinued at week 12, and PegIFN–RBV can be continued for another 36 weeks (refer to **Figure 2**; Class I, Level A).*
*9. If a BOC-containing regimen is used in treatment-naïve noncirrhotics, if HCV RNA declines by ≥1 $\log_{10}$ during the 4-week lead-in, and HCV RNA is undetectable at weeks 8–24, BOC–PegIFN–RBV for 24 weeks is sufficient. If HCV RNA is detectable at week 8, but < 100 IU/ml at week 12 and negative at week 24, BOC–PegIFN–RBV should be continued until week 36, followed by PegIFN–RBV alone for 12 more weeks. If HCV RNA declines by < 1 $\log_{10}$ during the lead-in, BOC–PegIFN–RBV can be contined for 44 weeks (refer to **Figure 3**; Class I, Level A).*
*10. If a BOC-containing regimen is used in treatment-naïve cirrhotics, 44 weeks of BOC–PegIFN–RBV is required after the 4-week lead-in (refer to **Figure 3**; Class I, Level A).*

Recommendations for treatment of nonresponders and relapsers with genotype 1 infection:
11. For patients who previously failed PegIFN–RBV , retreatment with BOC or RBV and PegIFN–RBV may be considered, particularly in patients who were relapsers (Class I, Level A).
*12. If a BOC-containing regimen is used for re-treatment of noncirrhotic prior partial responders or relapsers, the recommended treatment duration is 36 weeks if HCV RNA is undetectable from weeks 8–24. If HCV RNA is detectable at week 12, but < 100 IU/ml and is undetectable from weeks 24–36, BOC can be discontinued at week 36 and PegIFN–RBV can be continued for an additional 12 weeks (refer to **Figure 3**; Class I, Level B).*
*13. If a BOC-containing regimen is used for re-treatment in cirrhotics, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but < 100 IU/ml, and becomes undetectable from weeks 24–36 (refer to **Figure 3**; Class I, Level B).*
*14. If a BOC-containing regimen is used for re-treatment of prior null responders, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but < 100 IU/ml, and becomes undetectable from weeks 24–36 (refer to **Figure 3**; Class II, Level C).*
*15. If a TVR-containing regimen is used for re-treatment of prior relapsers, and HCV RNA is undetectable from weeks 4 and 12, TVR should be discontinued at week 12 and PegIFN–RBV should be continued for an additional 12 weeks. If HCV RNA is detectable, but < 1000 IU/ml at week 4 and/or 12, TVR can be discontinued at week 12, and PegIFN–RBV can be continued for an additional 36 weeks (refer to **Figure 2**; Class I, Level B).*
*16. If a TVR-containing regimen is used for re-treatment of prior partial responders or null responders, and HCV RNA is < 1000 IU/ml at weeks 4 and 12, TVR should be discontinued at week 12 and PegIFN alfa plus RBV should be continued for an additional 36 weeks (refer to **Figure 2**; Class I, Level B).*

Recommendations for dose modification:
*17. PegIFN alfa and RBV doses should be reduced in response to decreases in white blood cells, neutrophils, hemoglobin or platelets, as outlined in **Table 5** (Class I, Level A).*
18. If RBV is stopped for 7 days or more in patients who are concomitantly receiving BOC or TVR, then the PI also should be permanently discontinued (Class I, Level A).
19. HCV PIs should be either continued at full dose or discontinued (Class I, Level A).
20. Initial management of HCV treatment-related anemia should consist of RBV dose reduction in a symptomatic patient with a hemoglobin < 10 g/dl, or as clinically indicated. Erythropoietin may be administered in patients with symptomatic anemia related to PegIFN–RBV therapy with or without BOC/TVR to limit anemia-related RBV dose reductions or dose discontinuations (Class II, Level C).
21. Initial management of HCV treatment-related neutropenia should consist of PegIFN dose reduction for an ANC < 750, or as clinically indicated. Granulocyte colony-stimulating factor should not be given as primary therapy to prevent PegIFN alfa dose reductions (Class I, Level C).

Recommendations for treatment monitoring:
22. Patients should be monitored for treatment-related adverse effects at intervals of at least 2 weeks early in the course of therapy, and at intervals of 1–2 months during treatment as clinically indicated (Class I, Level C).
23. Patient adherence to therapy should be assessed at every visit (Class I, Level C).
24. Patients should be evaluated for depression, suicidal ideation, alcohol, and illicit drug use at each visit (Class I, Level C).
*25. Patients should be counseled about avoiding pregnancy by using two forms of contraception during treatment and for 6 months post-treatment, and pregnancy tests should be performed as indicated in (refer to "Monitoring Table" in **Supplementary Materials**). If a patient is receiving a BOC- or TVR-containing regimen, two alternative effective methods of contraception, such as intrauterine devices and barrier methods, should be used in at-risk patients and partners, during and for at least 6 months after treatment (Class I, Level B).*
*26. Serum markers of biochemical and virologic response should be measured, and treatment-related adverse effects monitored at intervals as outlined (refer to "Monitoring Table" in **Supplementary Materials**; Class I, Level C).*
27. In patients receiving TVR–PegIFN–RBV, all treatment should be stopped if any of the following occur: (1) HCV RNA level > 1,000 IU/ml at week 4 or 12; or (2) detectable HCV RNA levels at week 24 or at any timepoint thereafter; or (3) HCV RNA rebounds at any timepoint (≥1 log10 increase from the nadir HCV RNA) (Class I, Level C).
28. In patients receiving BOC–PegIFN–RBV, all treatment should be stopped if any of the following occur: (1) HCV RNA level ≥100 IU/ml at week 12 with a BOC-containing regimen; or (2) detectable HCV RNA levels at week 24 or at any timepoint thereafter; or (3) HCV RNA rebounds at any timepoint (≥1 log10 increase from the nadir HCV RNA; Class I, Level C).
29. If virologic failure occurs with a BOC- or TVR-containing regimen, the other PI must not be substituted (Class I, Level C).

Recommendations for PegIFN alfa with or without RBV treatment in genotype 1 patients:
30. PegIFN alfa monotherapy may be used to treat patients with contraindications to RBV (Class I, Level A).
31. For patients who achieve RVR and have a low baseline viral load (HCV RNA < 400,000 IU/ml), 24-weeks of treatment with PegIFN–RBV may be sufficient (Class I, Level B).

Recommendations in patients with mild disease:
32. Treatment can be deferred in patients with minimal inflammation and/or minimal portal fibrosis on liver biopsy (Class I, Level B).

Recommendations in patients with cirrhosis:
33. HCV genotype 1-infected patients with compensated cirrhosis (Child-Pugh Class < 7), adequate neutrophils (> 1.5 k/mm^3), and adequate platelet counts (> 75 k/mm^3) should be considered for treatment with BOC (for 44 weeks) or TVR (for 12 weeks) combined with PegIFN–RBV at standard doses for 48 weeks (Class I, Level B).
34. Patients with cirrhosis remain at risk for HCC and should undergo routine screening regardless of viral clearance status, in accordance with current guidelines (Class I, Level B).

Recommendation in African Americans:
35. BOC or TVR combined with PegIFN–RBV is the standard of care for genotype 1-infected African American patients (Class I, Level A).

Recommendations for treatment-naïve and -experienced patients with genotype 2 or 3 infection:
36. Treatment-naïve patients should be treated with PegIFN–RBV for 24 weeks (Class I, Level A).
37. For patients with low viral load (HCV RNA < 600,000 IU/ml) and mild fibrosis who achieve a RVR, 12–18 weeks of treatment may be sufficient (Class I, Level A).

38. For patients with genotype 3 infection and a high HCV RNA (>600,000 IU/ml), steatosis or advanced fibrosis, treatment beyond 24 weeks may improve response (Class I, Level B).
39. Retreatment duration is 48 weeks (Class I, Level A).

Recommendations in patients with genotype 4 infection:
40. Appropriate candidates with HCV genotype 4 infection should be treated with PegIFN alfa-2a 180 mcg per week or PegIFN alfa-2b 1.5 mcg/kg per week, plus RBV up to 1,400 mg per day for 48 weeks (Class I, Level A).

Recommendations in patients with decompensated cirrhosis:
41. Liver transplantation is the treatment of choice in patients with decompensated cirrhosis (Class I, Level B).
42. Antiviral therapy is contraindicated in most patients with decompensated cirrhosis (Class II, Level B).
43. IFN-based therapy in combination with RBV may be considered in patients awaiting liver transplantation with a Child-Pugh score < 7 and a MELD score ≤18 (Class I, Level A).
44. If antiviral therapy is undertaken, reduced IFN doses should be used and growth factors can be given to counteract treatment-associated cytopenias (Class II, Level B).

Recommendations in patients following solid organ transplantation:
45. IFN-based antiviral therapy is contraindicated following heart, lung or kidney transplantation (Class III, Level C).
46. In patients with biopsy-proven chronic HCV disease following liver transplantation, PegIFN–RBV for 48 weeks may be considered (Class IIa, Level B).
47. Toxicities of antiviral therapy should be managed with frequent monitoring, dose reductions, and growth factor support (Class IIa, Level B).
48. Post-liver transplant patients on antiviral therapy should be monitored closely for evidence of rejection, and antiviral therapy should be stopped if rejection is documented (Class IIa, Level B).
49. Pre-emptive antiviral therapy early post-transplantation in patients without histological recurrence should be avoided (Class IIa, Level B).

Recommendations in patients with renal disease:
*50. Patients should be considered for antiviral therapy with IFN (standard or pegylated) with RBV at modified doses (**Table 3**; Class IIa, Level C).*
51. Antiviral therapy for HCV treatment is not recommended in patients post-renal transplant; however, it may be considered if patients develop fibrosing cholestatic hepatitis (Class III, Level C).

Recommendations in patients with comorbid conditions:
52. In patients with limited life expectancy from comorbid conditions, antiviral therapy is not recommended (Class I, Level C).
53. In patients with significant comorbid conditions that will be exacerbated by PegIFN–RBV, treatment should be deferred (Class I, Level C).

Recommendations for patients on methadone:
54. Antiviral therapy should be offered to patients enrolled in a methadone maintenance program who meet criteria for therapy (Class I, Level A).
55. Treatment should be coordinated between HCV treatment providers and substance abuse specialists (Class I, Level B).

Recommendations in patients with ongoing alcohol use:
56. Patients should be encouraged to decrease alcohol consumption or to abstain, and should be referred for behavioral intervention to reduce alcohol use (Class I, Level B).
57. Antiviral therapy should be offered to patients who are otherwise appropriate candidates, regardless of prior alcohol use (Class I, Level B).
58. Alcohol consumption should be discouraged during antiviral treatment because alcohol reduces adherence and treatment response (Class I, Level B).

Recommendations in obese patients and those with hepatic steatosis:
59. Patients with a body mass index >30 should be considered for antiviral treatment (Class I, Level A).

60. Comorbid conditions common in obese patients such as diabetes, hypertension, and hyperlipidemia should be controlled before initiation of antiviral therapy (Class I, Level C).

Recommendations in patients with HIV-HCV coinfection:
61. Patients with controlled HIV infection and evidence of liver disease on biopsy should be considered for HCV antiviral therapy (Class I, Level B).
62. Patients should be treated with PegIFN–RBV at doses similar to those with HCV monoinfection (Class I, Level B).
63. Patients should be treated with PegIFN–RBV for 48 weeks, regardless of genotype (Class I, Level A).

Recommendations in patients with acute HCV infection:
64. Patients should be observed for a period of 8–20 weeks from time of initial exposure to monitor for spontaneous resolution of infection (Class I, Level C).
65. For those who fail to resolve infection spontaneously, treatment should be initiated with PegIFN alfa, with or without RBV for 24–48 weeks, based on genotype and HCV RNA response during therapy (Class I, Level B).