

An update on the management of chronic hepatitis C: Consensus guidelines from the Canadian Association for the Study of the Liver

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Chronic hepatitis C remains a significant medical and economic burden in Canada, affecting nearly 1% of the population. Since the last consensus conference on the management of chronic hepatitis C, major advances have warranted a review of recommended management approaches for these patients. Specifically, direct-acting antiviral agents with dramatically improved rates of virological clearance compared with standard therapy have been developed, and several single nucleotide polymorphisms associated with an increased probability of spontaneous and treatment-induced viral clearance have been identified. In light of this new evidence, a consensus development conference was held in November 2011; the present document highlights the results of the presentations and discussions surrounding these issues. It reviews the epidemiology of hepatitis C in Canada, preferred diagnostic testing approaches and recommendations for the treatment of chronically infected patients with the newly approved protease inhibitors (boceprevir and telaprevir), including those who have previously failed pegylated interferon and ribavirin therapy. In addition, recommendations are made regarding approaches to reducing the burden of hepatitis C in Canada.

Key Words: Antiviral; Boceprevir; Guideline; Hepatitis C; Interferon; Peginterferon; Protease inhibitor; Ribavirin; Telaprevir; Therapy; Treatment

PREAMBLE

The present guidelines were written to assist physicians and other health care professionals in the management of patients with chronic hepatitis C virus (HCV) infection. They were produced following a consensus conference of Canadian experts held in Toronto, Ontario, November 19 to 20, 2011. The meeting, which was organized by the Canadian Association for the Study of the Liver (CASL) with funding from the Canadian Liver Foundation, was open to all interested parties including health care professionals, patients, and representatives from government and the pharmaceutical industry. The information in the present guidelines represents a synthesis of the evidence presented at the meeting and available at the time of publication with supplementation by the expert opinion of the authors. Any recommendations should be considered preferred approaches to care of the HCV-infected patient as opposed to strict standards of care. To more fully characterize the quality of evidence supporting these recommendations, we have assigned a Class (reflecting benefit versus risk) and Level (assessing strength of certainty) of Evidence as adapted from the American College of Cardiology and the American Heart Association Practice Guidelines (1,2) and as used in similar practice guidelines of the American Association for the Study of Liver Diseases (3) (Table 1).

Mise à jour sur la prise en charge de l'hépatite C chronique : des lignes directrices consensuelles de l'Association canadienne pour l'étude du foie

L'hépatite C chronique demeure un fardeau médical et économique important au Canada, qui touche près de 1 % de la population. Depuis la dernière conférence consensuelle sur la prise en charge de l'hépatite C, des progrès importants ont justifié une analyse des démarches de prise en charge recommandées pour ces patients. Plus précisément, on a mis au point des antiviraux à action directe aux taux de clairance virologique considérablement plus élevés que ceux des thérapies standards et on a découvert plusieurs polymorphismes à nucléotide unique associés à une augmentation de la probabilité de clairance virale spontanée et induite par un traitement. À la lumière de ces nouvelles données probantes, une conférence consensuelle a eu lieu en novembre 2011. Le présent document fait ressortir les résultats des présentations et des discussions sur le sujet. Il traite de l'épidémiologie de l'hépatite C au Canada, des approches favorisées à l'égard des tests diagnostiques et des recommandations pour le traitement des patients atteints d'une infection chronique au moyen des inhibiteurs de la protéase approuvés depuis peu (bocéprévir et téléprévir), y compris les patients qui n'avaient pas répondu à un traitement à l'interféron pégylé et à la ribavirine. En outre, il contient des recommandations sur les démarches pour réduire le fardeau de l'hépatite C au Canada.

Since the most recent update of the CASL management guidelines for chronic hepatitis C in 2007 (4), two major advances have occurred: the development of direct-acting antiviral agents (DAAs) with dramatically improved rates of virological clearance compared with standard therapy (5-9); and the recognition of several single nucleotide polymorphisms (SNPs) associated with an increased probability of spontaneous and treatment-induced viral clearance (10-13). Presently, the impact of these advances is largely restricted to patients with HCV genotype 1. Therefore, the current consensus document was developed as an update to previous guidelines with a focus on the management of genotype 1-infected patients rather than an exhaustive review of hepatitis C. Where preferred management approaches for other patient populations (eg, with non-1 genotypes) have changed, the relevant recommendations have been updated.

INTRODUCTION

Chronic hepatitis C remains a significant medical and economic burden in Canada (14). Although no large-scale serological surveys have been conducted to define the exact prevalence of hepatitis C, modelling studies suggest that approximately 0.8% of Canadians – corresponding to nearly 245,000 individuals – were infected as of 2007

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TABLE 1
Grading system for recommendations

Classification	Description
Class of evidence	
Class 1	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective
Class 2	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 2a	Weight of evidence/opinion is in favour of usefulness/efficacy
Class 2b	Usefulness/efficacy is less well established by evidence/opinion
Class 3	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
Grade of evidence	
Level A	Data derived from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Only consensus opinions of experts, case studies, or standard-of-care

Adapted from references 1-3

(Table 2) (15). Provincial and territorial estimates of HCV prevalence suggest substantial regional variation, ranging from 0.13% in Newfoundland to 3.9% in the Yukon. In Canada, approximately 60% of HCV cases are among current or former injection drug users (IDUs), 20% are among infected immigrants and 11% have received contaminated blood products, including patients with hemophilia (Table 2). Of the nearly 8000 incident cases in Canada in 2007, approximately 80% are estimated to have occurred via sharing of injecting equipment among IDUs, and most of the remainder among immigrants from endemic countries. A significant number of the estimated cases in Canada remain undiagnosed, although the exact proportion is unclear (15). Modelling data suggest that the prevalence of hepatitis C has likely peaked in Canada, but the incidence of more advanced HCV-related sequelae (eg, decompensated liver disease, hepatocellular carcinoma [HCC] and liver transplantations) are expected to rise for at least another decade (Table 3 and Figure 1) (15).

Given the alarming estimates of future disease burden, more accurate information regarding the incidence and prevalence of hepatitis C and its sequelae are required to inform health care planning and the allocation of resources. The identification of undiagnosed cases and the dissemination of effective antiviral therapies should be prioritized to reduce complications of this disease.

Recommendations:

1. A large, population-based seroprevalence survey should be conducted to accurately define the prevalence of hepatitis C in Canada. The design of the study should include populations with an increased risk of hepatitis C, particularly IDUs and immigrants from endemic countries (Class 2a, Level C).
2. To reduce the future burden of HCV-related morbidity and mortality in Canada, strategies for case identification, harm reduction and disease management – including but not limited to antiviral therapy – should be developed and implemented (Class 2a, Level C).

ANTIVIRAL THERAPY

The primary objective of anti-HCV therapy is complete elimination of the virus, which is termed a sustained virological response (SVR).

TABLE 2
Modelled hepatitis C virus (HCV) prevalence according to exposure category in Canada, 2007*

Risk group	Population	HCV		Proportion of Canadian cases, %
		prevalence rate, %	Prevalent cases, n	
IDU, total	268,200	52	140,000	58
Current IDU	84,400	62	52,500	22
Previous IDU	183,800	48	87,500	36
Transfusion	3,325,700	0.8	25,900	11
Hemophilia	2200	40	900	0.4
Other	27,624,300	0.27	75,800	31
Total	31,220,500	0.8	243,000	100

*Numbers rounded to the nearest 100. IDU Intravenous drug user. Data adapted from reference 15

SVR is defined as undetectable serum HCV RNA at least 24 weeks following the end of treatment (Table 4) (16). Recent data suggest that earlier assessment of serum HCV RNA at 12 weeks after treatment is sufficient to define this outcome (17). Once achieved, an SVR is considered to be a cure of HCV infection because late relapses (which may actually represent reinfections) are rare (18,19). Additional benefits of SVR include improvements in quality of life (20,21), extrahepatic manifestations of HCV (eg, cryoglobulinemic vasculitis) (22), liver histology (23,24), and liver-related morbidity and mortality (25-27).

The landscape of antiviral treatment for hepatitis C is changing rapidly (28). Until recently, the standard therapy was the combination of peginterferon-alpha (PEG-IFN) and ribavirin (RBV), usually administered for 48 weeks in patients with genotype 1, 4, 5 and 6, and 24 weeks in those with genotypes 2 and 3 (4). Dual therapy achieves SVR rates of 40% to 50% in patients with genotype 1, and approximately 80% in those with genotypes 2 and 3. Although a significant advance from previously available treatments, PEG-IFN and RBV therapy is costly, associated with numerous adverse events and has only been used in a minority of infected individuals (29,30). Moreover, the majority of patients in Canada have HCV genotype 1 and have a lower likelihood of achieving viral eradication with dual therapy. Therefore, the recent emergence of DAAs, which offer a substantial improvement in SVR rates and the option of abbreviated therapy for many genotype-1-infected patients, represents a major advance in the field.

The treatment of hepatitis C is complex and time-consuming. Anti-HCV therapies require multiple modes of administration, can have numerous side effects, and require careful monitoring of symptoms and laboratory tests. Treatment complexity is further exacerbated by comorbid conditions that are more prevalent among HCV-infected patients, including mental health disorders (eg, depression) and addictions (eg, to alcohol and drugs). Therefore, the optimal management of hepatitis C requires a multidisciplinary approach that includes experienced physicians, nurses and allied health professionals (eg, psychologists, psychiatrists, addiction specialists and social workers). Currently in Canada, a relatively small number of physicians treat hepatitis C, leading in some cases to prolonged wait times for patients before being adequately evaluated and treated. Moreover, public funding for treatment nurses – who are a vital component of the management team – is not universally available. To achieve a meaningful reduction in the future burden of this disease, it will be vital to expand treatment capacity via additional training and funding of experienced personnel and enhanced access to publicly funded antiviral therapies (31).

Recommendations:

3. Increased resources are necessary to improve hepatitis C treatment capacity in Canada, including the training of expert treaters and public funding for treatment nurses (Class 2a, Level C).

TABLE 3
Modelled burden of hepatitis C virus (HCV) and sequelae according to five-year intervals in Canada, 1977 to 2027*

Year	HCV		Cirrhosis	Decompensated liver disease	Hepatocellular carcinoma	Liver transplants	Liver-related deaths
	Prevalence	Incidence					
1977	179,224	24,233	3611	743	69	99	77
1982	232,945	24,834	5605	1252	109	181	125
1987	264,095	18,497	7934	1940	158	304	189
1992	263,878	9486	10,477	2799	215	474	266
1997	254,165	8058	12,690	3748	266	688	346
2002	246,682	7899	14,421	4666	305	933	419
2007	242,521	7945	15,814	5495	338	1187	483
2012	239,134	8135	16,755	6186	360	1430	534
2017	236,343	8269	17,333	6721	373	1649	572
2022	232,684	8166	17,592	7101	378	1833	599
2027	227,371	7959	17,570	7333	379	1976	613

Data presented as n. *Estimates are not mutually exclusive. Data adapted from reference 15

INDICATIONS AND CONTRAINDICATIONS TO ANTIVIRAL TREATMENT

All patients with chronic hepatitis C who have compensated liver disease, are willing to undergo therapy and have no contraindications, should be considered candidates for antiviral treatment. The decision regarding if and when to initiate therapy should be based on the balance between the perceived benefits and risks of treatment and the wishes of the individual patient. Factors to consider include the probability of SVR and the likelihood of progression to advanced liver disease without viral eradication, the patient's anticipated tolerability of treatment and the life expectancy of the patient (eg, considering comorbidities). Women of childbearing potential may elect to undergo antiviral therapy before having children to reduce the risk of vertical transmission. The prospect of novel therapies with expected benefits over currently available treatments should also be considered. There is no absolute fibrosis threshold that should be used to preclude antiviral therapy; however, prompt initiation of treatment should be considered in patients with advanced liver fibrosis (F3 or F4 according to the METAVIR classification [bridging fibrosis or cirrhosis]) (32). These patients are at the highest risk of HCV-related complications including liver failure and HCC. Treatment of patients with lesser degrees of fibrosis (F0 to F2) should also be considered because progression to more advanced stages is associated with a reduced likelihood of SVR (5,6,33) but needs to be discussed on an individualized basis. Patients with extrahepatic manifestations of chronic hepatitis C including cryoglobulinemic vasculitis, porphyria cutanea tarda and glomerulonephritis should be considered for treatment regardless of their underlying liver disease severity because these conditions typically respond to viral eradication (22).

There are very few absolute contraindications to treatment with PEG-IFN and RBV-based therapy. As postmarketing experience with these medications has grown, many conditions previously regarded as absolute contraindications are now considered relative, and some may be present only temporarily (Table 5) (4). In most cases, treatment of these patients requires considerable expertise and, therefore, patients with relative contraindications should be treated in expert centres.

In some regions within Canada, public reimbursement for therapy is restricted to patients with elevated serum alanine aminotransferase (ALT) concentrations. Normal ALT is not a contraindication to treatment. These patients, which comprise approximately one-third of chronically infected individuals, respond as well to therapy as patients with elevated ALT levels (34). Moreover, approximately one-quarter of patients with persistently normal ALT levels have moderate to severe liver disease on biopsy (35).

Finally, patients who are incarcerated – a population with a high prevalence of HCV infection – should be considered for antiviral therapy as per nonincarcerated individuals. In appropriately selected

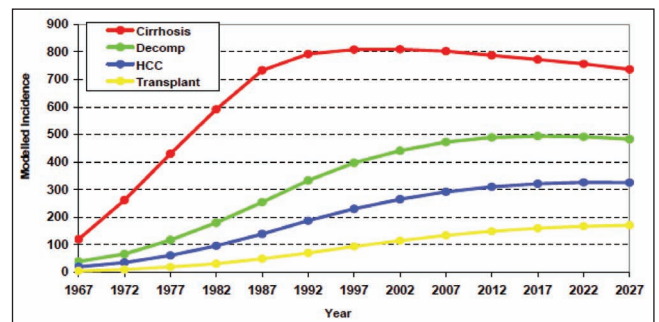


Figure 1) Modelled incidence of hepatitis C-related sequelae according to five-year intervals in Canada, 1967 to 2027. Estimates are not mutually exclusive. Reproduced with permission from reference 15. Decomp Decompensated liver disease; HCC Hepatocellular carcinoma

TABLE 4
Definitions of virological response to pegylated interferon (PEG-IFN) and ribavirin (RBV)-based therapy

Virological response	Definition
Rapid virological response	Undetectable HCV RNA at week 4 of therapy
Extended rapid virological response	Undetectable HCV RNA at weeks 4 and 12 of therapy in patients treated with telaprevir-based triple therapy
Early virological response	≥2 log ₁₀ decrease in HCV RNA at week 12 compared with baseline
End-of-treatment virological response	Undetectable HCV RNA at the end of treatment
Sustained virological response	Undetectable HCV RNA at least 24 weeks following the end of treatment
Null response	<2 log ₁₀ decrease in HCV RNA at week 12 compared with baseline in patients treated with PEG-IFN and RBV
Partial response	≥2 log ₁₀ decrease in HCV RNA but still detectable at week 12 in patients treated with PEG-IFN and RBV
Virological breakthrough	Reappearance of HCV RNA at any time during treatment after HCV RNA negativity has been achieved
Relapse	Reappearance of HCV RNA following treatment discontinuation after an end of treatment virological response has been achieved

HCV Hepatitis C virus

TABLE 5
Contraindications to treatment with pegylated interferon and ribavirin

Absolute contraindication	Pregnancy
Strong but not absolute contraindications	Alcohol abuse
	Hepatic decompensation
	Coronary artery disease
	Solid organ transplantation (except liver)
Relative contraindications	Major depression
	Major psychosis
	Autoimmune disease
	Renal failure (including dialysis)
Patient characteristics that are no longer considered to be contraindications	Normal alanine aminotransferase level
	Injection drug use
	Stable methadone maintenance
	Neutropenia, anemia or thrombocytopenia
	Controlled seizure disorder
	Older than 65 years of age
	Alcohol use

Table adapted with permission from reference 4

inmates, the ability to achieve an SVR with IFN-based therapy is similar to patients treated in the community (36,37). Treatment should be reserved for inmates deemed to be at low risk for HCV reinfection.

Recommendations:

- All patients with chronic HCV infection should be considered candidates for antiviral therapy, particularly those with evidence of liver fibrosis (Class 1, Level A).
- Patients with extrahepatic manifestations of HCV infection should be considered for antiviral therapy (Class 1, Level B).
- Persistently normal ALT does not exclude significant liver disease nor preclude the need for antiviral therapy (Class 1, Level A).

PRETREATMENT ASSESSMENT

Routine assessment

The routine assessment of patients with chronic hepatitis C should include risk factors for viral acquisition (eg, IDU, receipt of potentially contaminated blood products or tissues, and origin from a high prevalence region), signs and symptoms of advanced liver disease (eg, jaundice, ascites, encephalopathy, portal hypertension-related hemorrhage), presence of cofactors that may accelerate disease progression (eg, alcohol abuse, obesity, coinfections) and potential contraindications to IFN-based therapy (Table 5). Necessary laboratory testing includes virological tests to confirm and characterize HCV infection, liver biochemistry, abdominal ultrasound, and tests to rule out coinfections, direct vaccination and identify contraindications to treatment. In patients with abnormal liver biochemistry, serological tests to exclude coexisting liver diseases should be considered (Table 6).

Virological testing

Approximately one-quarter of patients who have been infected with HCV have cleared the virus spontaneously (38). Therefore, chronic HCV infection must be confirmed in all anti-HCV-positive individuals using a sensitive HCV RNA test. When contemplating therapy, HCV RNA should also be quantified to serve as a baseline for on-treatment monitoring of viral kinetics. HCV RNA detection and quantification using real-time polymerase chain reaction assays is standard due to their sensitivity, specificity, accuracy and broad dynamic range. Assays should be calibrated to the WHO international standard and results should be expressed in IU/mL. Quantitative assays with a lower limit of detection of approximately 10 IU/mL to 15 IU/mL are recommended. To facilitate management decisions, HCV RNA

TABLE 6
Routine testing of patients with chronic hepatitis C virus (HCV)*

Category of testing	Tests	Comments
Confirmation and characterization of chronic infection	HCV RNA	Confirms chronicity and baseline for treatment responses
	HCV genotype	Directs choice and duration of therapy
Assessment of liver disease	Complete blood count, ALT, AST, GGT, Alkaline phosphatase	Thrombocytopenia may indicate cirrhosis and portal hypertension. Platelets needed for APRI calculation. Normal value does not preclude significant fibrosis. AST needed for calculation of APRI
	Bilirubin, INR (or PT), Albumin	Elevated bilirubin or INR, or hypoalbuminemia may indicate significant liver dysfunction
	Creatinine, abdominal ultrasound	May suggest cirrhosis, in which case, serves as a baseline for HCC surveillance
	Viral coinfections	Immunoglobulin G anti-HAV
HBsAg		Exclude hepatitis B coinfection.
anti-HBs		If negative (and HBsAg-negative), vaccinate against hepatitis B
Exclude other causes of liver disease†	anti-HIV	Exclude HIV coinfection
	Alpha-1-antitrypsin	Alpha-1-antitrypsin deficiency
	Ceruloplasmin	Wilson disease
	Ferritin, serum iron, total iron-binding capacity	Iron overload
	Antinuclear antibody, smooth muscle antibody	Autoimmune hepatitis (AIH)
	Antimitochondrial antibody	Primary biliary cirrhosis (PBC)
	Immunoglobulin G	Often elevated in AIH and cirrhosis of any cause
Immunoglobulin A	Often elevated in fatty liver and alcoholic liver disease	
Immunoglobulin M	Often elevated in PBC	
Contraindications to treatment	Serum or urine β -HCG	Exclude pregnancy in women of reproductive age
	Electrocardiogram	If >50 years or history of cardiac disease
	Thyroid-stimulating hormone	Exclude thyroid disease, which may be exacerbated by IFN
	Fundoscopy	Exclude retinopathy in patients >50 years or with hypertension or diabetes mellitus

*Confirmed anti-HCV antibody positive; †Suggested tests only. Tailor testing to individual case. Anti-HBs Hepatitis B surface antibody; ALT Alanine aminotransferase; AST Aspartate aminotransferase; APRI AST/platelet ratio index; β -HCG Beta-human chorionic gonadotropin; GGT Gamma-glutamyltransferase; HBsAg Hepatitis B surface antigen; HCC Hepatocellular carcinoma; IFN Interferon; INR International normalized ratio; PT Prothrombin time

test results should be available within a timely fashion (seven days or less). The rapid identification of failing antiviral therapy will reduce patient exposure to costly and potentially toxic therapies, and likely

limit the development of antiviral-resistant variants (see below regarding discussion of futility rules).

The HCV genotype should also be assessed because it has important implications for the decision to initiate treatment, the choice of treatment, the dosage of RBV and the duration of therapy. With PEG-IFN and RBV treatment, knowledge of only the main genotype (1 to 6) is necessary. However, with the advent of the first-generation DAAs (telaprevir and boceprevir), knowledge of the subtype may be useful due to differing genetic barriers to resistance between HCV subtypes 1a and 1b (39,40).

Recommendations:

7. HCV RNA and genotype testing are essential to the management of patients with chronic hepatitis C (Class 1, Level C).
8. HCV RNA testing should be performed using a sensitive quantitative assay (lower limit of detection of 10 IU/mL to 15 IU/mL or less) with a broad dynamic range. Standardized results should be expressed in IU/mL and be available within a maximum of seven days to facilitate management decisions (Class 1, Level C).

Assessment of liver disease severity

Assessment of the severity of hepatic fibrosis is vital for determining the necessity of antiviral treatment and determining the prognosis of patients with chronic hepatitis C. Identification of patients with cirrhosis is particularly important due to their increased risk of hepatic complications (eg, HCC and end-stage liver disease), reduced responsiveness to antiviral treatment, and their need for surveillance for HCC and esophageal varices. Although the diagnosis of cirrhosis is obvious in some cases based on routine tests (eg, a nodular shrunken liver, splenomegaly or portal hypertensive collaterals on ultrasound), liver biopsy has traditionally been the reference method for staging liver fibrosis, determining the severity of other histological lesions (eg, necroinflammation, steatosis) and ruling out coexistent liver diseases (eg, iron overload). Various scoring systems have been validated for use in chronic hepatitis C and demonstrated sufficient reproducibility and interobserver variability to justify clinical use. The most widely used include the METAVIR, Scheuer, Ishak index and Knodell's Hepatic Activity Index classifications (41). However, liver biopsy has several limitations, most notably its invasiveness and the potential for serious complications including hemorrhage (approximately one in 1000) and death (approximately one in 10,000) (42,43). Other limitations include sampling error and variability in pathological interpretation (both of which may limit the accuracy of its findings), high cost and the difficulty of repeating biopsies to monitor temporal changes in fibrosis. In light of these limitations, numerous noninvasive alternatives to biopsy have been developed including serum markers, transient elastography (TE) and other imaging-based tools (44).

Serum marker panels that are available to stage fibrosis in patients with chronic hepatitis C can be categorized into three broad categories:

1. Panels based on routinely available biochemical and hematological parameters including ALT, aspartate aminotransferase (AST) and platelets (eg, the AST/ALT ratio [45], the AST/platelet ratio index [46] and Forns' index [47]);
2. Panels that include indirect markers of liver fibrosis such as alpha-2-macroglobulin and haptoglobin (eg, FibroTest [48], Hepascore [49] and FibroMeter [50]); and
3. Panels that include direct markers of fibrosis such as hyaluronic acid and tissue inhibitor of matrix metalloproteinase-1 (eg, FibroSpect II [51] and Enhanced Liver Fibrosis test [52]).

TE (FibroScan, Echosens, France) is an ultrasound-based method that measures liver stiffness as a surrogate of liver fibrosis. Numerous studies have validated this tool for staging of fibrosis in patients with chronic hepatitis C and other liver conditions (53-55). To obtain

accurate TE results, it is important to consider factors that may influence liver stiffness such as nonfibrotic histological lesions (eg, inflammation, vascular congestion and cholestasis) and obesity (55). In obese patients (body mass index [BMI] ≥ 30 kg/m²), it is advisable to use a specially designed probe (the FibroScan XL probe), which reduces the likelihood of TE failure compared with the standard M probe (56). Moreover, TE results must be interpreted cautiously when few valid measurements are obtained (ie, <10 valid shots or success rate <60%) or when the results are highly variable (ie, interquartile range of measurements over the median value >30%) (56-58).

Several additional imaging-based methods have been developed and hold promise for the noninvasive staging of liver fibrosis. These include acoustic radiation force impulse imaging, magnetic resonance (MR) elastography, diffusion-weighted MR imaging and MR spectroscopy (59,60). Although promising, the widespread adoption of these methods requires additional validation.

Although not universally available, a wealth of literature has now confirmed that serum biomarker panels and TE can be used instead of liver biopsy to stage HCV-related liver fibrosis with acceptable levels of accuracy and reproducibility. In general, these tests are highly accurate for diagnosing cirrhosis and have acceptable, but lower, performance for moderate to severe fibrosis ($\geq F2$). The identification of mild fibrosis (F1) and the differentiation between individual stages is poor; these limitations also apply to liver biopsy. The combination of two serum marker panels or TE with a serum marker panel can improve accuracy, although the added cost of this approach requires consideration (61,62). Emerging data have also demonstrated a correlation between these tests and clinical outcomes of HCV (63,64) as well as responsiveness to successful viral eradication (65,66). Future studies are necessary to determine the minimal clinically important changes in these markers to facilitate serial monitoring of fibrosis.

Recommendations:

9. All patients with HCV should undergo an assessment for the severity of liver fibrosis. Acceptable methods include liver biopsy, elastography (eg, FibroScan) and serum biomarker panels (eg, AST/platelet ratio index, FibroTest, FibroMeter), either alone or in combination (Class 2a, Level B).
10. Alternatively, cirrhosis can be diagnosed in some patients with clear clinical or radiographic evidence (Class 2a, Level C).

Utility of interleukin-28B testing

Genome-wide association studies have identified SNPs near the interleukin 28B (IL28B) gene on chromosome 19 that are strongly associated with both spontaneous and PEG-IFN- and RBV treatment-induced HCV clearance (10-13). Patients with the favourable CC genotype at rs12979860 have a more than twofold likelihood of spontaneous HCV clearance compared with heterozygotes (CT) and TT homozygotes (10). The CC genotype is also associated with a higher rate of SVR to PEG-IFN and RBV therapy. Caucasian patients with the CC IL28B genotype and HCV genotype 1 have an approximately 80% chance of SVR compared with just 40% among those with non-CC genotypes (11). There is marked ethnic variation in the prevalence of the IL28B genotypes. The CC genotype is highly prevalent in Asians, but relatively uncommon in Africans; Caucasians and Hispanics have an intermediate prevalence (11). Within ethnicities, the CC genotype is associated with an approximately twofold increase in SVR to PEG-IFN and RBV therapy compared with the unfavourable SNPs in patients with HCV genotype 1 (11). It is estimated that inter-racial differences in the prevalence of the IL28B genotypes account for approximately 50% of the ethnic variation in response rates to this therapy (11). Similar associations have been reported for the rs8099917 SNP, in which the favourable allele is coded with a T and the unfavourable allele with a G (13).

In patients with HCV genotype 1, the IL28B genotype is the strongest pretreatment predictor of response to PEG-IFN and RBV therapy (67). However, although patients with the favourable IL28B

TABLE 7
Futility rules in treatment-naive and previous treatment failure patients treated with boceprevir- or telaprevir-based triple therapy

Boceprevir	HCV RNA result*	Action
Week 12	≥100 IU/mL	Stop all therapy
Week 24	Detectable	Stop all therapy
Telaprevir	HCV RNA result*	Action
Week 4	>1000 IU/mL	Stop all therapy
Week 12	>1000 IU/mL	Stop all therapy
Week 24	Detectable	Stop all therapy

*Hepatitis C virus (HCV) RNA should be quantified using an assay with a lower limit of detection of no greater than 10 IU/mL to 15 IU/mL

CC genotype are likely to respond (approximately 80%), many patients with unfavourable genotypes will also respond (approximately 40%) (11). As such, the negative predictive value of the unfavourable genotypes is insufficient to preclude dual therapy in the individual patient. The impact of the IL28B genotype on treatment success is lower when treatment includes DAAs. Previously untreated patients with the favourable CC genotype are very likely to respond to combination therapy including DAAs, and the vast majority will qualify for shortened treatment. DAAs lead to a greater relative increase in SVR in non-CC patients (68,69). In treatment-experienced individuals, the IL28B genotype is of limited value (70); the outcome of DAA therapy in this population is largely dictated by the previous response to PEG-IFN and RBV, with prior relapsers showing two- to threefold higher SVR rates than null responders (8). The prior response is partly reflective of a patient's IL28B genotype and, hence, few null responders have the CC genotype. However, after stratification according to previous treatment response, there are no differences in rates of SVR to DAA-based therapy across IL28B genotypes (70). Similarly, on-treatment responses – to either dual or triple therapy – are better predictors of outcome than the IL28B genotype (67,69,71). Although non-CC patients achieve a rapid virological response (RVR; Table 4) to PEG-IFN and RBV less frequently than patients with the CC genotype, for those who do achieve an RVR, the rate of SVR is greater than that of CC patients who do not achieve RVR (71).

The mechanisms underlying the association of the IL28B genotype with antiviral treatment response are unknown. The SNPs lie in close proximity to – but not within – the IL28B gene, which codes for IL28B, also known as interferon (IFN) lambda. IFN-lambda is a type III IFN that signals similarly to type I IFNs (alpha or beta) but binds to a different receptor with a more limited tissue distribution (72). Because the IL28B genotype affects the response to IFN, it is most relevant in the least IFN-responsive HCV genotypes. Specifically, whereas the IL28B genotype is associated with SVR rates in genotypes 1 and 4 (73,74), its role in genotypes 2 and 3 is questionable (75,76).

In summary, IL28B genotyping may provide information regarding the likelihood of treatment response, but should not be used to determine the need or eligibility for therapy, or to determine the type of therapy used. Although patients with the favourable CC genotype are more likely to achieve an RVR to PEG-IFN and RBV, and may not all benefit from the addition of a DAA due to their high likelihood of SVR with dual therapy alone, there are insufficient data to support altering treatment paradigms based on the IL28B genotype.

Recommendations:

11. The IL28B genotype may provide some information regarding the likelihood of SVR and the probability of qualifying for shortened treatment duration in previously untreated patients with HCV genotype 1 (Class 1, Level A).
12. The role of IL28B genotyping is limited in treatment-experienced patients and those with HCV genotypes other than 1 and 4 (Class 3, Level A).

13. A nonfavourable IL28B genotype does not preclude antiviral therapy (Class 2b, Level C).

DAA AGENTS

Multiple steps in the HCV life cycle represent attractive targets for novel pharmacological therapies. Particularly promising agents target the nonstructural (NS) 3/4A (NS3/4A) serine protease, the NS5B RNA-dependent RNA polymerase and the NS5A protein (28). Several host-targeted agents, including the cyclophilin inhibitors, are also in development. Currently, the only DAAs to receive approval from Health Canada and the United States Food and Drug Administration are the NS3/4A protease inhibitors (PIs) boceprevir and telaprevir. When combined with PEG-IFN and RBV, these drugs lead to markedly improved SVR rates and permit shortened therapy in a significant proportion of patients with HCV genotype 1 (5-9). Based on currently available data, these agents should not be used in patients with non-1 genotypes. Importantly, the PIs must be used in combination with both PEG-IFN and RBV. If either of these medications is discontinued, the PI must also be discontinued.

TREATMENT-NAIVE PATIENTS WITH HCV GENOTYPE 1

Boceprevir

Boceprevir was formally evaluated in the Serine Protease Inhibitor Therapy 2 (SPRINT-2) trial, a phase 3 study that compared three regimens in two cohorts (nonblack and black) of treatment-naive patients with HCV genotype 1 infection (77). All patients were first treated with PEG-IFN-alfa-2b (1.5 µg/kg/week) and RBV (600 mg/day to 1400 mg/day based on body weight) for a four-week lead-in period. After the lead-in period, the control arm received an additional 44 weeks of PEG-IFN and RBV dual therapy. In the 'response-guided therapy' (RGT) arm, patients received PEG-IFN, RBV and boceprevir for 24 weeks after the lead-in period. In patients with undetectable (<10 IU/mL) HCV RNA from weeks 8 through 24, treatment was terminated, but if HCV RNA was detectable at any point from week 8 up to but not including week 24, an additional 20 weeks of PEG-IFN and RBV was administered. In the third arm, patients in the 'fixed-duration therapy' (FIXED) group received boceprevir plus PEG-IFN and RBV for 44 weeks after the lead-in period. The dosage of boceprevir was 800 mg three times daily (taken orally every 7 h to 9 h with food). All patients with detectable HCV RNA at week 24 were discontinued from treatment due to futility. A post hoc analysis has also identified that treatment continuation is futile in patients with HCV RNA ≥100 IU/mL at week 12 (Table 7) (78).

Overall, the rates of SVR in the SPRINT-2 trial were higher in boceprevir-treated patients (63% in the RGT arm and 66% in the FIXED arm) compared with those who received dual therapy (38%) (5). SVR rates in the nonblack patients were similar (RGT 67%; FIXED 68%; control 40%), whereas lower responses were observed among black patients (RGT 42%; FIXED 53%; control 23%). Treatment with a boceprevir-containing regimen was superior to dual therapy for most pretreatment factors including age, sex, race, viral load, body weight and BMI.

Forty-four per cent of boceprevir-treated patients had undetectable HCV RNA at treatment weeks 8 through 24 (early responders), compared with 12% of control patients, and would be eligible to shorten treatment to 28 weeks according to an RGT approach. In these patients, the SVR rates were 96%, 96% and 93% in the RGT, FIXED, and control groups, respectively (5). Overall, the SVR rates in the RGT and FIXED boceprevir arms were similar, supporting the use of RGT in most patients. In a subgroup analysis of the SPRINT-2 study, the SVR rate was superior in patients with cirrhosis (F4) in the FIXED arm (42%) compared with the RGT arm (31%). Although this difference was not statistically significant, the small number of cirrhotic patients in this analysis (n=40) supports a conservative approach in this difficult-to-cure subgroup. Therefore, in patients with cirrhosis, a

TABLE 8
Duration of therapy using response-guided therapy guidelines in patients treated with boceprevir- or telaprevir-based triple therapy

Boceprevir [†]	HCV RNA result*		Action
	Week 8	Week 24	
Previously untreated patients	Undetectable	Undetectable	Stop boceprevir, PEG-IFN and RBV at treatment week 28. Treatment is completed.
	Detectable	Undetectable	Continue boceprevir, PEG-IFN and RBV until treatment week 28 and then administer PEG-IFN and RBV until week 48.
Previous treatment failures (relapsers and partial responders)	Undetectable	Undetectable	Stop boceprevir, PEG-IFN and RBV at treatment week 36. Treatment is completed.
	Detectable	Undetectable	Continue boceprevir, PEG-IFN and RBV until treatment week 36 and then administer PEG-IFN and RBV until week 48.
Telaprevir [‡]	HCV RNA result		Action
	Week 4	Week 12	
Previously untreated patients and relapsers	Undetectable	Undetectable	Stop telaprevir at treatment week 12 and then continue PEG-IFN and RBV until week 24.
	Detectable [§]	Undetectable or detectable [§]	Stop telaprevir at treatment week 12 and then continue PEG-IFN and RBV until week 48.

*Hepatitis C virus (HCV) RNA should be quantified using an assay with a lower limit of detection of no greater than 10 IU/mL to 15 IU/mL; [†]Response-guided therapy to boceprevir is not recommended for patients with cirrhosis (F4), null responders to previous pegylated interferon (PEG-IFN) and ribavirin (RBV) therapy, or patients with a less than 1 log₁₀ decline in HCV RNA at treatment week 4 compared with baseline; [‡]Response-guided therapy to telaprevir is not recommended for patients with cirrhosis (F4) or previous partial or null responders to PEG-IFN and RBV therapy; [§]Detectable, but ≤1000 IU/mL. Higher values necessitate discontinuation of all therapy (see Table 7).

fixed duration of treatment consisting of 44 weeks of triple therapy after the lead-in phase is recommended. Similarly, patients who have less than a 1 log₁₀ decline in viral load from baseline to treatment week 4 during the lead-in period should receive an additional 44 weeks of triple therapy. While SVR rates among IFN-responsive patients in the SPRINT-2 trial were similar in the RGT and FIXED arms (approximately 80%), poorly responsive patients had a numerically higher SVR rate in the FIXED compared with the RGT arm (38% versus 28%) (5).

Recommendations (Figure 2):

- Patients should receive a four-week lead-in period of PEG-IFN and RBV before the initiation of boceprevir (Class 2b, Level A).
- Boceprevir is given at a dosage of 800 mg (4 × 200 mg capsules) every 8 h with food (Class 1, Level A).
- RGT (Table 8): In noncirrhotic patients with undetectable HCV RNA at treatment weeks 8 through 24 (ie, four and 20 weeks after starting boceprevir), all therapy may be discontinued at week 28 (Class 1, Level B).
- In patients with detectable HCV RNA at treatment week 8, triple therapy should be continued until week 28. At this point, boceprevir should be discontinued and PEG-IFN and RBV should be continued for an additional 20 weeks (Class 1, Level B).
- Patients with cirrhosis and those with <1 log₁₀ decline in HCV RNA after the four-week lead-in period should receive triple therapy for 44 weeks following the lead-in period (Class 2a, Level B).
- Futility rules (Table 7): All treatment should be discontinued in patients with HCV RNA ≥100 IU/mL at treatment week 12 or detectable HCV RNA at week 24 (Class 2a, Level B).

Telaprevir

Telaprevir has been evaluated in two phase 3 trials that included treatment-naïve patients with HCV genotype 1 infection (6,7). In the A New Direction in HCV Care: A Study of Treatment-Naïve Hepatitis C Patients with Telaprevir (ADVANCE) trial, patients were randomized to one of three treatment groups. The control arm received PEG-IFN-α-2a (180 µg/week) and RBV (1000 mg/day to 1200 mg/day based on body weight) for 48 weeks (PR48), while two telaprevir-treated groups also received telaprevir for the first 8 (T8PR) or 12 weeks (T12PR) in addition to PEG-IFN and RBV (6). Telaprevir was

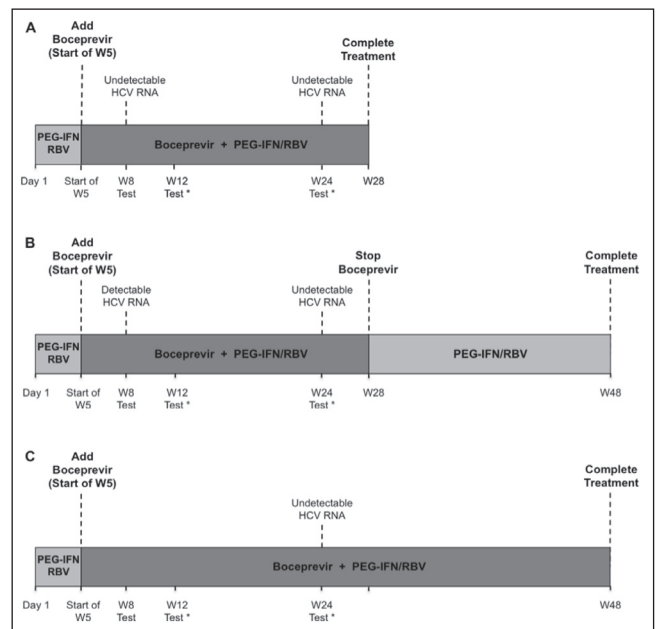


Figure 2) Algorithm for the management of treatment-naïve patients with hepatitis C virus (HCV) genotype 1 treated with pegylated interferon (PEG-IFN), ribavirin (RBV) and boceprevir. **A** Early responders (defined as HCV RNA-negative at weeks 8 through 24) are eligible for response-guided therapy (RGT) (28 weeks total treatment). **B** Late responders defined as HCV RNA-positive at week 8 should not receive RGT (ie, treat for 48 weeks total). **C** Patients with cirrhosis (F4) or <1 log₁₀ decrease in HCV RNA from baseline to week 4 after the lead-in phase should receive 48 weeks of treatment (ie, not RGT). *Indicates discontinuation of all treatment due to futility in patients with HCV RNA ≥100 IU/mL at treatment week 12 or detectable HCV RNA at week 24

administered at a dose of 750 mg every 8 h with high fat content food (approximately 20 g). Patients in the T8PR and T12PR groups who achieved an extended RVR (eRVR), defined as undetectable HCV RNA (<10 IU/mL) at weeks 4 and 12 (Table 4), stopped all therapy at week 24 according to an RGT approach. The rates of SVR were higher in both telaprevir-treated arms (T12PR, 75% and T8PR, 69%) than in the PR48 arm (44%) (6). Although the study was underpowered to compare the T12PR and T8PR groups, trends toward improved efficacy

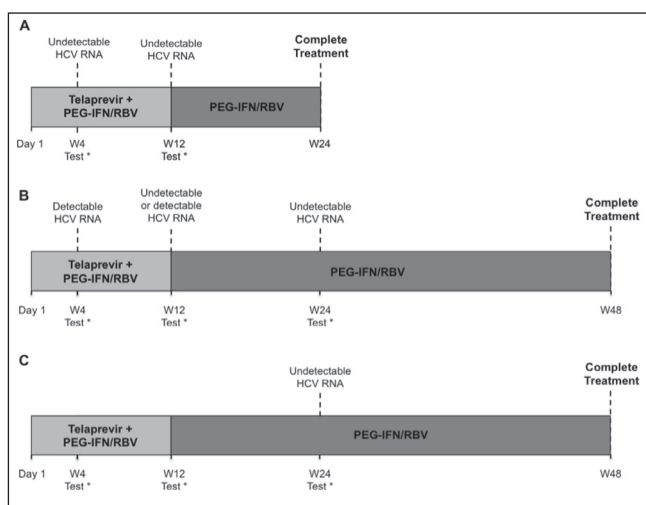


Figure 3 Algorithm for the management of treatment-naïve patients with hepatitis C virus (HCV) genotype 1 treated with pegylated interferon (PEG-IFN), ribavirin (RBV) and telaprevir. **A** Patients with an extended rapid virological response (HCV RNA-negative at weeks 4 and 12) are eligible for response-guided therapy (RGT) (24 weeks total treatment). **B** Patients who do not achieve an extended rapid virological response should not receive RGT (ie, treat for 48 weeks total). **C** Patients with cirrhosis should receive 48 weeks of treatment (ie, not RGT). *Indicates discontinuation of all treatment due to futility in patients with HCV RNA >1000 IU/mL at treatment weeks 4 or 12, or detectable HCV RNA at week 24

in some difficult-to-cure subgroups (eg, genotype 1a, high viral load and advanced fibrosis) and reduced emergence of antiviral-resistant variants were noted in the T12PR arm. Although 12-week dosing of telaprevir is likely preferable, the data suggest that if a patient must discontinue telaprevir prematurely due to adverse effects, high rates of SVR remain possible.

In addition to higher SVR rates, many patients were able to shorten treatment with the addition of telaprevir to PEG-IFN and RBV. Using an RGT approach, 57% to 58% of telaprevir-treated patients had an eRVR (compared with only 8% of PR patients) and were able to discontinue therapy at 24 weeks. The SVR rate for those who achieved eRVR was 89% in the T12PR arm and 83% in the T8PR group (versus 97% in the PR group), indicating that eRVR is a very robust predictor of SVR (6). To validate RGT as an appropriate strategy, the Illustrating the Effects of Combination Therapy with Telaprevir (ILLUMINATE) trial randomly assigned patients achieving an eRVR after 12 weeks of telaprevir-based triple therapy to 24 or 48 weeks of total treatment (7). Of the 540 patients included, 65% achieved an eRVR and were randomized. The SVR rates in patients with eRVR treated for 24 and 48 weeks were 92% and 88%, respectively, indicating that treatment can be shortened in patients who achieve an eRVR without a loss in the rate of SVR (7). However, RGT may not be the preferred strategy in patients with cirrhosis. In the ILLUMINATE trial, 61 patients (11%) had cirrhosis at baseline and 30 patients (49%) achieved an eRVR. Of these 30 patients, only 12 of the 18 (67%) randomly assigned to stop therapy at 24 weeks achieved SVR, compared with 11 of the 12 (92%) who were treated for a full 48 weeks (7). Based on these data, it is recommended that all patients with cirrhosis receive 12 weeks of telaprevir-based triple therapy followed by an additional 36 weeks of PEG-IFN and RBV. Other predictors of poor IFN responsiveness, such as high viral load and black race, had smaller effects on treatment outcome and, hence, RGT is still recommended for these subgroups.

Patients treated with telaprevir who have HCV RNA levels >1000 IU/mL at weeks 4 or 12 should stop all treatment because no patients meeting these futility rules in the phase 3 trials achieved SVR (6-8,79,80). Notably, in almost all patients with viral levels exceeding 1000 IU/mL at weeks 4 or 12, the viral titre is rising rather than falling

due the presence of telaprevir resistance. Continuation of therapy in the presence of resistance may promote compensatory mutations in the resistant variants that will improve their replicative fitness over time (81). In addition, continuation of futile therapy adds to cost and the potential for adverse effects.

Recommendations (Figure 3):

20. Telaprevir should be started simultaneously with PEG-IFN and RBV and given for the initial 12 weeks of therapy (Class 1, Level A).
21. Telaprevir is given at a dosage of 750 mg (2 × 375 mg tablets) every 8 h with high-fat food (Class 1, Level A).
22. RGT (Table 8): In noncirrhotic patients with undetectable HCV RNA at treatment weeks 4 and 12 (eRVR), telaprevir should be discontinued at week 12 and PEG-IFN and RBV should be continued for an additional 12 weeks (Class 1, Level A).
23. In patients with detectable HCV RNA at weeks 4 or 12, telaprevir should be stopped at week 12 and PEG-IFN and RBV should be continued for an additional 36 weeks (Class 1, Level A).
24. Patients with cirrhosis should receive 12 weeks of triple therapy followed by an additional 36 weeks of PEG-IFN and RBV (Class 2a, Level B).
25. Futility rules (Table 7): All treatment should be discontinued in patients with HCV RNA >1000 IU/mL at treatment weeks 4 or 12, or detectable HCV RNA at week 24 (Class 1, Level A).

Dual therapy in patients with RVR to PEG-IFN and RBV

Genotype 1-infected patients with an RVR, defined as undetectable HCV RNA after 4 weeks of PEG-IFN and RBV therapy (Table 4), may not benefit from the addition of a PI. In the SPRINT-2 (5), ADVANCE (6) and Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) trials (33), 8% to 12% of treatment-naïve patients who received PEG-IFN and RBV dual therapy achieved an RVR. The majority of these patients had the favourable IL28B genotype (CC). In patients who achieved RVR in these trials, dual therapy for 48 weeks led to an SVR in 86% to 97% of patients, similar to rates achieved with PI-based triple therapy (RGT and fixed duration). In the small subset of patients with RVR and low baseline viral load (<400,000 IU/mL), dual therapy for only 24 weeks yielded SVR rates comparable with 48 weeks of PEG-IFN and RBV treatment (82). The obvious benefits of avoiding a DAA in this patient subgroup include reduced exposure to PI-related adverse events, lower cost and the avoidance of emergent antiviral resistant variants in the small proportion of patients who subsequently fail this treatment. On the other hand, there are several hurdles to using this strategy. Notably, a lead-in strategy was used only in the phase 3 trials of boceprevir (not telaprevir) for treatment-naïve patients. Although a lead-in approach could be adopted before use of either PI, the decision to add a PI in patients who do not achieve an RVR would require rapid access to HCV RNA test results, which is not currently widely available. Second, whether this approach leads to comparable efficacy with PI-based triple therapy in all patient subgroups with RVR, including those with advanced fibrosis, is unclear. Before recommending this strategy, appropriately designed randomized trials, including short duration triple therapy (eg, 12 weeks) and cost-effectiveness analyses (from a Canadian perspective) are necessary.

PATIENTS WITH HCV GENOTYPE 1 AND PREVIOUS TREATMENT FAILURE

HCV-infected individuals who have failed to obtain an SVR to IFN-based treatment can be categorized into three groups based on viral kinetics during their previous course of therapy: relapsers, partial responders and null responders (Table 4). Because most treatment-experienced patients in Canada have failed dual therapy with PEG-

IFN and RBV, the remainder of this discussion refers to this subgroup. Retreatment of treatment-experienced patients infected with HCV genotype 1 using either boceprevir or telaprevir, along with PEG-IFN and RBV, has been studied in two phase 3 trials (8,9).

Boceprevir

In the Retreatment with HCV Serine Protease Inhibitor Boceprevir and Peginteron/Rebetol 2 (RESPOND-2) trial (9), relapsers and partial responders were randomly assigned to one of three treatment groups; null responders were not included in this study. All patients were initially treated with a four-week lead-in period of PEG-IFN-alpha-2b and RBV. Patients in the control arm received an additional 44 weeks of PEG-IFN and RBV. In the RGT arm, individuals who achieved undetectable HCV RNA levels by week 8 and remained undetectable through week 12 (compared with week 24 in the treatment-naive study) were assigned triple therapy until week 36. Those with persistently detectable HCV RNA at week 8 received triple therapy to week 36 followed by an additional 12 weeks of PEG-IFN and RBV dual therapy. Finally, patients in the FIXED group received 44 weeks of triple therapy after the four-week lead-in period. All patients with detectable HCV RNA at treatment week 12 were discontinued from treatment due to futility. Of note, the Canadian product monograph for boceprevir recommends a different stopping rule to avoid missing individuals who may achieve an SVR (78,83). Specifically, all treatment should be discontinued in patients with HCV RNA ≥ 100 IU/mL at week 12 or detectable HCV RNA at week 24 (78).

In terms of efficacy, the overall SVR in the control group was 21% compared with 59% in the RGT arm and 66% in the FIXED arm (9). Boceprevir-treated patients were more likely to achieve SVR than those who received dual therapy; however, the difference between the RGT and FIXED arms was not statistically significant. SVR rates among previous relapsers were 29% in the control arm versus 69% and 75% in the RGT and FIXED boceprevir arms, respectively. Corresponding SVR rates among partial responders were 7%, 40% and 52%, respectively. Because null responders were not included in RESPOND-2, a subsequent study (PROVIDE) evaluated the success of triple therapy including boceprevir among 48 patients who failed to achieve at least a 2 log₁₀ reduction in HCV RNA after 12 weeks of dual therapy from the control arms of SPRINT-2 and RESPOND-2 (84). In a preliminary report, an SVR was reported in 38% of patients; additional data are forthcoming. Based on these data, Health Canada and the United States Food and Drug Administration have approved boceprevir for the treatment of previous null responders.

Telaprevir

Telaprevir therapy for the retreatment of patients with HCV genotype 1 who failed to respond to dual therapy was evaluated in the Re-treatment of Patients with Telaprevir-based Regimen to Optimize Outcomes (REALIZE) phase 3 study (8). As in the RESPOND-2 trial, there were three treatment groups. The first group received a four-week lead-in period of PEG-IFN-alpha-2a and RBV, followed by 12 weeks of triple therapy including telaprevir and an additional 32 weeks of dual therapy. The second group received 12 weeks of triple therapy followed by 36 weeks of dual therapy (ie, no lead-in), and the control arm received 48 weeks of dual therapy. RGT was not assessed in this study. Telaprevir was discontinued in patients with HCV RNA >100 IU/mL at weeks 4, 6 or 8; PEG-IFN and RBV were continued in this situation. All treatment was discontinued in individuals with <2 log₁₀ decrease in HCV RNA level at week 12 in the telaprevir group with no lead-in (arm 2) and in the control group (arm 3); at week 16 in the telaprevir group that received a lead-in (group 1); and in all patients with detectable HCV RNA at weeks 24 or 36. Of note, the stopping rules in this study differ from those listed in the Canadian product monograph for telaprevir, which recommends discontinuation of all therapy if HCV RNA exceeds 1000 IU/mL at week 4 or 12, or is detectable at week 24 (the same criteria recommended for treatment-naïve individuals) (80).

Overall, the SVR rate in the control group was 17% compared with 66% in telaprevir-treated patients who received a lead-in (group 1) and 64% in those who started telaprevir immediately (group 2). The response rates did not differ between the two telaprevir-containing regimens (8). In subgroup analyses according to previous treatment response, relapsers demonstrated excellent responses with an SVR observed in 86% of telaprevir-treated patients compared with 24% among controls. In partial responders, SVR rates were 57% with telaprevir and 15% among controls. Among previous null-responders, SVR rates were 31% with telaprevir compared with only 5% among controls.

Although RGT was not assessed in the REALIZE trial, data from phase 2 studies support this approach in previous relapsers treated with telaprevir (85,86). Specifically, 78% (52 of 67) of relapsers in these trials achieved eRVR with 12 weeks of telaprevir-based triple therapy, which was followed by PEG-IFN and RBV for 12 weeks. An SVR was observed in 94% (49 of 52) of these patients (87). For comparison, among relapsers with an eRVR in the REALIZE trial, an SVR rate of 96% (91 of 95) was observed with a regimen including 36 weeks of dual therapy after an initial 12 weeks of triple therapy (8).

Patients with cirrhosis

In the RESPOND-2 trial, 12% (n=39) of individuals treated with boceprevir had compensated cirrhosis (F4) (88). The rates of SVR among these individuals categorized according to previous treatment response are not available. However, cirrhotic patients treated with triple therapy for 48 weeks were more likely to experience an SVR (77%) than those treated with RGT (35%) (78). In patients with advanced fibrosis (F3 or F4), corresponding SVR rates were 68% and 44%, respectively. In the REALIZE study, 23% (n=137) of telaprevir-treated individuals had compensated cirrhosis at baseline (8). Compared with the control group, SVR rates among cirrhotic subjects who received telaprevir were 87% (48 of 55) versus 13% (two of 15) for relapsers, 34% (11 of 32) versus 20% (one of five) for partial responders, and 14% (seven of 50) versus 10% (one of 10) for null responders (80). In light of limitations in the available data, including the absence of an RGT arm in the REALIZE trial, retreatment of cirrhotic individuals with either boceprevir or telaprevir should include 48 weeks of total therapy. Although data are limited, patients with bridging fibrosis (F3) may also benefit from prolonged therapy, particularly because many of these patients may actually have cirrhosis (due to the error of fibrosis assessment using biopsy and other tools).

Recommendations:

26. Noncirrhotic patients with HCV genotype 1 who have demonstrated relapse to previous PEG-IFN and RBV therapy should be offered retreatment with RGT including PEG-IFN, RBV, and boceprevir or telaprevir. Previous partial responders can be offered RGT with triple therapy including boceprevir or 48 weeks of total therapy (ie, non-RGT) including telaprevir (Class 1, Level A). Recommended management algorithms are as follows:
 - a. Boceprevir in relapsers and partial responders (Figures 4A and 4B): Use four weeks of lead-in therapy with PEG-IFN and RBV followed by the addition of boceprevir. If HCV RNA is undetectable at weeks 8 through 24, discontinue triple therapy at 36 weeks. If HCV RNA is detectable at week 8 and undetectable at week 24, discontinue triple therapy at 36 weeks and continue PEG-IFN and RBV dual therapy to week 48.
 - b. Telaprevir in relapsers (Figure 5A and 5B): Use telaprevir, PEG-IFN and RBV triple therapy. If HCV RNA is undetectable at weeks 4 and 12 (ie, eRVR), use triple therapy for a total of 12 weeks followed by PEG-IFN and RBV dual therapy for an additional 12 weeks (24 weeks total treatment). If HCV RNA is detectable at week 4 and/or 12, use triple therapy for 12 weeks followed by PEG-IFN and RBV dual therapy for an additional 36 weeks (48 weeks total treatment).

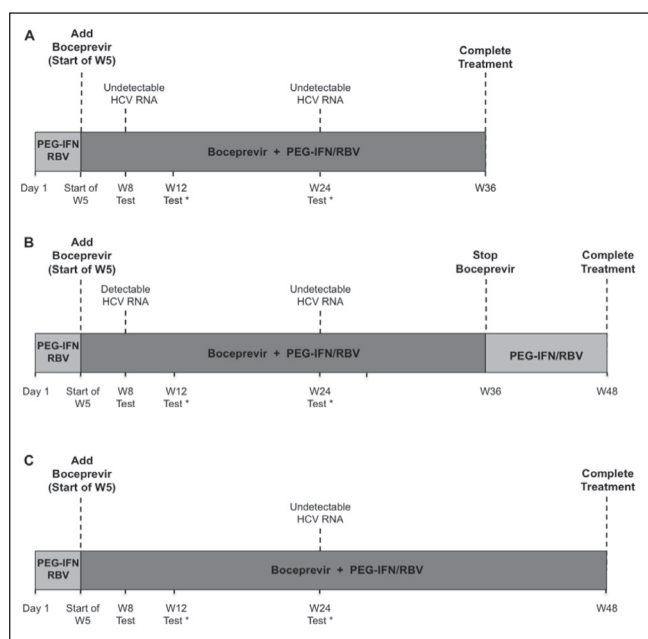


Figure 4) Algorithm for the management of previously treated patients with hepatitis C virus (HCV) genotype 1 treated with pegylated interferon (PEG-IFN), ribavirin (RBV) and boceprevir. **A** Previous partial responders and relapsers who have an early response (defined as HCV RNA-negative at weeks 8 through 24) are eligible for response-guided treatment (RGT) (36 weeks total treatment). **B** Previous partial responders and relapsers who have a late response (defined as HCV RNA-positive at week 8) should not receive RGT (ie, treat for 48 weeks total). **C** Patients with a previous null response and those with cirrhosis (F4) regardless of previous response should receive 48 weeks of treatment (ie, not RGT). *Indicates discontinuation of all treatment due to futility in patients with HCV RNA ≥ 100 IU/mL at treatment week 12 or detectable HCV RNA at week 24

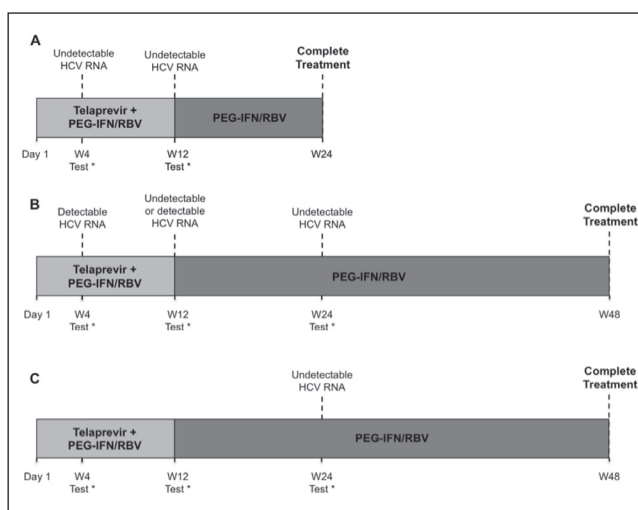


Figure 5) Algorithm for the management of previously treated patients with hepatitis C virus (HCV) genotype 1 treated with peginterferon (PEG-IFN), ribavirin (RBV) and telaprevir. **A** Patients with a previous relapse who achieve an extended rapid virological response (HCV RNA negative at weeks 4 and 12) are eligible for response-guided therapy (RGT) (24 weeks total treatment). **B** Patients with a previous relapse who do not achieve an extended rapid virological response should not receive RGT (ie, treat for 48 weeks total). **C** Patients with a previous partial response or null response, and those with cirrhosis (F4) regardless of previous response should receive 48 weeks of treatment (ie, not RGT). *Indicates discontinuation of all treatment due to futility in patients with HCV RNA >1000 IU/mL at treatment weeks 4 or 12 or detectable HCV RNA at week 24

- c. Telaprevir in partial responders (Figure 5C): Use telaprevir, PEG-IFN and RBV triple therapy for 12 weeks followed by PEG-IFN and RBV dual therapy for an additional 36 weeks (48 weeks total treatment).
27. Noncirrhotic patients with HCV genotype 1 who have demonstrated a null response to previous PEG-IFN and RBV therapy should be considered for triple therapy including PEG-IFN, RBV, and boceprevir or telaprevir (Class 1, Level B).
- a. Boceprevir in null responders (Figure 4C): Use 4 weeks of lead-in therapy with PEG-IFN and RBV followed by an additional 44 weeks of triple therapy including boceprevir (48 weeks total treatment).
 - b. Telaprevir in null responders (Figure 5C): Use triple therapy for 12 weeks followed by PEG-IFN and RBV dual therapy for an additional 36 weeks (48 weeks total treatment).
28. Treatment-experienced patients with HCV genotype 1 and cirrhosis should not be retreated with RGT (Class 3, Level B). Recommended management algorithms are as follows:
- a. Boceprevir (Figure 4C): Use four weeks of lead-in therapy with PEG-IFN and RBV followed by an additional 44 weeks of triple therapy including boceprevir (48 weeks total treatment).
 - b. Telaprevir (Figure 5C): Use triple therapy for 12 weeks followed by PEG-IFN and RBV dual therapy for an additional 36 weeks (48 weeks total treatment).

- 29. In patients with HCV genotype 1 in whom the previous treatment response cannot be determined, the optimal management approach is unclear. In noncirrhotic patients, RGT as described for relapsers (see Recommendation 26) can be considered, although the risk of relapse may be increased compared with 48 weeks of treatment. Patients with cirrhosis should be treated for 48 weeks (Class 2b, Level C).
- 30. Futility rules (Table 7): Futility rules in patients with previous treatment failure are identical to those described for treatment-naïve patients (see Recommendations 19 and 25 above).

ADVERSE EVENTS OF TELAPREVIR AND BOCEPREVIR

Patients treated with PI-based combination therapy experience more adverse effects than those treated with PEG-IFN and RBV alone. There are no data to support switching from one PI to another as a strategy to manage toxicity.

The addition of boceprevir to PEG-IFN and RBV leads to an increased incidence of anemia. In the phase 3 trials, hemoglobin levels fell below 100 g/L in 49% of patients receiving boceprevir compared with 29% of those on dual therapy. Severe anemia (hemoglobin <85 g/L) was reported in 9% of boceprevir-treated patients and 3% required transfusions (5,88). Hemoglobin level typically reaches a nadir on average 10 g/L to 15 g/L lower than with dual therapy at four to eight weeks after starting boceprevir (and telaprevir) and resolves on discontinuation of therapy (78,89). In the phase 3 trials of boceprevir, anemia was managed with RBV dosage reduction (by 200 mg decrements) and/or erythropoietin supplementation. Erythropoietin (provided by the study sponsor) was used in 44% of boceprevir-treated patients compared with 24% of control subjects (5,88). SVR rates were higher among patients with a significant decline in hemoglobin

concentration, likely due to increased RBV exposure. Moreover, similar SVR rates were observed between anemic patients managed with RBV dose reduction and those who received erythropoietin (or both) (90). While anemia is reversible with discontinuation of boceprevir, the dosage of boceprevir should not be reduced for anemia because of the increased risk of antiviral drug resistance in the setting of sub-therapeutic drug exposure. Patients treated with boceprevir also reported a higher rate of dysgeusia compared with controls (approximately 40% versus approximately 20%) (5,88).

The addition of telaprevir to PEG-IFN and RBV led to an increased incidence of anemia, dermatological side effects and gastrointestinal symptoms (eg, nausea and diarrhea). In the phase 3 trials, hemoglobin levels <100 g/L were reported in 41% of telaprevir-treated patients compared with 22% of controls (6-8). Severe anemia (<85 g/L) was reported in 9% of telaprevir-treated patients. Risk factors for anemia include older age, lower baseline hemoglobin and BMI, more advanced fibrosis and genotype 1b infection (91). Because erythropoietin use was not permitted in these trials, anemia was managed mainly with RBV dose reductions. Neither anemia nor RBV dose reduction had a detrimental impact on treatment response to telaprevir-based therapy (92). Because RBV dose modifications followed the product monograph (ie, first decrease to 600 mg/day), this degree of RBV dose modification (versus the typical standard of 200 mg decrements) is the preferred approach to anemia management in patients treated with telaprevir. Clinical trial and postmarketing experience suggest that the transfusion of packed red blood cells is more frequently required to manage severe symptomatic anemia in patients undergoing PI-based therapy (both boceprevir and telaprevir), particularly those with cirrhosis (93). In the REALIZE trial, 7% of patients treated with telaprevir required blood transfusions compared with <1% in the control arm (8).

Rash was reported in 56% of telaprevir-treated patients compared with 32% of controls (6,8). The rash associated with telaprevir was typically eczematous and maculopapular in nature, usually occurred within the first four weeks of therapy, and resolved with drug discontinuation. Although most rashes were mild to moderate, severe rashes (affecting >50% of the body surface area) occurred in 6% of patients. Stevens-Johnson syndrome and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome – both potentially lethal complications – occurred in fewer than 1% of telaprevir-treated patients, but no deaths were reported in the trials. Severe rash necessitates prompt drug discontinuation and dermatology consultation. If telaprevir is discontinued early due to rash, PEG-IFN and RBV treatment can continue. Patients treated with telaprevir also reported a higher incidence (29%) of anorectal symptoms including pain, burning and pruritus. These symptoms did not lead to drug discontinuation and generally responded to topical therapies (6,8).

Recommendations:

31. Close monitoring of hemoglobin levels is essential during antiviral treatment for HCV, particularly during the administration of PIs (Class 1, Level C).
32. Management of anemia may include any of the following strategies: RBV dose reduction (Class 1, Level A), transfusion of packed red blood cells (Class 1, Level C), and/or erythropoietin administration (Class 2a, Level C).

ANTIVIRAL RESISTANCE

Emergence of antiviral-resistant variants during PI-based treatment has been reported in all trials and is associated with incomplete virological response, virological breakthrough and relapse. Due to the high replication rate of HCV and the low fidelity of its RNA-dependent RNA polymerase, these variants are present at low frequencies before DAA exposure. Indeed, pretreatment testing in phase 3 trials of boceprevir and telaprevir has confirmed the presence of these variants in 5% to 7% of patients using poorly sensitive methods (ie, population

sequencing) (5,6). Because pre-existing variants do not appear to impact the probability of SVR or treatment decisions with the first-generation PIs, routine pretreatment resistance testing is not recommended.

In the SPRINT-2 and ADVANCE trials of treatment-naïve patients, antiviral-resistant variants emerged in 16% and 12% of patients treated with boceprevir and telaprevir, respectively (5,6). Similar viral variants, which are clustered around the catalytic site of the NS3/4A serine protease, are selected during treatment with both agents suggesting cross-resistance between PIs. In these studies, the majority of patients (80% to 90%) who experienced incomplete viral suppression, breakthrough or relapse on treatment cessation harboured resistant variants. However, resistance testing is not needed in cases of treatment failure because the results will not influence subsequent patient management. HCV genotype 1a has a higher risk of resistance than genotype 1b due to the higher genetic barrier of the latter subtype (39,40). Moreover, the emergence of antiviral resistance is inversely related to IFN responsiveness. For example, in the SPRINT-2 trial of boceprevir, resistance-associated variants were identified in 46% of patients with <1 log₁₀ decrease in HCV RNA during the lead-in phase versus only 5% of patients with greater virological suppression (5).

The clinical implications of emergent antiviral resistance, including implications for the future selection of DAAs and the success of retreatment, are unclear. During longitudinal follow-up of patients who developed antiviral resistance in the telaprevir phase 2/3 trials, 17% had persistent resistant variants documented by population sequencing after a median follow-up period of 29 months (40). Among patients treated with boceprevir, 25% of such subjects still had at least one substitution detected by population sequencing after 2.5 years of follow-up (89). Because population sequencing can only detect variants that represent at least 20% of the population of circulating virus, it is possible that patients who test negative by this technique still harbour a significant quantity of resistant variants. The clinical significance of 'disappearance' of resistance by population sequencing after stopping therapy remains unclear because data on retreatment of such patients are not available. Despite these uncertainties, every effort should be made to minimize the development of antiviral resistance. Patients who meet futility rules indicating a high likelihood of treatment failure (Table 7) should discontinue therapy immediately, and dosage reductions of boceprevir and telaprevir should not be utilized to manage treatment-related side effects. Finally, PIs cannot be used alone and, therefore, should be stopped if either PEG-IFN or RBV are discontinued.

Recommendations:

33. To reduce the development of antiviral resistance to the PIs, patients who meet futility rules indicating a high likelihood of treatment failure should discontinue therapy immediately (Class 1, Level A).
34. Dosage reductions of boceprevir and telaprevir should not be utilized to manage treatment-related side effects (Class 2a, Level C).
35. To prevent resistance, PIs must be stopped if either PEG-IFN or RBV are discontinued (Class 1, Level A).

DRUG-DRUG INTERACTIONS

Before the initiation of boceprevir or telaprevir, potential drug-drug interactions must be considered, including those attributable to prescription and over-the-counter pharmaceuticals and herbal preparations. Identification of potential interactions requires knowledge of the metabolism of these agents. Boceprevir is primarily metabolized by aldo-keto reductase, partially metabolized by cytochrome P450 (CYP3A4/5), and is a potent inhibitor of CYP3A4/5 activity. Therefore, boceprevir is contraindicated with medications that are potent inducers of CYP3A4/5 (that would reduce plasma concentrations and the therapeutic effect of boceprevir) and those that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated

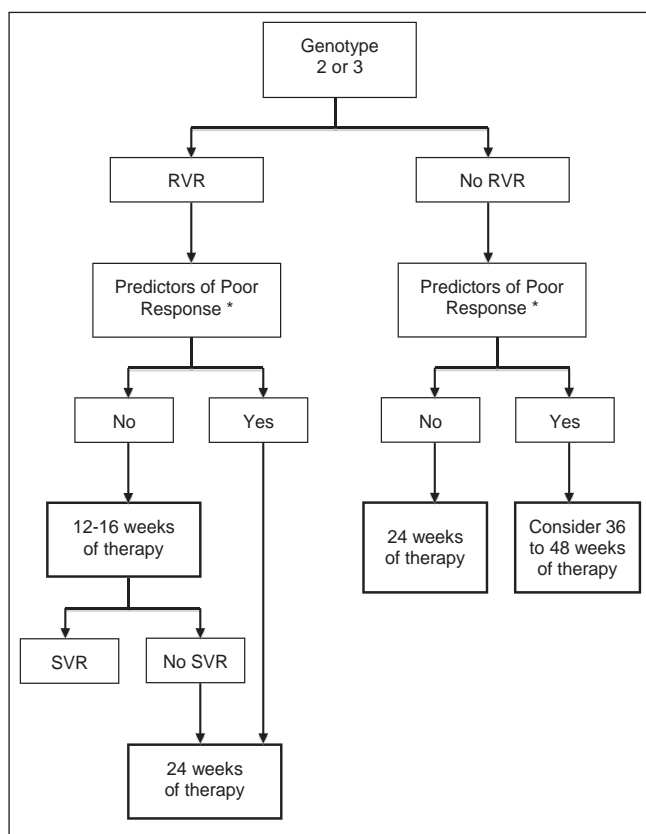


Figure 6 Algorithm for the management of previously untreated patients with hepatitis C genotypes 2 or 3 treated with peginterferon and ribavirin therapy. *Predictors of poor response to therapy include advanced fibrosis, black race, obesity and metabolic syndrome/insulin resistance. Shortened treatment (12 to 16 weeks) in patients with rapid virological response (RVR) should be restricted to those treated with weight-based ribavirin dosing. SVR Sustained virological response

with serious and/or life-threatening events (narrow therapeutic index) (78). Telaprevir is primarily metabolized by CYP3A4 and is an inhibitor of CYP3A and P-glycoprotein. Therefore, telaprevir is contraindicated when combined 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. Telaprevir should not be administered with drugs that strongly induce CYP3A and, thus, may lead to lower exposure and loss of efficacy.

Medications with potential drug-drug interactions with boceprevir or telaprevir are numerous and include the following classes: antiarrhythmics, anticoagulants, anticonvulsants, antihistamines, antibacterials, antiretrovirals, statins, herbal products (eg, St John's Wort), immunosuppressants, phosphodiesterase inhibitors and some sedatives/hypnotics. Due to an interaction between the PIs and oral contraceptives that can reduce the efficacy of the latter, a second method of contraception should be used during treatment with these agents. Because a complete listing of these agents is beyond the scope of these guidelines, and because knowledge regarding possible drug-drug interactions is constantly evolving, the reader is referred to the appropriate product monographs (78,80) and updated online databases (eg, www.hep-druginteractions.org).

TREATMENT-NAIVE PATIENTS WITH HCV GENOTYPES OTHER THAN 1

Since the last Canadian guidelines on the management of hepatitis C were published in 2007 (4), the treatment of patients with genotypes other than 1 has not changed substantially. In these patients,

the combination of PEG-IFN and RBV remains the standard therapy because data documenting a beneficial effect of the PIs on non-1 genotypes are limited. The treatment of these patients should consider on-treatment viral kinetics and patient-related factors that influence treatment response including the severity of fibrosis, race, obesity, metabolic syndrome/insulin resistance and viral load. The utility of IL28B genotyping in patients with non-1 genotypes (except genotype 4) is limited (73-76). The following are general recommendations for the treatment of previously untreated patients with HCV genotypes other than 1.

Recommendations for patients with genotypes 2 or 3 (Figure 6):

36. Patients with genotypes 2 or 3 should be treated with either of the following: PEG-IFN-alpha-2a (Pegasys RBV, Hoffmann-La Roche Ltd, Canada) 180 µg subcutaneously once weekly and RBV 800 mg per day given orally in two divided doses; or PEG-IFN-alpha-2b (Pegetron, Merck & Co, Inc, Canada) 1.5 µg/kg subcutaneously once weekly and weight-based RBV (600 mg to 1400 mg per day given orally in two divided doses) (Class 1, Level A).
37. The standard duration of therapy in patients with genotypes 2 or 3 is 24 weeks. Patients who do not achieve EVR should discontinue therapy at week 12 (Class 1, Level A).
38. In patients with genotypes 2 or 3 who achieve an RVR with PEG-IFN and weight-based RBV therapy, shortening of treatment to 12 to 16 weeks can be considered. Abbreviated treatment should not be considered in patients with cofactors that reduce the likelihood of treatment success (eg, advanced fibrosis, black race, obesity, metabolic syndrome/insulin resistance) even if an RVR is achieved. If a patient relapses following a shortened course of treatment, retreatment for 24 weeks should be considered (Class 1, Level A).
39. In patients with genotype 3 who do not achieve an RVR but have an EVR, extending treatment to 36 to 48 weeks may be considered, particularly in the setting of cofactors that reduce the likelihood of treatment success (Class 2a, Level C).

Recommendations for patients with genotypes 4 to 6:

40. Patients with genotypes 4 to 6 should be treated with either of the following: PEG-IFN-alpha-2a (Pegasys RBV, Hoffmann-La Roche Ltd, Canada) 180 µg subcutaneously once weekly and RBV 1000 mg (if weight <75 kg) to 1200 mg (if weight ≥75 kg) per day given orally in two divided doses; or PEG-IFN-alpha-2b (Pegetron, Merck & Co, Inc, Canada) 1.5 µg/kg subcutaneously once weekly and RBV 600 mg/day to 1400 mg/day given orally in two divided doses (Class 1, Level A).
41. The standard duration of therapy in patients with genotypes 4 to 6 is 48 weeks. Treatment should be discontinued in patients who do not achieve an EVR at week 12 or if HCV RNA remains detectable at week 24 (Class 1, Level A).
42. Patients with genotype 4 who have mild fibrosis (METAVIR F0 to F2) and low baseline viral load (<800,000 IU/mL) can be treated for 36 weeks (Class 1, Level B).

PATIENTS WITH GENOTYPES OTHER THAN 1 AND PREVIOUS TREATMENT FAILURE

Data describing the retreatment of patients with non-1 genotypes who have failed a previous course of PEG-IFN and RBV are limited. However, data from the EPIC study provide evidence to consider retreatment of patients with HCV genotypes 2 or 3 and at least moderate fibrosis (METAVIR F2 to F4) (94). In this study, retreatment with PEG-IFN-alpha-2b and weight-based RBV for 48 weeks led to an SVR in 57% of relapsers and 36% of nonresponders (detectable HCV RNA at the end their previous therapy). Overall SVR rates in genotype 2/3-infected patients with F2, F3 and F4 fibrosis (irrespective of previous treatment response) were 55%, 55% and 45%, respectively (94). There are currently

no data to support retreatment of these patients with triple therapy including a DAA.

Recommendations:

43. In patients with genotypes 2 or 3 who have failed a previous 24-week course of PEG-IFN and RBV and have at least stage 2 fibrosis, retreatment with a 48-week course of PEG-IFN and RBV may be considered (Class 1, Level B).

OPTIMIZING TREATMENT SUCCESS

Adherence

Adherence to PEG-IFN and RBV dual therapy and triple therapy including PIs is associated with improved rates of SVR (95,96). Failure to adhere to the recommended treatment schedules and stopping rules when using the PIs may also increase the risk of resistance. Numerous characteristics of these regimens have a negative impact on adherence including the necessity to take multiple medications for prolonged periods, by different routes of administration and with numerous adverse effects. Several features of the first-generation PIs will add further treatment complexity including the increased pill burden (up to 12 extra pills per day), different dosing schedules (three times daily versus twice daily dosing), additional adverse effects, specific dietary constraints and potentially dangerous drug-drug interactions. Importantly, experts in multidisciplinary settings have treated the vast majority of individuals that have received these medications to date.

Recommendations:

44. Adherence to treatment and to futility rules, and close monitoring of concomitant drugs and side effects are particularly important with PI-based therapy. Optimal management of this population should be conducted by well-trained, experienced personnel.

Body weight

Numerous studies have suggested that increased body weight, and particularly, high BMI, is associated with accelerated fibrosis progression in the setting of chronic hepatitis C (97). Some (98,99), but not all (33), studies also suggest that increased body weight has a negative impact on the probability of SVR to dual therapy with PEG-IFN and RBV. With combination therapy including telaprevir or boceprevir, obesity does not appear to significantly influence treatment responses (5,6). In light of these findings, specific recommendations for weight loss before PI-based therapy in an attempt to improve rates of SVR (as has been advocated by some for dual therapy [100]) cannot be made.

Erythropoietin for treatment-induced anemia

Anemia remains a common adverse effect of all currently available anti-HCV therapies. A significant proportion of the decrease in hemoglobin levels is due to RBV, which is likely to remain one of the cornerstones of HCV therapy even with the development of IFN-free regimens. As previously described, the addition of boceprevir or telaprevir to PEG-IFN and RBV is associated with an increased incidence and severity of anemia. In the phase 3 trials evaluating boceprevir, erythropoietin was administered to approximately 40% of patients (5,88). Erythropoietin administration has been shown to improve hemoglobin levels during therapy, reduce requirements for RBV dose reduction, and improve the quality of life of patients undergoing PEG-IFN and RBV treatment (101,102), but there is no definitive evidence that its use increases the likelihood of SVR (90). Nevertheless, erythropoietin may be considered in anemic patients who have not responded adequately to RBV dose reduction.

Neutropenia

Neutropenia is a common complication of IFN-based therapy, particularly among African-Americans and patients with cirrhosis, and is the leading indication for PEG-IFN dose reduction (98,99). Triple therapy including boceprevir (not telaprevir) further increases the risk of

neutropenia (79,89). However, there is no evidence that treatment-induced neutropenia is associated with an increased risk of infection in individuals receiving anti-HCV therapy (103,104). Similarly, the use of granulocyte-colony stimulating factor has not been shown to reduce the incidence of on-treatment infections or improve rates of SVR (105). Therefore, there is insufficient evidence to recommend the use of granulocyte-colony stimulating factor to manage neutropenia during HCV therapy.

Thrombocytopenia

Thrombocytopenia is observed in up to 25% of individuals with HCV; most cases are mild to moderate in severity (106,107). Severe thrombocytopenia (platelets $<40 \times 10^9/L$) is most often observed in patients with cirrhosis and portal hypertension. While treatment with PEG-IFN and RBV often causes or exacerbates pre-existing thrombocytopenia, bleeding complications are rare and platelet counts often improve following successful antiviral treatment (108,109). Triple therapy including boceprevir or telaprevir is associated with an increased incidence of thrombocytopenia (78,80). The Canadian product monographs for PEG-IFN-alpha-2a and -2b advise caution when starting antiviral therapy in patients with platelet counts less than $90 \times 10^9/L$ to $100 \times 10^9/L$, and recommend PEG-IFN dosage reduction and discontinuation if platelets fall below $50 \times 10^9/L$ and $25 \times 10^9/L$, respectively. These limits have been challenged by experts who suggest that PEG-IFN dose reductions are not necessary until the platelet count falls below $30 \times 10^9/L$, with discontinuation if the platelets fall below $20 \times 10^9/L$ (4).

Eltrombopag, a thrombopoietin receptor agonist, is licensed in Canada for the treatment of chronic immune (idiopathic) thrombocytopenic purpura. It has also been studied in HCV-infected patients with thrombocytopenia. When administered before PEG-IFN and RBV therapy, eltrombopag can increase platelet counts and, thus, increase patient eligibility for treatment (110). A recent phase 3, randomized controlled trial (Eltrombopag to iNtiate and maintain interferon Antiviral treatment to Benefit subjects with hepatitis C related Liver disease [ENABLE 1]) reported that the use of eltrombopag led to improved SVR to PEG-IFN and RBV therapy in patients with pre-treatment platelet counts $<75 \times 10^9/L$ (111). SVR rates in the eltrombopag and control arms were 23% and 14%, respectively. The utility of eltrombopag in patients receiving PI-based triple therapy is unknown. Importantly, eltrombopag has been associated with an increased risk of liver dysfunction and thrombotic complications, including portal venous thrombosis. In light of the absence of data with DAAs, potential complications and lack of regulatory approval for this indication, there are insufficient data to recommend use of this treatment.

Vitamin D deficiency

Several small studies have described an increased prevalence of vitamin D deficiency among patients with HCV infection, particularly those with advanced liver disease (112-114). There are some data suggesting that vitamin D deficiency impairs the response to anti-HCV therapy (114,115) and unconvincing evidence that vitamin D supplementation improves SVR rates to PEG-IFN and RBV therapy (114,116). Based on these limited data, additional studies are necessary regarding the role of vitamin D deficiency, testing and supplementation in HCV patients before any definitive recommendations can be made.

TREATMENT OF HCV IN ACTIVE ILLICIT DRUG USERS

In Canada, the majority of new cases of HCV infection occur among users of illicit drugs (except cannabis). The relative importance of this population – which is estimated to represent more than 60% of prevalent cases and 75% of incident cases in Canada – is expected to grow in the future (15). These patients have a high prevalence of psychiatric disease, medical comorbidities (including HIV and hepatitis B virus coinfections), and face significant social challenges such as

homelessness and lack of supports (117,118). As a result, most individuals with HCV in this population remain untreated (119,120). The last 2007 Canadian consensus guidelines recommended that research funds be allocated to improve care strategies for HCV-infected illicit drug users (4). Since then, reports have shown that it is feasible to offer PEG-IFN and RBV therapy to these patients under the supervision of experienced physicians (121-123). Evidence obtained from these trials has demonstrated that properly selected HCV-infected IDUs can achieve SVR rates comparable to those of non-IDU populations (124). This strategy has also shown lower than expected risk of HCV reinfection, possibly due to a combination of a change in risk-taking behaviours (possibly related to successful engagement in care) and acquired immunological protection (125-127).

Recommendations:

45. All patients with a past or present history of illicit drug use should be screened for hepatitis B, hepatitis C and HIV (Class 1, Level C).
46. Any HCV-infected individual with a past history of illicit drug use should be considered for treatment as per any other individual according to the current guidelines (Class 1, Level B).
47. The decision to treat HCV-infected IDUs with recent or ongoing illicit drug use should be made on an individualized basis by experienced physicians, ideally in a multidisciplinary setting. Treatment of substance abuse and mental health comorbidities and optimization of social conditions should be implemented to enhance the outcomes of anti-HCV therapy. Teaching and implementation of harm-reduction strategies is an integral component of the global care of these patients (Class 1, Level C).

TREATMENT OF HCV IN OTHER SPECIAL POPULATIONS

There are limited data describing the utility of first-generation PIs in many 'special' populations that have the greatest need for treatment (eg, patients with decompensated cirrhosis, post-liver transplantation, and HIV/HCV coinfection). These patients have the most aggressive disease, yet the lowest probability of success with PEG-IFN and RBV therapy. Studies are ongoing to evaluate the safety and efficacy of boceprevir and telaprevir in these patient populations. Particular attention will be necessary to avoid drug-drug interactions, especially between the PIs and immunosuppressants in post-transplant patients and antiretrovirals in those with HIV/HCV coinfection. It is also

expected that adverse events, particularly anemia, will be more prevalent among these high-risk subgroups. Preliminary data suggest that SVR rates among HIV/HCV coinfecting patients treated with triple therapy including boceprevir or telaprevir are comparable with those observed in HCV monoinfected patients (128,129). However, until further data are available, treatment of these special populations should be restricted to experienced centres. Highly selected patients with decompensated cirrhosis should only be treated in centres with access to liver transplantation. The efficacy and safety of these agents in pediatric patients and those with acute HCV infection is unknown.

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REFERENCES

1. American Heart Association. <http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/documents/downloadable/ucm_319826.pdf> (Accessed February 1, 2012).
2. Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: A proposal from the Conference on Guideline Standardization. *Ann Intern Med* 2003;139:493-8.
3. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011;54:1433-44.
4. Sherman M, Shafran S, Burak K, et al. Management of chronic hepatitis C: Consensus guidelines. *Can J Gastroenterol* 2007;21(Suppl C):25C-34C.
5. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1195-206.
6. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011;364:2405-16.
7. Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med* 2011;365:1014-24.
8. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011;364:2417-28.
9. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1207-17.
10. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature* 2009;461:798-801.
11. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009;461:399-401.
12. Kurbanov F, Abdel-Hamid M, Latanich R, et al. Genetic polymorphism in IL28B is associated with spontaneous clearance of hepatitis C virus genotype 4 infection in an Egyptian cohort. *J Infect Dis*;204:1391-4.
13. Tanaka Y, Nishida N, Sugiyama M, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet* 2009;41:1105-9.
14. Myers RP, Liu M, Shaheen AA. The burden of hepatitis C virus infection is growing: A Canadian population-based study of hospitalizations from 1994 to 2004. *Can J Gastroenterol* 2008;22:381-7.

15. Remis RS. Modelling the incidence and prevalence of hepatitis C infection and its sequelae in Canada, 2007. Final Report. Public Health Agency of Canada. <www.phac-aspc.gc.ca/sti-its-surv-epi/model/pdf/model07-eng.pdf> (Accessed February 1, 2012).
16. Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: A cure and so much more. *Clin Infect Dis* 2011;52:889-900.
17. Martinot-Peignoux M, Stern C, Maylin S, et al. Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. *Hepatology* 2010;51:1122-6.
18. Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. *Gastroenterology* 2010;139:1593-601.
19. Maylin S, Martinot-Peignoux M, Moucari R, et al. Eradication of hepatitis C virus in patients successfully treated for chronic hepatitis C. *Gastroenterology* 2008;135:821-9.
20. Myers RP, Cooper C, Sherman M, et al. Outcomes of chronic hepatitis C therapy in patients treated in community versus academic centres in Canada: Final results of APPROACH (A Prospective study of Peginterferon alfa-2a and Ribavirin at Academic and Community Centres in Canada). *Can J Gastroenterol* 2011;25:503-10.
21. Neary MP, Cort S, Bayliss MS, Ware JE Jr. Sustained virologic response is associated with improved health-related quality of life in relapsed chronic hepatitis C patients. *Semin Liver Dis* 1999;19(Suppl 1):77-85.
22. Cacoub P, Ratziu V, Myers RP, et al. Impact of treatment on extra hepatic manifestations in patients with chronic hepatitis C. *J Hepatol* 2002;36:812-8.
23. Poynard T, McHutchison J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology* 2002;122:1303-13.
24. Poynard T, McHutchison J, Davis GL, et al. Impact of interferon alfa-2b and ribavirin on progression of liver fibrosis in patients with chronic hepatitis C. *Hepatology* 2000;32:1131-7.
25. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med* 2007;147:677-84.
26. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clin Gastroenterol Hepatol* 2011;9:509-16.
27. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. *Clin Gastroenterol Hepatol* 2010;8:280-8.
28. Kronenberger B, Zeuzem S. New developments in HCV therapy. *J Viral Hepat* 2012;19(Suppl 1):48-51.
29. Falck-Ytter Y, Kale H, Mullen KD, Sarbah SA, Sorescu L, McCullough AJ. Surprisingly small effect of antiviral treatment in patients with hepatitis C. *Ann Intern Med* 2002;136:288-92.
30. Doucette KE, Robson V, Shafran S, Kunimoto D. Improving access to care by allowing self-referral to a hepatitis C clinic. *Can J Gastroenterol* 2009;23:421-4.
31. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: A multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 2010;138:513-21.
32. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology* 1994;20:15-20.
33. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009;361:580-93.
34. Zeuzem S, Diago M, Gane E, et al. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. *Gastroenterology* 2004;127:1724-32.
35. Puoti C, Magrini A, Stati T, et al. Clinical, histological, and virological features of hepatitis C virus carriers with persistently normal or abnormal alanine transaminase levels. *Hepatology* 1997;26:1393-8.
36. Allen SA, Spaulding AC, Osei AM, Taylor LE, Cabral AM, Rich JD. Treatment of chronic hepatitis C in a state correctional facility. *Ann Intern Med* 2003;138:187-90.
37. Martin CK, Hostetter JE, Hagan JJ. New opportunities for the management and therapy of hepatitis C in correctional settings. *Am J Public Health* 2010;100:13-7.
38. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: A systematic review of longitudinal studies. *J Viral Hepat* 2006;13:34-41.
39. Sarrazin C, Kieffer TL, Bartels D, et al. Dynamic hepatitis C virus genotypic and phenotypic changes in patients treated with the protease inhibitor telaprevir. *Gastroenterology* 2007;132:1767-77.
40. Sherman KE, Sulkowski MS, Zoulim F, et al. Follow-up of SVR durability and viral resistance in patients with chronic hepatitis C treated with telaprevir-based regimens: Interim analysis of the EXTEND study (Abstract 248). *Hepatology* 2011;54 (Suppl 4):485A (Abst).
41. Bedossa P. Liver biopsy. *Gastroenterol Clin Biol* 2008;32:4-7.
42. Myers RP, Fong A, Shaheen AA. Utilization rates, complications and costs of percutaneous liver biopsy: A population-based study including 4275 biopsies. *Liver Int* 2008;28:705-12.
43. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. *Hepatology* 2009;49:1017-44.
44. Guha IN, Myers RP, Patel K, Talwalkar JA. Biomarkers of liver fibrosis: What lies beneath the receiver operating characteristic curve? *Hepatology* 2011;54:1454-62. doi:10.1002/hep.24515.
45. Sheth SG, Flamm SL, Gordon FD, Chopra S. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. *Am J Gastroenterol* 1998;93:44-8.
46. Shaheen AA, Myers RP. Diagnostic accuracy of the aspartate aminotransferase-to-platelet ratio index for the prediction of hepatitis C-related fibrosis: A systematic review. *Hepatology* 2007;46:912-21.
47. Forns X, Ampurdanes S, Llovet JM, et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. *Hepatology* 2002;36:986-92.
48. Poynard T, Imbert-Bismut F, Munteanu M, et al. Overview of the diagnostic value of biochemical markers of liver fibrosis (FibroTest, HCV FibroSure) and necrosis (ActiTest) in patients with chronic hepatitis C. *Comp Hepatol* 2004;3:8.
49. Adams LA, Bulsara M, Rossi E, et al. Hepascore: An accurate validated predictor of liver fibrosis in chronic hepatitis C infection. *Clin Chem* 2005;51:1867-73.
50. Boursier J, Bacq Y, Halfon P, et al. Improved diagnostic accuracy of blood tests for severe fibrosis and cirrhosis in chronic hepatitis C. *Eur J Gastroenterol Hepatol* 2009;21:28-38.
51. Patel K, Benhamou Y, Yoshida EM, et al. An independent and prospective comparison of two commercial fibrosis marker panels (HCV FibroSURE and FIBROSpect II) during albinterferon alfa-2b combination therapy for chronic hepatitis C. *J Viral Hepatol* 2009;16:178-86.
52. Parkes J, Guha IN, Roderick P, et al. Enhanced Liver Fibrosis (ELF) test accurately identifies liver fibrosis in patients with chronic hepatitis C. *J Viral Hepat* 2010;18:23-31.
53. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: A meta-analysis. *Gastroenterology* 2008;134:960-74.
54. Myers RP, Elkashab M, Ma M, Crotty P, Pomier-Layrargues G. Transient elastography for the noninvasive assessment of liver fibrosis: A multicentre Canadian study. *Can J Gastroenterol* 2010;24:661-70.
55. Castera L. Transient elastography and other noninvasive tests to assess hepatic fibrosis in patients with viral hepatitis. *J Viral Hepatol* 2009;16:300-14.
56. Myers RP, Pomier-Layrargues G, Kirsch R, et al. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. *Hepatology* 2012;55:199-208.
57. Lucidarme D, Foucher J, Le Bail B, et al. Factors of accuracy of transient elastography (fibrosan) for the diagnosis of liver fibrosis in chronic hepatitis C. *Hepatology* 2009;49:1083-9.
58. Myers RP, Pomier-Layrargues G, Kirsch R, et al. Discordance in fibrosis staging between liver biopsy and transient elastography using the FibroScan XL probe. *J Hepatol* 2012;56:564-70.
59. Talwalkar JA, Yin M, Fidler JL, Sanderson SO, Kamath PS, Ehman RL. Magnetic resonance imaging of hepatic fibrosis: Emerging clinical applications. *Hepatology* 2008;47:332-42.
60. Friedrich-Rust M, Nierhoff J, Lupsor M, et al. Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: A pooled meta-analysis. *J Viral Hepat* 2012;19:e212-e219.

61. Boursier J, de Ledinghen V, Zarski JP, et al. Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: New algorithms are more precise and entirely noninvasive. *Hepatology* 2012;55:58-67.
62. Sebastiani G, Halfon P, Castera L, et al. Comparison of three algorithms of non-invasive markers of fibrosis in chronic hepatitis C. *Aliment Pharmacol Ther* 2012;35:92-104.
63. Vergniol J, Foucher J, Terrebonne E, et al. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. *Gastroenterology* 2011;140:1970-9,1979 e1971-1973.
64. Ngo Y, Munteanu M, Messous D, et al. A prospective analysis of the prognostic value of biomarkers (FibroTest) in patients with chronic hepatitis C. *Clin Chem* 2006;52:1887-96.
65. Poynard T, Ngo Y, Munteanu M, et al. Biomarkers of liver injury for hepatitis clinical trials: A meta-analysis of longitudinal studies. *Antivir Ther* 2010;15:617-31.
66. Vergniol J, Foucher J, Castera L, et al. Changes of non-invasive markers and FibroScan values during HCV treatment. *J Viral Hepat* 2009;16:132-40.
67. Thompson AJ, Muir AJ, Sulkowski MS, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. *Gastroenterology* 2010;139:120-9, e118.
68. Poordad F, Bronowicki JP, Gordon SC, et al. IL28B polymorphism predicts virologic response in patients with hepatitis C genotype 1 treated with boceprevir combination therapy. *J Hepatol* 2011;54(Suppl 1):S6.
69. Jacobson IM, Catlett I, Marcellin P, et al. Telaprevir substantially improves SVR rates across all IL28B genotypes in the ADVANCE trial. *J Hepatol* 2011;54(Suppl 1):S1369.
70. Pol S, Aerssens J, Zeuzem S, et al. Similar SVR rates in IL28B CC, CT or TT prior relapse, partial- or null-responder patients treated with telaprevir/peginterferon/ribavirin: Retrospective analysis of the REALIZE study (Abstract 13). *J Hepatol* 2011;54(Suppl 1):S6.
71. Mangia A, Thompson AJ, Santoro R, et al. Limited use of interleukin 28B in the setting of response-guided treatment with detailed on-treatment virological monitoring. *Hepatology* 2011;54:772-80.
72. O'Brien TR. Interferon-alfa, interferon-lambda and hepatitis C. *Nat Genet* 2009;41:1048-50.
73. Asselah T, De Muynck S, Broet P, et al. IL28B polymorphism is associated with treatment response in patients with genotype 4 chronic hepatitis C. *J Hepatol* 2012;56:527-32.
74. De Nicola S, Aghemo A, Grazia Rumi M, et al. Interleukin 28B polymorphism predicts pegylated interferon plus ribavirin treatment outcome in chronic hepatitis C genotype 4. *Hepatology* 2012;55:336-42.
75. Mangia A, Thompson AJ, Santoro R, et al. An IL28B polymorphism determines treatment response of hepatitis C virus genotype 2 or 3 patients who do not achieve a rapid virologic response. *Gastroenterology* 2010;139:821-7, 827 e821.
76. Moghaddam A, Melum E, Reinton N, et al. IL28B genetic variation and treatment response in patients with hepatitis C virus genotype 3 infection. *Hepatology* 2011;53:746-54.
77. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*;364:1195-206.
78. Merck Canada Inc. Product monograph: Victrelis (boceprevir). <www.merckfrosst.ca/assets/en/pdf/products/VICTRELIS-PM_E.pdf> (Accessed February 1, 2012).
79. Department of Health and Human Services, Food and Drug Administration. Antiviral Products Advisory Committee: Telaprevir NDA briefing document. <www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/DrugsAntiviralDrugsAdvisoryCommittee/UCM252561.pdf> (Accessed February 1, 2012).
80. Vertex Pharmaceuticals (Canada) Incorporated. Product Monograph: Incivek (Telaprevir tablets). <http://pi.vrtx.com/files/canadapm_telaprevir_en.pdf> (Accessed February 1, 2012).
81. Sarrazin C, Zeuzem S. Resistance to direct antiviral agents in patients with hepatitis C virus infection. *Gastroenterology* 2010;138:447-62.
82. Moreno C, Deltenre P, Pawlotsky JM, Henrion J, Adler M, Mathurin P. Shortened treatment duration in treatment-naive genotype 1 HCV patients with rapid virological response: A meta-analysis. *J Hepatol* 2010;52:25-31.
83. Jacobson IM, Marcellin P, Zeuzem S, et al. Treatment week 12/24 stopping rules for boceprevir (BOC) combination therapy with peginterferon + ribavirin (PR): Exploratory analysis of SPRINT-2 and RESPOND-2 (Abstract 954). *Hepatology* 2011;54:808A.
84. Vierling JM, Flamm SL, Gordon SC, et al. Efficacy of boceprevir in prior null responders to peginterferon/ribavirin: The PROVIDE study (Abstract 931). *Hepatology* 2011;54:796A (Abst).
85. McHutchison JG, Manns MP, Muir AJ, et al. Telaprevir for previously treated chronic HCV infection. *N Engl J Med* 2010;362:1292-303.
86. Berg T, McHutchison JG, Adda N, et al. SVR with telaprevir, peginterferon alfa-2a and ribavirin in HCV patients with well-characterized prior null response, partial response, viral breakthrough or relapse after PR (Abstract 4). *J Hepatol* 2010;52(Suppl 1):S2.
87. Adda N, Muir A, Adiwijaya B, et al. Response-guided telaprevir combination treatment in genotype 1 chronic hepatitis C patients who had a prior relapse to peginterferon alfa-2a/ribavirin (Abstract 26). *Can J Gastroenterol* 2012;26 Suppl A:81A (Abst).
88. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1207-17.
89. Food and Drug Administration Background Material for Boceprevir Advisory Committee Division of Antiviral Products (DAVP), April 27, 2011. <www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/drugs/AntiviralDrugsAdvisoryCommittee/ucm252341.pdf> (Accessed February 1, 2012).
90. Sulkowski MS, Poordad F, Manns MP, et al. Anemia during treatment with peginterferon alfa-2b/ribavirin with or without boceprevir is associated with higher SVR rates: Analysis of previously untreated and previous treatment-failure patients (Abstract 476). *J Hepatol* 2011;54(Suppl 1):S195-196.
91. Roberts S, Andreone P, Pol S, et al. Impact of anemia and ribavirin dose reduction on SVR to a telaprevir-based regimen in patients with HCV genotype 1 and prior peginterferon/ribavirin treatment failure in the phase III REALIZE study (Abstract 1368). *Hepatology* 2011;54:253A (Abst).
92. Sulkowski M, Reddy R, Afdhal NH, et al. Anemia had no effect on efficacy outcomes in treatment-naive patients who received telaprevir-based regimen in the ADVANCE and ILLUMINATE phase 3 studies (Abstract 477). *J Hepatol* 2011;54(Suppl 1).
93. Hezode C, Dorival C, Zoulim F, et al. Safety of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin, in cirrhotic non responders. First results of the French Early Access Program (ANRS CO20-CUPIC) in real-life setting (HepDart 2011 Abstract 46). <www.informedhorizons.com/hepdart2011/pdf/FinalProgram&Abstract%20Book_HEPDART2011.pdf> (Accessed March 8, 2012).
94. Poynard T, Colombo M, Bruix J, et al. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. *Gastroenterology* 2009;136:1618-28.
95. McHutchison JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology* 2002;123:1061-9.
96. Gordon SC, Lawitz EJ, Bacon BR, et al. Adherence to assigned dosing regimen and sustained virologic response among hepatitis C genotype 1 treatment-naive and PEG/ribavirin treatment-failures treated with boceprevir plus peginterferon alfa-2b/ribavirin (Abstract 428). *J Hepatol* 2011;54(Suppl 1):S173 (Abst).
97. Powell EE, Jonsson JR, Clouston AD. Steatosis: Co-factor in other liver diseases. *Hepatology* 2005;42:5-13.
98. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: A randomised trial. *Lancet* 2001;358:958-65.
99. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975-982.
100. Hickman IJ, Clouston AD, Macdonald GA, et al. Effect of weight reduction on liver histology and biochemistry in patients with chronic hepatitis C. *Gut* 2002;51:89-94.
101. Pockros PJ, Shiffman ML, Schiff ER, et al. Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. *Hepatology* 2004;40:1450-8.

102. Afdhal NH, Dieterich DT, Pockros PJ, et al. Epoetin alfa maintains ribavirin dose in HCV-infected patients: A prospective, double-blind, randomized controlled study. *Gastroenterology* 2004;126:1302-11.
103. Cooper CL, Al-Bedwawi S, Lee C, Garber G. Rate of infectious complications during interferon-based therapy for hepatitis C is not related to neutropenia. *Clin Infect Dis* 2006;42:1674-8.
104. Soza A, Everhart JE, Ghany MG, et al. Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. *Hepatology* 2002;36:1273-9.
105. Tandon P, Doucette K, Fassbender K, Vandermeer B, Durec T, Dryden DM. Granulocyte colony-stimulating factor for hepatitis C therapy-associated neutropenia: Systematic review and economic evaluation. *J Viral Hepat*;18:e381-93.
106. Louie KS, Micallef JM, Pimenta JM, Forssen UM. Prevalence of thrombocytopenia among patients with chronic hepatitis C: A systematic review. *J Viral Hepat* 2011;18:1-7.
107. Giannini EG, Savarino V. Epidemiology of thrombocytopenia in patients with chronic hepatitis C: More than meets the eye. *J Viral Hepatol* 2011;18:8-10.
108. Roomer R, Hansen BE, Janssen HL, de Knegt RJ. Thrombocytopenia and the risk of bleeding during treatment with peginterferon alfa and ribavirin for chronic hepatitis C. *J Hepatol* 2010;53:455-9.
109. Iga D, Tomimatsu M, Endo H, Ohkawa S, Yamada O. Improvement of thrombocytopenia with disappearance of HCV RNA in patients treated by interferon-alpha therapy: Possible etiology of HCV-associated immune thrombocytopenia. *Eur J Haematol* 2005;75:417-23.
110. McHutchison JG, Dusheiko G, Shiffman ML, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med* 2007;357:2227-36.
111. Afdhal N, Dusheiko G, Giannini EG, et al. Final results of ENABLE 2, a phase 3, multicenter study of eltrombopag as an adjunct for antiviral treatment of hepatitis C virus-related chronic liver disease associated with thrombocytopenia (Abstract LB-3). *Hepatology* 2011;54(4 Suppl):1427A (Abst).
112. Arteh J, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. *Dig Dis Sci* 2010;55:2624-2628.
113. Cacopardo B, Camma C, Petta S, et al. Diagnostic and therapeutic role of vitamin D in chronic hepatitis C virus infection. *Front Biosci (Elite Ed)* 2012;4:1276-86.
114. Petta S, Camma C, Scazzone C, et al. Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. *Hepatology* 2010;51:1158-67.
115. Bitetto D, Fattovich G, Fabris C, et al. Complementary role of vitamin D deficiency and the interleukin-28B rs12979860 C/T polymorphism in predicting antiviral response in chronic hepatitis C. *Hepatology* 2011;53:1118-26.
116. Bitetto D, Fabris C, Fornasiere E, et al. Vitamin D supplementation improves response to antiviral treatment for recurrent hepatitis C. *Transpl Int* 2011;24:43-50.
117. Sylvestre DL, Litwin AH, Clements BJ, Gourevitch MN. The impact of barriers to hepatitis C virus treatment in recovering heroin users maintained on methadone. *J Subst Abuse Treat* 2005;29:159-65.
118. Strathdee SA, Latka M, Campbell J, et al. Factors associated with interest in initiating treatment for hepatitis C Virus (HCV) infection among young HCV-infected injection drug users. *Clin Infect Dis* 2005;40(Suppl 5):S304-12.
119. Mehta SH, Genberg BL, Astemborski J, et al. Limited uptake of hepatitis C treatment among injection drug users. *J Community Health* 2008;33:126-33.
120. Grebely J, Raffa JD, Lai C, Krajden M, Kerr T, Fischer B, Tyndall MW. Low uptake of treatment for hepatitis C virus infection in a large community-based study of inner city residents. *J Viral Hepatol* 2009;16:352-8.
121. Mauss S, Berger F, Goelz J, Jacob B, Schmutz G. A prospective controlled study of interferon-based therapy of chronic hepatitis C in patients on methadone maintenance. *Hepatology* 2004;40:120-4.
122. Grebely J, Raffa JD, Meagher C, et al. Directly observed therapy for the treatment of hepatitis C virus infection in current and former injection drug users. *J Gastroenterol Hepatol* 2007;22:1519-25.
123. Jeffrey GP, MacQuillan G, Chua F, et al. Hepatitis C virus eradication in intravenous drug users maintained with subcutaneous naltrexone implants. *Hepatology* 2007;45:1111-7.
124. Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: A review of the available evidence. *Clin Infect Dis* 2009;49:561-73.
125. Mehta SH, Cox A, Hoover DR, et al. Protection against persistence of hepatitis C. *Lancet* 2002;359:1478-83.
126. Backmund M, Meyer K, Edlin BR. Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users. *Clin Infect Dis* 2004;39:1540-3.
127. Grebely J, Conway B, Raffa JD, Lai C, Krajden M, Tyndall MW. Hepatitis C virus reinfection in injection drug users. *Hepatology* 2006;44:1139-45.
128. Dieterich DT, Soriano V, Sherman KE, et al. Telaprevir in combination with pegylated interferon-a-2a+RBV in HCV/HIV-co-infected patients: A 24 week treatment interim analysis (19th Conference on Retroviruses and Opportunistic Infections 2012, Abstract 46). <www.retroconference.org/2012b/Abstracts/42969.htm> (Accessed March 8, 2012).
129. Sulkowski M, Pol S, Fainboim H, et al. Boceprevir + pegylated interferon + ribavirin for the treatment of HCV/HIV-co-infected patients: end of treatment (week-48) interim results (19th Conference on Retroviruses and Opportunistic Infections 2012, Abstract 47). <www.retroconference.org/2012b/Abstracts/44725.htm> (Accessed March 8, 2012).