TITLE: Treatments for Patients with Genotype 1 Chronic Hepatitis C: A Review of Evidence-based Guidelines

DATE: 23 June 2014

CONTEXT AND POLICY ISSUES

Approximately 242,000 Canadians are infected with the hepatitis C virus (HCV), although there are believed to be a number of infected individuals who are unaware that they have HCV. Of those infected, approximately 25% clear infection spontaneously (range 15% to 45%) and the remainder develop chronic hepatitis C (CHC).[1-3] There are six genotypes and treatment strategy tends to differ depending on genotype.

Genotype 1 infections account for most HCV infections in Canadians (55% to 65%).[4-6] For these patients, standard therapy has traditionally been pegylated interferon plus ribavirin (PR) therapy, administered for 48 weeks, however newer agents for treatment of HCV have recently been developed.[7] Greater understanding of the hepatitis C viral replication cycle has resulted in the development of direct-acting antiviral agents (DAAs) that target several types of proteins used to support viral replication. The first two DAAs, telaprevir (Notice of Compliance [NOC] 16 August 2011)[8] and boceprevir (NOC 29 July 2011),[9] are protease inhibitors approved in combination with PR for treatment of genotype 1 CHC infection. Recently, two new DAA agents have been approved by Health Canada, simeprevir (NOC 18 November 2013)[10] and sofosbuvir (NOC 13 December 2013).[11] Simeprevir is a protease inhibitor approved for the treatment of genotype 1 CHC, while sofosbuvir employs a novel mechanism of action targeting an HCV polymerase and is approved for the treatment of CHC of multiple genotypes.

This report will review evidence-based guidelines and recommendations for treatment options and timing of treatment initiation in patients infected with genotype 1 CHC.

RESEARCH QUESTION

What are the evidence-based guidelines for the treatment of patients with genotype 1 CHC?

KEY FINDINGS

The two newest CHC drugs, simeprevir and sofosbuvir, in combination with each other or with other agents (PR, ribavirin or daclatasvir) are currently the recommended treatments for various sub-populations of patients with genotype 1 CHC according to the most recent guidelines. These recommendations are based on randomized controlled trial (RCT) and non-RCT evidence and do not take into consideration cost and cost-effectiveness.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and May 22, 2014.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to the selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with genotype 1 CHC <u>Sub-populations</u>: · Treatment naïve, treatment experienced-relapsers, partial responders or null responders to PR therapy · Fibrosis levels (F0 to F4) · Genotype subtype (1a/1b) · Q80k polymorphism (present/ absent) · HIV co-infection · Inadequate response (failure or intolerance) to prior DAA + PR therapy
Intervention	Any DAA combination
Comparator	Not specified
Outcomes	Guidelines and recommendations for: · Treatment options · Timing of treatment initiation · Treatment of sub-populations
Study Designs	Evidence-based guidelines (North American and European)

CHC=chronic hepatitis C, DAA=direct acting antivirals, PR=peginterferon+ ribavirin

Exclusion Criteria

Guidelines were excluded if they did not meet the selection criteria, were published prior to 2011, were duplicate publications, if a more recent version was available, or for which the methodology for guideline development was unclear (i.e., unclear if a systematic review of the literature was conducted for evidence to support the guideline).

Critical Appraisal of Individual Studies

The quality of guidelines was evaluated by one reviewer using the AGREE II tool.[12] Numeric scores for this evaluation are not reported and a narrative and tabular description of the strengths and limitations of each included guideline is presented instead.

SUMMARY OF EVIDENCE

Quantity of Research Available

The selection of guidelines is summarized in Appendix 1. The literature search yielded 155 citations. After screening of abstracts, 47 potentially relevant guidelines were selected for full text review. Another four guidelines were identified from other sources. Of these, five evidence-based guidelines met the inclusion criteria.

Additional references of potential interest which did not meet the selection criteria are provided in Appendix 2.

Summary of Guideline Characteristics

Information on the characteristics of the included evidence-based guidelines is provided in Appendix 3, Table 3.1

Three guidelines published in 2014 included those by the American Association for the Study of Liver Diseases (AASLD),[13] the European Association for the Study of the Liver (EASL),[14] and the World Health Organization (WHO).[15] Two guidelines were published in 2013 by the British HIV Association[16] and the Scottish Intercollegiate Guidelines Network (SIGN).[17]

Country of Origin

One guideline was generated in the United States of America,[13] one was European,[14] one was generated in Britain,[16] another in Scotland,[17] and finally one guideline came from the WHO.[15]

Guideline Development Methodology

Four guidelines[13,14,16,17] specified the databases searched. Specific information about the literature search for the WHO review was not available at the time of this review, and therefore, it is unclear which databases were searched. Four guidelines included a search of the grey literature.[13,15-17] It was unclear as to whether or not the fifth guideline (EASL) considered the grey literature in their review of the evidence. Inclusion criteria were based on Patients, Interventions, Comparators, Outcomes and Study designs (PICOS) in three guidelines[15-17] and not clearly specified in the other two guidelines. Recommendations were developed by panels

of experts. Criteria for the grading of recommendations and levels of evidence are included in Appendix 3, Table 3.2.

Population

All guidelines included the population of interest, genotype 1 CHC patients. Recommendations were also made for the sub-populations of interest (see Table 1). One guideline by the British HIV Association was specific to HCV-HIV co-infected patients.[16]

Outcomes

All guidelines included recommendations for treatment options of patients infected with genotype 1 CHC. Timing of treatment initiation was addressed in three of the five guidelines: AASLD, EASL, and WHO.

Summary of Critical Appraisal

A tabular description of the strengths and limitations of the included guidelines are summarized in Appendix 4, Table 4.1.

Overall, the included guidelines were of high quality. Guidelines' objectives were clearly stated and the methods used for formulating the recommendations were described. The guidelines were developed by experts in the field of hepatology and infectious disease, and patient views were elicited in three[15-17] of the five guidelines. All guidelines were externally peer-reviewed prior to publication.

In two guidelines[13,14] the systematic methods used in the search for evidence, for example the search strategy and inclusion/ exclusion criteria, were only partially described. In all five guidelines, each recommendation was linked to key trials upon which the recommendations were based; only two guidelines[14,15] commented on the trials' strengths and limitations, although all guidelines rated the level of evidence.

Only two guidelines[13,15] documented funding source. Conflict of interest of the panel members were taken into consideration in all guidelines.

Summary of Findings

Overall, the guidelines published in 2014 have similar recommendations which take into consideration the newly approved CHC agents. The tables in Appendix 5 report further information on drug doses, duration of treatment, and grading of recommendations.

A. Treatment Initiation

AASLD recommends delaying treatment for some patients with documented early fibrosis, METAVIR score F0 to F2 (a higher score implies worsening liver fibrosis).

EASL recommends that treatment be prioritized for patients with significant fibrosis (F3 to F4) and that treatment is justified in patients with moderate fibrosis (F2). In patients with no or mild disease (F0 to F1), the indication for and timing of therapy can be individualized.

WHO states that treatment of HCV infection with interferon-containing regimens must be commenced before the onset of decompensated liver disease.

B. Treatment Options

Guidelines published in 2014

Any patient

EASL recommends different options for patients with genotype 1 CHC including:

- Sofosbuvir in combination with PR (also recommended by WHO)
- Simeprevir in combination with PR (also recommended by WHO)
- Sofosbuvir in combination with simeprevir
- Sofosbuvir in combination with daclatasvir
- Sofosbuvir in combination with ribavirin (in interferon-ineligible patients when no other interferon-free option is available; also recommended by WHO)

WHO recommends PR, although it is further stated that treatment with telaprevir or boceprevir in combination with PR is recommended rather than PR alone.

Treatment-naïve patients

AASLD recommends sofosbuvir with PR in patients who are interferon-eligible. For those who are interferon-ineligible, a combination of sofosbuvir and simeprevir, with or without ribavirin is recommended.

WHO recommends telaprevir with PR or boceprevir with PR.

Treatment-naïve patients with genotype 1a, without detectable Q80K polymorphism

AASLD and WHO recommend a treatment of simeprevir in combination with PR in patients who are interferon-eligible. Of note, EASL clearly states that this regimen is not recommended for patients infected with subtype 1a who have detectable Q80K polymorphism.

Treatment-naïve patients with genotype 1b

AASLD and WHO recommend a treatment of simeprevir in combination with PR in patients who are interferon-eligible.

Treatment-experienced patients who are non-responders/ treatment failures

AASLD recommends treatment with a combination of sofosbuvir and simeprevir, with or without ribavirin. Alternative treatments include sofosbuvir with PR, simeprevir with PR, or sofosbuvir with ribavirin.

EASL recommends the following treatments in patients who failed regimens which contained:

- Sofosbuvir – use sofosbuvir in combination with simeprevir or daclatasvir
- Simeprevir – use a combination of sofosbuvir and daclatasvir
- Telaprevir – use a combination of sofosbuvir and daclatasvir
- Boceprevir – use a combination of sofosbuvir and daclatasvir
- Daclatasvir – use a combination of sofosbuvir and simeprevir
- Sofosbuvir with simeprevir – use a combination of sofosbuvir and daclatasvir
- Sofosbuvir with daclatasvir – use a combination of sofosbuvir and simeprevir

WHO recommends a regimen of simeprevir in combination with PR.

Patients with HCV-HIV co-infection

AASLD recommends the following:

- Treatment-naïve patient, interferon-eligible – use sofosbuvir with PR
- Treatment-naïve patient, interferon-ineligible – use sofosbuvir with ribavirin or sofosbuvir with simeprevir with or without ribavirin
- Patient with prior relapse, interferon-eligible – use sofosbuvir with PR
- Patient with prior relapse, interferon-ineligible – use sofosbuvir with ribavirin or sofosbuvir with simeprevir with or without ribavirin
- Treatment-experienced patient, history of non-response – use sofosbuvir with ribavirin or sofosbuvir with simeprevir with or without ribavirin
- Treatment-experienced patient, history of non-response to telaprevir or boceprevir – treat as recommended for HCV mono-infected patients

EASL recommends treating patients co-infected with HCV-HIV with the same regimens as those patients with HCV mono-infections.

WHO recommends treatment with PR. Patients may also be treated with PR and boceprevir, PR and telaprevir, PR and simeprevir, sofosbuvir and PR, or sofosbuvir and ribavirin.

Patients with liver cirrhosis

In treatment-naïve patients, AASLD recommends the same regimens as for patients without cirrhosis. In patients with decompensated cirrhosis, a combination of sofosbuvir and ribavirin is recommended.

EASL recommends an interferon-free regimen in patients with compensated cirrhosis. An interferon-based regimen may also be considered in patients who can tolerate it.

Guidelines published in 2013

Treatment-naïve patients

SIGN recommends triple therapy with PR and a protease inhibitor.

Treatment-experienced patients

SIGN recommends triple therapy with PR and a protease inhibitor.

Treatment of patients with relapse or treatment failure

Treatment with a protease inhibitor based regimen is recommended by SIGN.

HCV-HIV co-infection

The British HIV Association[16] recommends a treatment of triple therapy of telaprevir or boceprevir in combination with PR

SIGN recommends that treatment which includes a protease inhibitor be considered. Treatment-naïve patients who cannot use a protease inhibitor should consider treatment with PR.

Liver cirrhosis

SIGN recommends that patients with compensated cirrhosis be considered for therapy, unless contraindicated.

Limitations

The guidelines published in 2013 were written before the newer CHC agents (simeprevir and sofosbuvir) were approved and these guidelines may be outdated and not reflective of current clinical practice.

Despite being based on the same body of evidence, the 2014 guidelines have some differences in their recommendations. Specifically, whereas EASL recommends that treatment of patients with METAVIR F2 may be justified and that initiation of treatment of patients with METAVIR F0 and F1 should be individualized, AASLD recommends delaying treatment in these patients. Furthermore, WHO recommends treatment with telaprevir or boceprevir, whereas EASL and AASLD do not have recommendations that include treatment with these two drugs.

The WHO guidelines are intended for low and middle income countries and some recommendations would have taken resource use into consideration. The recommendations may not be applicable to Canadians.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

In this review of treatment options for patients with genotype 1 CHC, five high quality evidence-based guidelines were published since 2011. Two guidelines were published in 2013 and three were published in 2014. With the landscape of CHC treatment changing rapidly as new medications are constantly being discovered, the 2013 guidelines differed in its recommendations from the 2014 guidelines and they may no longer be of clinical value.

The 2014 guidelines recommended a combination of sofosbuvir or simeprevir with PR or with ribavirin alone (without peg-interferon) depending on interferon-eligibility. A combination of sofosbuvir and simeprevir was another treatment option. Daclatasvir (not marketed in Canada) in combination with PR or with sofosbuvir was also mentioned as treatment options by EASL. Treatment of HCV-HIV co-infected patients was similar to HCV mono-infected patients. Whereas the WHO guidelines recommended telaprevir or boceprevir in combination with PR in treatment naïve patients and in HCV-HIV co-infected patients, AASLD clearly stated that it did not recommend this treatment regimen for any patient. The rationale was that this regimen had relatively poor efficacy, required a prolonged duration of therapy (48 weeks), and had a poor side effect profile.

These recommendations are likely to change as drug trials are completed and new medications are approved. Decision-makers and clinicians may wish to periodically check for revised versions of these guidelines.

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REFERENCES

1. Kamal SM. Acute hepatitis C: a systematic review. Am J Gastroenterol. 2008 May;103(5):1283-97.

2. Maheshwari A, Ray S, Thuluvath PJ. Acute hepatitis C. Lancet. 2008 Jul 26;372(9635):321-32.

3. Maheshwari A, Thuluvath PJ. Management of acute hepatitis C. Clin Liver Dis. 2010 Feb;14(1):169-76.

4. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, 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 Sep 22;358(9286):958-65.

5. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002 Sep 26;347(13):975-82.

6. Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1195-206.

7. Myers RP, Ramji A, Bilodeau M, Wong S, Feld JJ. An update on the management of hepatitis C: consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol [Internet]. 2012 Jun [cited 2014 May 29];26(6):359-75. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3378284/pdf/cjg26359.pdf

8. Summary basis of decision (SBD) for PrIncivek™ [Internet]. Ottawa: Health Canada; 2012. [cited 2014 Jun 20]. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2012_incivek_142482-eng.php#a2

9. Summary basis of decision (SBD) for PrVictrelis™ [Internet]. Ottawa: Health Canada; 2011. [cited 2014 Jun 20]. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2011_victrelis_141556-eng.php#a2

10. Summary basis of decision (SBD) for PrGalexos [Internet]. Ottawa: Health Canada; 2014. [cited 2014 Jun 20]. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_galexos_164021-eng.php

11. Summary basis of decision (SBD) for PrSovaldi [Internet]. Ottawa: Health Canada; 2014. [cited 2014 Jun 20]. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_sovaldi_165043-eng.php

12. Brouwers M, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in healthcare [Internet].The AGREE Research Trust; 2009 May; updated Sept 2013. [cited 2014 May 7]. Available from: http://www.agreetrust.org/wp-content/uploads/2013/10/AGREE-II-Users-Manual-and-23-item-Instrument_2009_UPDATE_2013.pdf

13. American Association for the Study of Liver Diseases. Recommendations for testing, managing, and treating hepatitis C [Internet]. Alexandria (VA): AASLD; 2014. [cited 2014 Jun 3]. Available from: http://www.hcvguidelines.org/full-report-view

14. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2014 [Internet]. Geneva: The Association; 2014 May 9. [cited 2014 May 26]. Available from: http://files.easl.eu/easl-recommendations-on-treatment-of-hepatitis-C.pdf

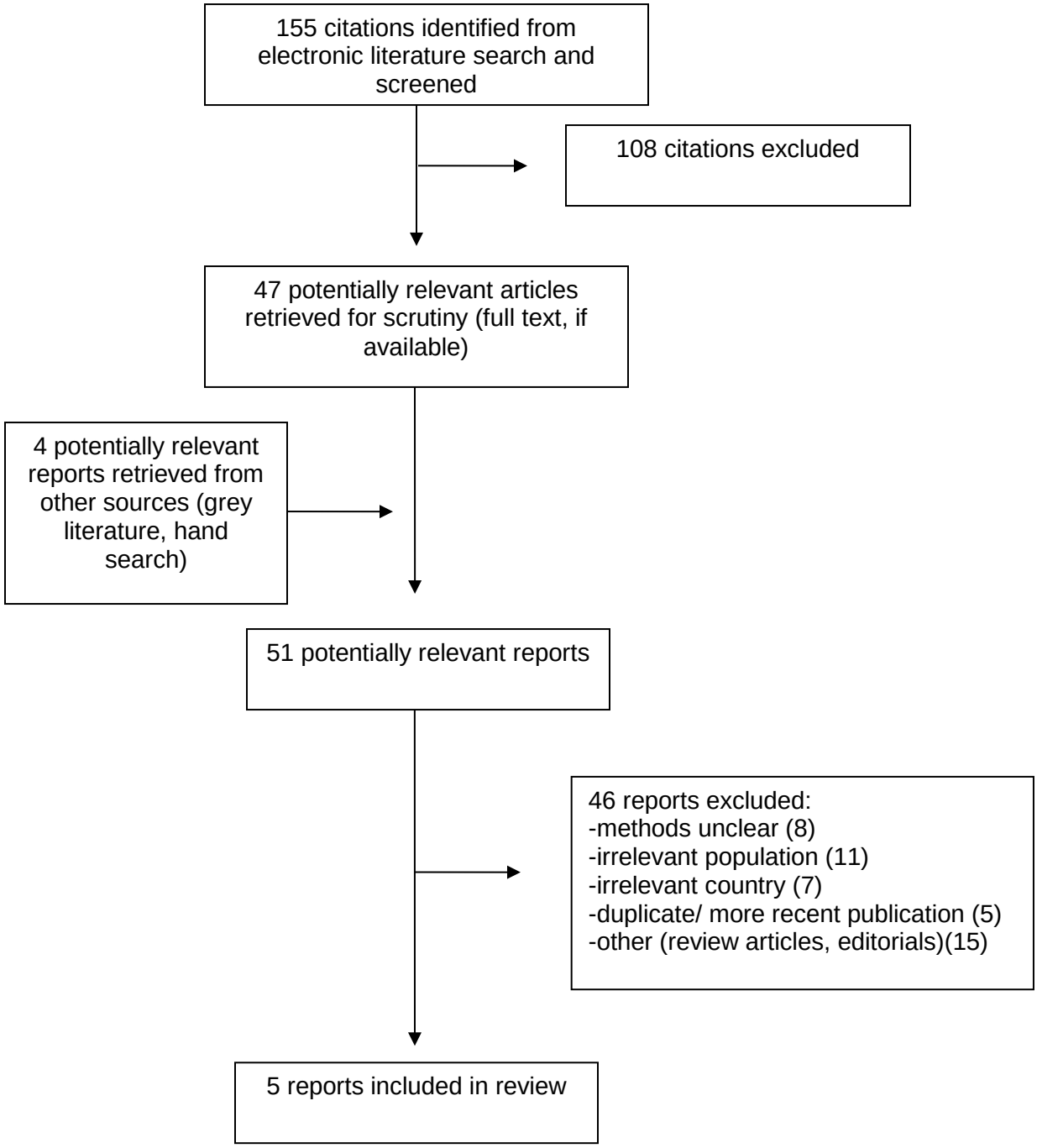
15. World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection [Internet]. Geneva: WHO; 2014. [cited 2014 Jun 3]. Available from: http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf?ua=1&ua=1

16. Wilkins E, Nelson M, Agarwal K, Awoyemi D, Barnes E, Bhagani S, et al. British HIV Association guidelines for the management of hepatitis viruses in adults infected with HIV 2013. HIV Med. 2013 Nov;14 Suppl 4:1-71.

17. Scottish Intercollegiate Guidelines Network. Management of hepatitis C: a national clinical guideline [Internet]. Edinburgh, Scotland: SIGN; 2013. [cited 2014 Jun 3]. (SIGN 133). Available from: http://www.sign.ac.uk/pdf/sign133.pdf

18. European Association for Study of Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. J Hepatol [Internet]. 2014 Feb [cited 2014 May 29];60(2):392-420. Available from: http://www.easl.eu/assets/application/files/bdb06ff135c7ccb_file.pdf

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Additional Information

Methods for Guidelines Development Unclear (unclear if a systematic review of the literature was done)

Italian Association for the Study of the Liver (AISF), Coco B, Caraceni P, Aghemo A, Bitetto D, Bruno R, et al. Triple therapy with first-generation protease inhibitors for patients with genotype 1 chronic hepatitis C: recommendations of the Italian Association for the Study of the Liver (AISF). Dig Liver Dis. 2014 Jan;46(1):18-24.

Miller MH, Agarwal K, Austin A, Brown A, Barclay ST, Dundas P, et al. Review article: 2014 UK consensus guidelines - hepatitis C management and direct-acting anti-viral therapy. Aliment Pharmacol Ther. 2014 Apr 22.

Hull M, Klein M, Shafran S, Tseng A, Giguere P, Cote P, et al. CIHR Canadian HIV Trials Network Coinfection and Concurrent Diseases Core: Canadian guidelines for management and treatment of HIV/hepatitis C coinfection in adults. Can J Infect Dis Med Microbiol [Internet]. 2013 [cited 2014 May 23];24(4):217-38. Available from: http://www.pulsus.com/pdfs/15871_hull.pdf

Lagging M, Duberg AS, Wejstal R, Weiland O, Lindh M, Aleman S, et al. Treatment of hepatitis C virus infection in adults and children: updated Swedish consensus recommendations. Scand J Infect Dis. 2012 Jul;44(7):502-21.

Leroy V, Serfaty L, Bourliere M, Bronowicki JP, Delasalle P, Pariente A, et al. Protease inhibitor-based triple therapy in chronic hepatitis C: guidelines by the French Association for the Study of the Liver. Liver Int. 2012 Nov;32(10):1477-92.

Myers RP, Ramji A, Bilodeau M, Wong S, Feld JJ. An update on the management of hepatitis C: consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol [Internet]. 2012 Jun [cited 2014 May 23];26(6):359-75. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3378284

Yee HS, Chang MF, Pocha C, Lim J, Ross D, Morgan TR, et al. Update on the management and treatment of hepatitis C virus infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. Am J Gastroenterol. 2012 May;107(5):669-89.

Ramachandran P, Fraser A, Agarwal K, Austin A, Brown A, Foster GR, et al. UK consensus guidelines for the use of the protease inhibitors boceprevir and telaprevir in genotype 1 chronic hepatitis C infected patients. Aliment Pharmacol Ther. 2012 Mar;35(6):647-62.

APPENDIX 3: Summary of Guideline Characteristics

Table 3.1: Evidence-based Guideline Characteristics

Author, year, origin	Objective of guideline	Evidence collection, selection and synthesis
American Association for The Study of Liver Disease(AASLD)		
AASLD 2014[13] US	To provide up-to-date recommendations to health care practitioners on the optimal screening, management, and treatment for adults with HCV infection in the United States, considering the best available evidence.(page 4)	Guidelines were developed by an expert panel.(page 4) Data from the following sources were considered: research published in the peer-reviewed literature or presented at major national or international scientific conferences, safety warnings from FDA or other regulatory agencies or from manufacturers, drug interaction data, prescribing information from FDA-approved products, and registration data for new products under FDA review. Inclusion criteria for literature search: articles published in English from 2010 to November 2013 (page 6)
European Association for the Study of the Liver (EASL)		
EASL 2014[14] Europe	To assist physicians and other healthcare providers, as well as patients and other interested individuals, in the clinical decision-making process by describing the optimal management of patients with acute and chronic HCV infections (page 1)	The guidelines were developed by a panel of experts chosen by their Governing Board. The recommendations were peer-reviewed by external expert reviewers and approved by the Governing Board. The guidelines were based on evidence from existing publications, and, if evidence was unavailable, the experts' personal experiences and opinion. (page 1) Data collected from PubMed and Cochrane database searches. (page 1)
World Health Organization (WHO)		
WHO 2014[15] International	To provide evidence-based recommendations on screening for HCV infection, and the care and treatment of persons with HCV infection (page 12)	The guidelines were developed by a Guidelines Development Group. (pages 7 and 42) Systematic reviews and meta-analyses of the primary literature were conducted to address the research questions and patient-important outcomes. Criteria for inclusion and exclusion of literature (e.g. study design, sample size, duration of follow up) for the reviews were based on the evidence needed and available to answer the research questions. Existing national and international guidelines were also evaluated. (pages 14 and 39)

Author, year, origin	Objective of guideline	Evidence collection, selection and synthesis
British HIV Association		
Wilkins et al.,2013[16] Britain	To provide guidance on best clinical practice in the treatment and management of adults with HIV and viral hepatitis co-infection (page 6)	The guideline was developed by a Writing Group comprising professional group members and an elected community representative.(page 6) The literature search dates were 1 January 2009 to 30 October 2012, and included Medline, Embase and the Cochrane library. Abstracts from selected conferences were searched between 1 January 2009 and 30 October 2012. For each topic and health care question, evidence was identified and evaluated by Guideline Writing Group members with expertise in that field. (page 6 and Appendix II)
Scottish Intercollegiate Guidelines Network (SIGN)		
SIGN 2013[17] Scotland	To provide evidence based recommendations covering all stages of the patient care pathway; screening, testing, diagnosis, referral, treatment, care and follow up of infants, children and adults with, or exposed to HCV infection (page 2)	SIGN guidelines were developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence.(page 44) A systematic review of the literature was carried out using an explicit search strategy. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2006-2012. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. (page 43)

FDA=Federal Drug Administration, HCV=hepatitis C virus, US=United States

Table 3.2: Grading of Recommendations

Guideline	Level of Recommendation	Level of Evidence
AASLD[13] (page 8)	**"Class I**: conditions for which there is evidence and or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective **Class II**: conditions for which there is conflicting evidence and or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment **Class IIa**: weight of evidence and or opinion is in favour or usefulness and efficacy **Class IIb**: usefulness and efficacy are less well established by evidence and or opinion **Class III**: conditions for which there is evidence and or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful"	**"Level A**: data derived from multiple RCTs or meta-analyses **Level B**: data derived from a single randomized trial or non-randomized studies **Level C**: consensus opinion of experts, case studies, or standard of care"
EASL[14,18] (page 2)	**"Grade 1**: factors influencing the strength of the recommendation included the quality of the evidence, presume patient-important outcomes, and cost (Strong) **Grade 2**: variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption (Weak)"	**"Level A**: further research is very unlikely to change our confidence in the estimate of effect (High) **Level B**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate (Moderate) **Level C**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change in estimate is uncertain. (Low)"

Guideline	Level of Recommendation	Level of Evidence
WHO[15] (page 40)	**"Strong**: the panel was confident that the benefits of the intervention outweighed the risks **Conditional**: the benefits of the intervention probably outweighed the risks"	**"High**: we are very confident that the true effect lies close to that of the estimate of the effect **Moderate**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect **Very low**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect"
British HIV Association[16] (Appendix I)	**"Grade 1**: strong recommendation to do (or not do) something, where benefits clearly outweigh risks (or vice versa) for most, if not all, patients. **Grade 2**: weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Alternative approaches or strategies may be reasonable depending on the individual patient's circumstances, preferences and values."	**"Grade A:** evidence means high-quality evidence that comes from consistent results from well-performed RCTs, or overwhelming evidence from another source (such as well-executed observational studies with consistent strong effects and exclusion of all potential sources of bias). Grade A implies confidence that the true effect lies close to the estimate of the effect. **Grade B:** evidence means moderate-quality evidence from randomised trials that suffers from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with specific strengths such as observational studies with consistent effects and exclusion of the majority of the potential sources of bias. **Grade C** evidence is low-quality evidence from controlled trials with several serious limitations, or observational studies with limited evidence on effects and exclusion of most potential sources of bias. **Grade D** evidence is based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there can be little confidence in the effect estimate."

Guideline	Level of Recommendation	Level of Evidence
SIGN[17] (after cover page)	**"Grade A**: at least one meta-analysis, systematic review, or RCT rated as 1_{++}, and directly applicable to the target population; *or* a body of evidence consisting principally of studies rated as 1_{+}, directly applicable to the target population, and demonstrating overall consistency of results **Grade B**: a body of evidence including studies rated as 2_{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* extrapolated evidence from studies rated as 1_{++} or 1_{+} **Grade C**: a body of evidence including studies rated as 2_{+},directly applicable to the target population and demonstrating overall consistency of results; *or e*xtrapolated evidence from studies rated as 2_{++} **Grade D**: evidence level 3 or 4; or extrapolated evidence from studies rated as 2_{+}"	**"Level 1++**: high quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias **Level 1+**: well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias **Level 1 -**: meta-analyses, systematic reviews, or RCTs with a high risk of bias **Level 2++**: high quality systematic reviews of case control or cohort studies; high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal **Level 2+**: well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal **Level 2 -**: case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal **Level 3**: case reports, case series **Level 4**: expert opinion"

RCT=randomized controlled trial

APPENDIX 4: Summary of Critical Appraisal

Table 4.1: Tabular Description of Strengths and Limitations of Guidelines using AGREE II

	AASDL	EASL	WHO	British	SIGN
Overall objectives of guideline is described					
	Yes	**Yes**	**Yes**	**Yes**	**Yes**
Health questions covered by the guideline is described					
	Yes	**Yes**	**Yes**	**Yes**	**Yes**
Population to whom guidelines is meant to apply is described					
	Yes	**Yes**	**Yes**	**Yes**	**Yes**
Guidelines development group includes all relevant professional groups					
	Yes	Unclear	**Yes**	**Yes**	**Yes**
Views and preferences of target population were sought					
	No	No	**Yes**	**Yes**	**Yes**
Target users of guidelines is defined					
	Yes	**Yes**	**Yes**	**Yes**	**Yes**
Systematic methods are used to search for evidence					
	Partial	Partial	**Yes**	**Yes**	**Yes**
Criteria for selecting evidence are described					
	Partial	No	**Yes**	**Yes**	No
Strengths and limitations of the body of evidence are described					
	No	**Yes**	**Yes**	No	No
Methods for formulation of the recommendations are described					
	Yes	**Yes**	**Yes**	**Yes**	**Yes**
Health benefits, side effects and risks have been considered in formulating the recommendations					
	Yes	**Yes**	**Yes**	**Yes**	**Yes**
There is an explicit link between the recommendation and the supporting evidence					
	Yes	**Yes**	**Yes**	**Yes**	**Yes**
Guidelines has been externally reviewed by experts prior to publication					
	Yes	**Yes**	**Yes**	**Yes**	**Yes**
A procedure for updating the guideline is provided					
	Yes	Partial	Partial	**Yes**	**Yes**
Recommendations are clearly presented					
	Yes	**Yes**	**Yes**	Partial	Partial
Applicability of guidelines is discussed					
	No	Partial	**Yes**	**Yes**	**Yes**
Funding body is stated					
	Yes	No	**Yes**	No	No
Conflict of interest of group members is stated					
	Yes	**Yes**	**Yes**	**Yes**	**Yes**

APPENDIX 5: Summary of Recommendations for Treatment of Genotype 1 CHC

Table 5.1: American Association for The Study of Liver Disease[13]

Population	Recommendations
Treatment naïve	
IFN-eligible	Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly peg-IFNα for 12 weeks (page 30) **Rating: Class I, Level A**
IFN-eligible with: HCV genotype 1b or HCV genotype 1a infection in whom the Q80K polymorphism is not detected prior to treatment	Daily simeprevir (150 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly peg-IFNα for 24 weeks (page 32) **Rating: Class IIa, Level A**
IFN-ineligible	Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg] for 12 weeks (page 31) **Rating: Class I, Level B**
Non-responders*	
regardless of IFN eligibility or subtype	Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 12 weeks (page 45) **Rating: Class IIa, Level B**
Alternative treatments	
IFN-eligible, regardless of sub-type	Daily sofosbuvir (400 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly peg-IFNα for 12 to 24 weeks (pages 46 and 47) **Rating: Class IIb, Level C**
INF-eligible(subtype not specified)	Daily simeprevir (150 mg) for 12 weeks plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) and weekly peg-IFNα for 48 weeks (All patients with cirrhosis who are receiving simeprevir should have well compensated liver disease.) (page 47) **Rating: Class IIa, Level A**
IFN-ineligible, regardless of sub-type	Daily sofosbuvir (400 mg) for 24 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks (page 47) **Rating: Class IIb, Level C**
HCV- HIV co infection**	
Treatment-naive and prior relapser	<u>INF-eligible</u> Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg] daily) plus weekly peg-IFNα for 12 weeks (page 71) **Rating: Class I, Level B** <u>IFN ineligible or unwilling to receive IFN</u> Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg] daily) for 24 weeks (page 71) **Rating: Class I, Level B** Sofosbuvir (400 mg once daily) plus simeprevir (150 mg once daily), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg] daily) for 12 weeks (page 71) **Rating: Class IIa Level C**

Population	Recommendations
treatment-experienced patients with a history of PR nonresponse regardless of IFN eligibility	Sofosbuvir (400 mg once daily) plus simeprevir (150 mg once daily) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg] daily) (page 72) **Rating: Class IIa, Level C**
treatment-experienced patients with a history of PR + TEL or BOC nonresponse	Treat as recommended for HCV-mono infected individuals (page 72) **Not graded**
Alternative treatments	
treatment-naive or treatment-experienced (prior PR relapse)	<u>IFN-eligible</u> Simeprevir (150 mg once daily) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg] daily) plus weekly peg-IFNα for 24 weeks in persons with either HCV genotype 1b or HCV genotype 1a infection in whom the Q80K polymorphism is not detected prior to treatment (page 75) **Rating: Class IIa, Level B**
	<u>ineligible or unwilling to receive IFN</u> None (page 75)
treatment-experienced (PR non responders)	<u>IFN-eligible</u> Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg] daily) plus weekly peg-IFNα for 12 weeks (page 75) **Rating: Class IIb, Level C**
	<u>IFN-ineligible</u> Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg] daily) for 24 weeks (page 75) **Rating: Class IIb, Level C**
Liver cirrhosis (page 64)	
treatment naive	Same treatment as recommended for patients without cirrhosis. **Rating: Class I, Level A**
patients with any HCV genotype who have decompensated cirrhosis who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.	Daily sofosbuvir (400 mg) plus weight-based RBV (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks **Rating: Class IIb, Level B**
Timing of treatment initiation (page 45)	
In many instances it may be advisable to delay treatment for some patients with documented early fibrosis stage (F 0-2), because waiting for future highly effective, pangenotypic, combinations in IFN-free regimens may be prudent.	

BOC=boceprevir, HCV=hepatitis C, HIV=human immunodeficiency virus, INF=interferon, peg=pegylated, PR=peg-interferon + ribavirin, RBV=ribavirin, TEL=telaprevir

* retreatment of a person with chronic HCV infection in whom prior therapy has failed

**simeprevir should only be used with antiretroviral drugs with which it does not have significant interactions: raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir,emtricitabine, lamivudine, and abacavir

Table 5.2: European Association for the Study of the Liver[14]

Recommendations
Any Population - see within recommendations (pages 5-6)
Option 1 weekly peg-IFNα, daily weight-based RBV (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks **Recommendation A1**
Option 2 weekly peg-IFNα, daily weight-based RBV (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily simeprevir (150 mg) **Recommendation A1** · This combination is not recommended in patients infected with subtype 1a who have a detectable Q80K substitution in the NS3 protease sequence at baseline, as assessed by population sequencing **Recommendation A2** · Simeprevir should be administered 12 weeks in combination with PR. PR should then be administered alone for an additional 12 weeks (total treatment duration 24 weeks) in treatment-naïve and prior relapser patients, including cirrhotics, and for an additional 36 weeks (total treatment duration 48 weeks) in prior partial and null responders*, including cirrhotics **Recommendation B1**
Option 3 *Subtype 1b* weekly peg-IFNα, daily weight-based RBV (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily daclatasvir (60 mg) 24 weeks **Recommendation B1** · This combination should not be proposed to patients infected with subtype 1a, given the preliminary data available, pending results of on-going large-scale studies **Recommendation B1** · Daclatasvir should be administered 12 weeks in combination with PR. Daclatasvir should be continued in combination with PR an additional 12 weeks (total duration 24 weeks) in patients who do not achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10. PR should be continued alone between week 12 and 24 (total duration 24 weeks) in patients who achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10 **Recommendation B2**
Option 4 *IFN-intolerant or IFN-ineligible* daily weight-based RBV (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 24 weeks **Recommendation B2** · This combination should be proposed to these patients exclusively when no other IFN-free option is available **Recommendation B2**
Option 5 daily sofosbuvir (400 mg) and daily simeprevir (150 mg) for 12 weeks **Recommendation B1** · Preliminary results do not indicate a major advantage of adding RBV to this regimen. However, adding daily weight-based RBV (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis **Recommendation B1**

Recommendations
Option 6 daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients, including those who failed on a triple combination of PR and either TEL or BOC (pending data with 12 weeks of therapy in treatment-experienced patients) **Recommendation B1** · Preliminary results do not indicate a major advantage to adding RBV to this regimen. However, adding daily weight-based RBV (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis **Recommendation B1**
Retreatment of non-sustained virological responders (page 12)
Patients who failed on a regimen containing sofosbuvir as the only DAA can be retreated with a combination of sofosbuvir and simeprevir, or a combination of sofosbuvir and daclatasvir **Recommendation B1** Patients who failed on a regimen containing simeprevir, TEL or BOC as the only DAA can be retreated with a combination of sofosbuvir and daclatasvir **Recommendation B1** Patients who failed on a regimen containing daclatasvir as the only DAA can be retreated with a combination of sofosbuvir and simeprevir **Recommendation B** Patients who failed on a regimen containing sofosbuvir and simeprevir can be retreated with a combination of sofosbuvir and daclatasvir **Recommendation B1** Patients who failed on a regimen containing Sofosbuvir and daclatasvir can be retreated with a combination of sofosbuvir and simeprevir **Recommendation B1** Alternatively, patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/ or daclatasvir can wait until new treatment combinations are available if they do not need urgent therapy **Recommendation B1**
HCV - HIV co infection (page 5)
Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection **Recommendation A1** The same treatment regimens can be used in HIV-co infected patients as in patients without HIV infection, as the virological results of therapy are identical **Recommendation A1** The use of cobicistat-based regimens, efavirenz, delavirdine, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir, is not recommended in HIV-infected patients receiving simeprevir **Recommendation A1** The daily daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ ritonavir and to 90 mg daily in those receiving efavirenz **Recommendation B2**

Recommendations
No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs **Recommendation A2**
Liver cirrhosis (page 15)
Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short- to mid-term complications **Recommendation A1** IFN-free combination regimens should be preferred in patients with compensated cirrhosis **Recommendation B1** If a 12-24 week IFN-based DAA regimen is considered tolerable in patients with compensated cirrhosis and good liver function and without cytopaenia, these patients can be treated as recommended above across genotypes **Recommendation B1**
Timing of treatment initiation (page 6)
All treatment-naïve and -experienced patients with compensated disease due to HCV should be considered for therapy **Recommendation A1** Treatment should be prioritized for patients with significant fibrosis (METAVIR score F3 to F4) **Recommendation A1** Treatment is justified in patients with moderate fibrosis (METAVIR score F2) **Recommendation A2** In patients with no or mild disease (METAVIR score F0-F1), the indication for and timing of therapy can be individualized **Recommendation B1** Patients with decompensated cirrhosis who are on the transplant list should be considered for IFN-free, ideally ribavirin-free therapy **Recommendation A1**

BOC=boceprevir, DAA=direct acting antivirals HCV=hepatitis C, HIV=human immunodeficiency virus, INF=interferon, peg=pegylated, PI=protease inhibitor, PR=peg-interferon + ribavirin, RBV=ribavirin, RVR=rapid virologic response, SVR=sustained virologic response, TEL=telaprevir

*non response not defined

Table 5.3: World Health Organization[15]

Treatment	Recommendations	Treatment Duration
Peg-interferon + ribavirin (pages 67 and 69)	PR is recommended rather than non-peg INF + RBV **Strong recommendation, moderate quality of evidence**	PR is recommended in persons with HCV mono-infection as well as those with HIV/HCV co-infection for 48 weeks. This can be extended to 72 weeks in those with a delayed virological response or shortened to 24 weeks in those with an RVR.
Telaprevir or boceprevir (page 70)	Treatment with TEL or BOC in combination with PR is recommended rather than PR alone. **Conditional recommendation, moderate quality of evidence**	TEL with PR for treatment-naïve patients for 24–48 weeks depending on the response to treatment (TEL is given for 12 weeks only). BOC with PR in treatment-naïve patients for 28–48 weeks depending on the response to treatment. Treatment duration in previously treated patients varies by previous response to treatment.
Sofosbuvir (page 74)	Sofosbuvir in combination with RBV with or without peg-INF is recommended rather than PR alone (or no treatment in patients who cannot tolerate INF) **Strong recommendation, high quality evidence**	*INF-eligible*: Sofosbuvir + PR for 12 weeks *IFN-intolerant*: Sofosbuvir + RBV for 24 weeks
Simeprevir (page 78)	Simeprevir in combination with PR is recommended for persons with genotype 1b and genotype 1a without Q80K polymorphism rather than PR alone. **Strong recommendation, high quality evidence**	Simeprevir + PR for 12 weeks followed by an additional 12 weeks of PR for a total of 24 weeks treatment for all treatment-naive and prior relapsed patients. Prior non-responder* patients (including partial or null-responders) should undergo an additional 36 weeks of PR for a total of 48 weeks of treatment.
HCV - HIV co infection (page 91)		
HCV infection among persons with HIV co-infection can be treated with PR (see above). These persons can also be treated with PR and BO, TEL or simeprevir and may also be treated with sofosbuvir + RBV or sofosbuvir + PR. Simeprevir is not recommended to be used with several HIV treatment regimens, including cobistat, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz, nevirapine, delavirdine, etravirine and any HIV PI-containing regimen		
Liver cirrhosis (page 96)		
Treatment of HCV infection with IFN-containing regimens must be commenced before the onset of decompensated disease as it may precipitate liver failure and death if administered at this stage.		

BOC=boceprevir, INF=interferon, HCV=hepatitis C, HIV=human immunodeficiency virus, INF=interferon, peg=pegylated, PI=protease inhibitor, PR=peg-interferon + ribavirin, RBV=ribavirin, RVR=rapid virologic response, SVR=sustained virologic response, TEL=telaprevir

*Non-response is defined as detectable HCV RNA throughout treatment

Table 5.4: British HIV Association[16]

Recommendations (HCV-HIV co infection, pages 15 and 51)	**Treatment duration**
Where there is a current clinical need for treatment (i.e., Metavir F4/cirrhosis), or if the patient wishes to be treated, the standard of care is triple therapy with PR and either TEL or BOC **Recommendation 1C** Non-cirrhotic patients who were previously null responders, partial responders or who experienced breakthrough should, wherever possible, wait for the availability of INF-sparing regimens or INF-based regimens including at least two new agents. For patients with non-cirrhotic disease, there is the option to defer treatment until newer funded therapies or a suitable clinical trial become available.	We recommend 48 weeks of total treatment with a TEL- or BOC-based regimen for patients who do not have cirrhosis **Recommendation 1C** We recommend a total of 48 weeks of treatment in patients with cirrhosis and for those who do not achieve an RVR.

BOC=boceprevir, HIV=human immunodeficiency virus, INF=interferon, RVR=rapid virologic response, TEL=telaprevir

Table 5.5: Scottish Intercollegiate Guidelines Network[17]

Population	**Recommendations***	**Treatment duration** (page 25)
All patients (page 22)	All patients with chronic HCV infection should be considered for antiviral therapy. **Recommendation A**	
Mild CHC (page 26)	Patients with mild CHC should be considered for treatment. **Recommendation B**	
Treatment naïve (pages 23 and 25)	All treatment-naive patients should be considered for treatment with peg-IFN and weight-based RBV with the addition of a protease inhibitor as triple therapy. **Recommendation A** Response-guided therapy can only be used in treatment-naive patients and previous treatment relapsers who are not cirrhotic. **Recommendation A**	The optimal duration of treatment is 48 weeks. **Level 1^{++} Evidence** Patients who fail to achieve an EVR at 12 weeks should be considered for cessation of treatment. **Recommendation A** Patients with an EVR at 12 weeks should continue treatment for 48 weeks. Those who are still HCV RNA positive at 24 weeks should discontinue treatment. **Recommendation A**
Treatment experienced (page 23)	All treatment-experienced patients should be considered for treatment with peg-IFN and weight-based RBV with the addition of a protease inhibitor as triple therapy. **Recommendation A**	

Population	Recommendations*	Treatment duration (page 25)
Relapse or failed treatment (pages 23 and 33)	Response-guided therapy can only be used in treatment-naive patients and previous treatment relapsers who are not cirrhotic. **Recommendation A** Patients who have had unsuccessful treatment with non-peg IFN and ribavirin should be considered for peg-IFN and RBV retreatment. **Recommendation D** Patients who have had any unsuccessful treatment should be considered for treatment with a protease inhibitor based regimen. **Recommendation A**	Treatment-naïve patients and minimal or no fibrosis low viral load (less than 400,000 IU/ml), who achieve an RVR following a lead in with peg-IFN and weight-based RBV for four weeks can be considered for 24 weeks of treatment without the addition of a protease inhibitor. **Recommendation B**
HCV - HIV co infection (pages 26 and 27)	Co-infected patients should be considered for treatment with a regimen which includes an HCV protease inhibitor. **Recommendation C** Treatment-naïve patients who are unsuitable for treatment with a regimen which includes HCV protease inhibitors should be considered for treatment with peg-IFN and weight-based RBV for 48-72 weeks depending on viral response. **Recommendation B**	
Liver cirrhosis** (page 34)	Patients with compensated cirrhosis should be considered for therapy, unless contraindicated. **Recommendation A**	

EVR=early viral response, HCV=hepatitis C virus, HIV=human immunodeficiency virus, INF=interferon, peg=pegylated, RBV=ribavirin, RVR=rapid virologic response

*No direct comparison studies of boceprevir and telaprevir were identified, therefore neither drug can be recommended over the other. No evidence was identified suggesting that a particular peg-IFN should be used in combination with a particular protease inhibitor.

**There was insufficient evidence on the treatment of patients with HCV and decompensated cirrhosis to make a recommendation.