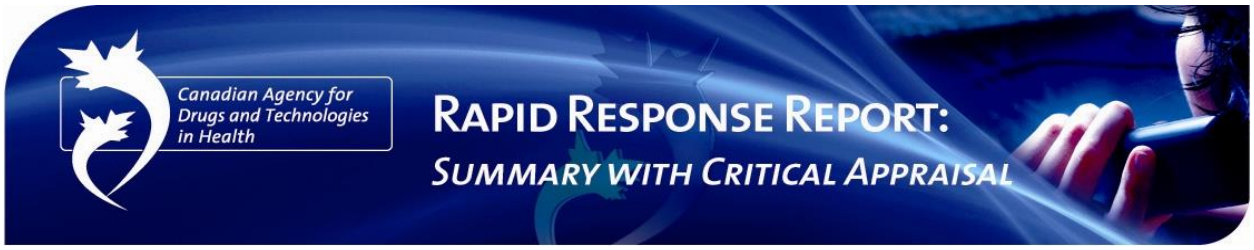

TITLE: Screening and Treatment for Patients with NS5A Resistance-Associated Variants of Hepatitis C Virus: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

DATE: 27 June 2016

CONTEXT AND POLICY ISSUES

Hepatitis C virus (HCV) infection is a serious health problem worldwide.[1] It is estimated that approximately 150 to 170 million individuals worldwide are infected with HCV.[2,3] Greater than 350,000 deaths occur annually due to HCV related complications.[2,3] At the end of 2011, it was estimated that 220,697 to 245,987 Canadians were living with chronic HCV infection, which is equivalent to 0.6% to 0.7% of the total Canadian population.[4] Based on 2012 national surveillance data, the rate of HCV diagnoses has declined steadily.[5] Chronic HCV infection is the leading cause of cirrhosis, hepatocellular carcinoma, and other liver complications.[2,6] Although the number of new cases detected has been declining, it is projected that morbidity and mortality due to HCV infection will continue to rise in future years.[6] It is estimated that 50% to 75% of individuals currently infected with HCV are undiagnosed and are untreated, and many of them will have progression to cirrhosis, hepatocellular carcinoma or other liver complications. HCV has several genotypes (GTs) and genotype 1 (GT 1) is most prevalent.[5,7,8] In Canada, among those infected with HCV, 65% have GT 1 (56% GT 1a and 33% GT 1b), 14% have GT 2, 20% have GT 3 and GT 4, 5, and 6 are rare (<5% of HCV cases).[5,9]

Treatment for HCV infection includes interferon- (IFN) and ribavirin- (RBV) based therapy, and more recently, therapy with direct acting antivirals (DAAs) have been introduced. DAAs include NS3/4A inhibitors, NS5A inhibitors and NS5B inhibitors which respectively target three regions within the HCV genome: NS3/4A protease, and NS5A and NS5B RNA-dependent polymerase.[10]

NS5A inhibitors have a dual mechanism of action. They play a role in blocking the replication complex and inhibiting the release and assembly of viral particles.[11,12] NS5A inhibitors include daclatasvir (DCV), velpatasvir (VLV), ledipasvir (LDV), elbasvir (EBR), and ombitasvir (OMV).[12]

There is a suggestion that the presence of baseline resistance-associated variants (RAVs) in patients infected with HCV may affect the sustained virologic response (SVR) rates obtainable with therapy.[13,14] Prevalence of NS5A RAVs in patients infected with HCV is variable and has

been reported in the range between 1% and 23% from several studies[7,8,15-17] which were conducted in different countries, suggesting geographic variation. There is some debate as to whether HCV-infected patients should be tested or screened for the presence of baseline NS5A RAVs before initiating therapy with DAA.

The purpose of this report is to review the clinical effectiveness of HCV pharmacotherapies containing NS5A inhibitors in DAA–naive patients infected with HCV GT 1 and with NS5A RAVs at baseline and the cost-effectiveness of screening for these variants, and to review the evidence-based guidelines regarding the testing or screening and treatment of HCV infected patients with NS5A RAVs.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of hepatitis C pharmacotherapies containing NS5A inhibitors in direct-acting antiviral–naive patients infected with NS5A resistance-associated variants of hepatitis C virus at baseline?

2. What is the cost-effectiveness of screening for NS5A resistance-associated variants of hepatitis C virus?

3. What are the evidence-based guidelines regarding testing or screening and treatment for NS5A resistance-associated variants of hepatitis C virus?

KEY FINDINGS

The majority of the studies were on hepatitis C virus (HCV) genotype (GT) 1b patients treated with daclatasvir (DCV) plus asunaprevir (ASV). In general, for HCV GT 1b infected patients, who were treated with DCV+ASV, the proportion of patients achieving SVR12 was less in patients with NS5A resistance-associated variants (RAVs) at baseline, compared to those without NS5A RAVs.

There were limited studies on treatment regimens including velpatasvir, ledipasvir, elbasvir, and comparing SVR rates in patients infected with HCV GT 1, who had or did not have NS5A RAVs at baseline, hence definitive conclusions are difficult.

One guideline recommended that testing for resistance-associated variants that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors should be conducted for patients with HCV GT 1, regardless of subtype, who have compensated cirrhosis or reasons for urgent retreatment, and have failed either previous treatment with any HCV NS5A inhibitor or HCV protease inhibitor, simeprevir (SMV) plus sofosbuvir (SOF) (with no prior NS5A treatment). Another guideline recommended that patients with HCV GT 1b infection, who were being considered DCV+ASV treatment should be tested for NS5A RAVs prior to treatment initiation.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including MEDLINE via Ovid; Embase via Ovid, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. 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 30, 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients infected with HCV genotype 1
Intervention	Q1: Hepatitis C pharmacotherapies containing NS5A inhibitors (elbasvir, daclatasvir, ombitasvir, ledipasvir and velpatasvir) in direct-acting antiviral–naive patients infected with HCV genotype 1 with NS5A resistance-associated variants (M28, Q30, L31, Y93) Q2, Q3: Screening for NS5A resistance-associated variants (M28, Q30, L31, Y93) and subsequent treatment
Comparator	Q1: Hepatitis C pharmacotherapies containing NS5A inhibitors (elbasvir, daclatasvir, ombitasvir, ledipasvir and velpatasvir) in direct-acting antiviral–naive patients infected with HCV genotype 1 without NS5A resistance-associated variants Q2: No screening and usual care Q3: No comparator necessary
Outcomes	Q1: Treatment response (SVR12) Q2: Cost-effectiveness outcomes (e.g., cost per QALY) Q3: Evidence-based guidelines regarding screening and treatment for patients infected with HCV genotype 1 with NS5A resistance-associated variants (M28, Q30, L31, Y93)
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCT), non-randomized studies, economic studies, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011. Conference abstracts and posters were excluded. At the first level screening, if the abstract of the study did not mention NS5A resistance associated variants, the full text article was not retrieved for further scrutiny. Studies on populations including patients with prior DAA treatment were excluded if results were not presented separately for the DAA-naïve group, unless the proportion of prior DAA treated patients in the study population was < 10%. Studies on mixed populations of patients infected with HCV of different genotypes, were excluded if results were not separately presented for the GT 1 group.

Critical Appraisal of Individual Studies

The included pooled analysis was appraised using AMSTAR checklist,[18] randomized studies and observational studies were appraised using the Downs and Black checklist,[19] and guidelines were assessed with the AGREE II instrument.[20] Summary scores were not calculated for the included studies; rather, a narrative review of the strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 716 citations were identified in the literature search. Following screening of titles and abstracts, 680 citations were excluded and 36 potentially relevant reports from the electronic search were retrieved for full-text review. Six potentially relevant publications were retrieved from the grey literature and hand search. Of these 42 potentially relevant articles, 26 publications were excluded for various reasons, while 16 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection. The 16 publications were comprised of eight RCT reports,[6-8,13,16,21-23] five observational study reports,[3,17,24-26] one analysis[15] based on data from five studies, and two guidelines.[27,28] It should be noted that two reports[8,21] of the same RCT were included as the main results were reported in one report[8] with some additional details in a second report.[21] Findings from RCT reports were based on secondary analyses that were not accounted for in randomization. As such, these analyses are considered non-randomized and results are reported with observational studies.

Summary of Study Characteristics

Characteristics of the included clinical studies and guidelines are summarized below and details are available in Appendix 2, Tables A1 and A2.

Clinical Studies

Thirteen relevant studies,[3,6-8,13,15-17,22-26] reported in 14 publications, were identified. Of six studies published in 2016, three studies[3,8,25] were from Japan, and one study each was from the USA,[16] Germany,[13] and China.[24] Four studies were published in 2015; two studies were from the USA,[15,22] and two studies were multinational.[23,26] Two studies were published in 2014 and both studies[6,7] were from the USA. One study[17] published in 2013 was from Japan. All studies were

on adult patients infected with HCV GT 1. The numbers of patients in the studies varied between 43 and 988. In 11 studies,[3,6-8,13,15,16,22,23,25,26] mean or median age varied between 44 and 71 years, in one study[21] the age was reported as a range of 20 to 75 years, and in one study[26] age was not reported. All the studies included analyses comparing SVR rates in patients with baseline NS5A RAVs versus either those without NS5A RAVs at baseline, or the entire population (i.e. with and without NS5A RAVs). Treatment regimens were DCV+asunaprevir (ASV) in six studies,[3,7,15-17,25] DCV+ASV+becaluvir (BCV) in one study,[26] DCV+simeprevir (SMV) ± RBV in one study,[13] LDV+sofosbuvir (SOF) ±RBV in two studies,[6,8] VLV+SOF±RBV in one study,[22] and EBR+grazoprevir (GZR) in one study.[23] All (except one study[17]) reported on SVR at post-treatment week 12 (SVR12); this one study[17] did not specify the post treatment week and just mentioned SVR.

Guidelines

Two guidelines[27,28] on the management of patients with HCV were included. Both guidelines had a broad focus and contained some information on testing for NS5A RAVs. One guideline[27] was published by American Association for the Study of Liver Disease (AASLD) and the Infection Disease of America (IDSA) from USA in 2016 and one guideline[28] was published by the Korean Association for the Study of Liver disease (KASL) from Korea in 2016. Both guidelines were developed to provide guidance to healthcare providers involved in the treatment of patients with HCV. Both guidelines used a grading system to grade recommendations. Numerical values were used to classify the strength of recommendations, with lower numbers indicating higher strength and the level of evidence was graded from A to C with A indicating the highest level and then declining sequentially (Appendix 3, Table A3).

Summary of Critical Appraisal

Critical appraisal of the included clinical studies and guidelines is summarized below and details are available in Appendix 4, Tables A4 and A5.

Clinical studies

Pooled analysis:
The included report[15] which was a pooled analysis of five studies clearly stated the objective. It was unclear if a systematic review literature search was conducted. Details of article selection, data extraction, and characteristics of the individual studies were lacking. It was unclear if quality of the included studies was assessed, publication bias was explored, or if pooling was appropriate. The study was funded by industry.

Randomized Studies and Observational Studies:
All the included studies[3,6-8,13,16,17,22-26] clearly stated the objectives. The objectives of these studies, however were different from the research questions to be addressed in this report. These studies were included as they provided some insights to these research questions by providing findings from analyses (which were not specified a priori in the study methods). Inclusion and exclusion criteria were provided in all the studies except in one study[25] which was on consecutive patients, hence inclusion and exclusion criteria were not applicable. Patient characteristics, interventions and outcomes were described in all the studies. In all studies, conflicts of interest were mentioned. All of the studies had industry support.

Guidelines

The two included guidelines[27,28] clearly stated the scope and purpose. For both guidelines, the guideline development group included experts in hepatology and one guideline[27] the development group also included a HCV community representative. For both guidelines multiple databases were searched but the methods used for evidence selection and data extraction were unclear. Both guidelines used a grading system to grade recommendations. Cost implications were discussed to some extent in one guideline[27] but it was unclear if they were considered in formulating recommendations. In one guideline[28] cost implications were not discussed. Both guidelines were internally reviewed, and in addition one guideline[28] was externally reviewed and one guideline[27] was reviewed by the AASLD-IDSA Governing Board. All members of the guideline development group were required to provide disclosures of conflicts of interest.

Summary of Findings

What is the clinical effectiveness of hepatitis C pharmacotherapies containing NS5A inhibitors in direct-acting antiviral–naive patients infected with NS5A resistance-associated variants of hepatitis C virus at baseline?

Findings are summarized below and details are provided in Appendix 5, Tables A6.

Regimens including DCV

It was generally found that for patients with HCV GT1b infection who were treated with regimens with DCV+ASV, the proportion of patients who achieved SVR12 was smaller when the patients had the NS5A RAVs at baseline compared to those who did not have NS5A RAVs (Table 2). The proportion of patients with NS5A RAVs and achieving SVR12 varied between 38% and 42% (in four studies,[3,7,15,16]) and varied between 59% and 77% depending on the type of NS5A RAVs (in one study[25]). The proportion of patients without NS5A RAVs at baseline and achieving SVR12 varied between 88% and 99% (in five studies[3,15,16,24,25]). One study[17] reported results qualitatively and indicated a loose association between baseline NS5A RAVs and virologic outcome.

One study[26] showed that for treatment with DCV+ASV+BCV, the proportion of patients with NS5A RAVs who achieved SVR12 was 74% for HCV GT 1a and 100% for HCV GT 1b and the corresponding values were 89% and 98% respectively for the full population (those with and without NS5A RAVs; data for the group without NS5A RAVs were not available separately) (Table 3). One study[13] showed that for treatment with DCV+SMV±RBV, the proportion of patients with HCV 1b who achieved SVR12 was 50% for patients with NS5A RAVs and 91% for patients without NS5A RAVs (Table 3).

Two studies[7,16] also presented results of multivariate regression analyses of baseline factors showing that NS5A RAVs (at positions L31 and Y93) were negative predictors of SVR12 (Appendix 5, Table A6). Both studies used data from the same RCT but analyzed slightly different patient groups.

Table 2: SVR 12 achieved with treatment regimens including DCV+ASV

Study	Study type	Population	Treatment regimen	% of patients achieving SVR12	
				For patients with NS5A	For patients without NS5A
Iio,[3] 2016, Japan	Observational study, multicenter, 1 arm	chronic HCV-GT1b, treatment naïve and treatment experienced	DCV+ASV	48	88
Kao,[16] 2016,USA, HALLMARK DUAL study	RCT - only analysis results used	HCV-GT1b, treatment naïve or non-responders, intolerant or ineligible to prior IFN+RBV	DCV+ASV	39	90
Karino,[17] 2013, Japan	Observational study, phase 2, open label, 1 arm	HCV GT1b, non-responders or ineligible/ intolerant to prior IFN+RBV	DCV+ASV	loose association with a baseline NS5A polymorphism on virologic outcome	
Manns,[7] 2014, HALLMARK DUAL study	RCT, phase 3, multicenter - analysis	HCV-GT1b, treatment naïve or non-responders or ineligible/ intolerant to prior IFN+RBV	DCV+ASV	38 to 41	NR
McPhee,[15] 2015, USA	Analysis with data pooled from 5 studies (RCT and observational)	HCV-GT1b, treatment naïve and treatment experienced	DCV+ASV	39	94
Uchida,[25] 2016, Japan	Obsevational study, 1 arm, single center (consecutive patients)	HCV-GT1b, treatment naïve or non-responders or ineligible/ intolerant to prior IFN+RBV	DCV+ASV	83, 59, and 77 for NS5A-L31M, NS5A-Y93H, and NS5A-R30Q/H/L, respectively	95
Wei,[24] 2016, China	Observational, phase 3, open label,1 arm	HCV 1b infection, ineligible or intolerant to prior INF±RBV	DCV+ASV	42	99

ASV = asunaprevir, DCV = daclatasvir, GT = genotype, HCV = hepatitis C virus, RCT = randomized controlled trial, SVR = sustained viral response, SVR12 = SVR at post treatment w eek 12

Table 3: SVR 12 achieved with treatment regimens including DCV+ASV+BCV or DCV+SMV±RBV

Study	Study type	Population	Treatment regimen	% of patients achieving SVR12	
				For patients with NS5A	For patients without NS5A
Poordad,[26] 2015, multinational, UNITY 1	Observational, open label, 1-arm, multi-center	HCV-GT1, who were treatment naïve or treatment experienced	DCV+ASV+BCV	74 for GT 1a, 100 for GT 1b	89 for GT 1a, 98 for GT 1b (For all [i.e. w/ and w/o NS5A])
Zeuzem,[13] 2016, Germany	RCT - only analysis results used	HCV GT1b treatment naïve or non-responders to prior PEG-INF+RBV treatment	DCV+SMV±RBV	50	91

ASV = asunaprevir, BCV = beclabuvir, DCV = daclatasvir, GT = genotype, HCV = hepatitis C virus, RBV = ribavirin, RCT = randomized controlled trial, SVR = sustained viral response, SVR12 = SVR at post treatment week 12

Regimens including LDV

For treatment with LDV+SOF±RBV, one study[8] showed the proportion of patients with HCV GT1 who achieved SVR12 was the same (99%) irrespective of the baseline NS5A RAV status (Table 4). Another study[6] showed that for treatment with LDV+SOF±RBV, the proportion of patients with HCV GT1 who achieved SVR12 was slightly less (90%) for patients with NS5A RAVs compared to the full population of those with and without NS5A RAVs (data for the group without NS5A RAVs were not available separately) (Table 4).

Regimens including VLV

One study[22] showed that for treatment with VLV+SOF, the proportion of patients with HCV GT1 who achieved SVR12 was 80% for patients with NS5A RAVs and 96% for patients without NS5A RAVs and for treatment with VLV+SOF+RBV, the corresponding values were 100% and 98%, respectively (Table 4).

Regimens including EBR

One study[23] showed that for treatment with EBR+GZR, the proportion of patients with HCV GT1a who achieved SVR12 was 58% for patients with baseline NS5A RAVs and 96% for patients without baseline NS5A RAVs and the corresponding values for patients with HCV GT 1b were 94% and 100% respectively (Table 4).

Additional information such as SVR values at different post treatment weeks, SVR12 values in different subgroups were available in some instances and are presented in the Appendix 5 Table A6.

Table 4. SVR 12 achieved with treatment regimens including LDV, VLV or EBR

Study	Study type	Population	Treatment	% of patients achieving SVR12	
				For patients with NS5A	For patients without NS5A
Kowdley,[6] 2014, USA, ION-3	RCT - only analysis results used	HCV-GT1, treatment naïve	LDV+SOF±RBV	90	95 For all [i.e. w/ and w/o NS5A]
Mizokami,[8] 2016, Japan	RCT - only analysis results used	HCV-GT1, who were treatment naïve or treatment experienced	LDV+SOF±RBV	99	99
Curry,[22] 2015, USA, ASTRAL 4	RCT - only analysis results used	HCV GT-1a,1b	VLV+SOF±RBV	80 for (VLV+SOF) 100 for (VLV+SOF +RBV)	96 for (VLV+SOF) 98 for (VLV+SOF+RBV)
Zeuzem,[23] 2015, multinational, C-EDGE	RCT - only analysis results used	HCV GT1, treatment naïve	EBR+GZR	58 for GT1a 94 for GT1b	94 for GT1a 100 for GT1b

EBR = beclabuvir, GT = genotype, GZR = grazoprevir, HCV = hepatitis C virus, LDV = ledipasvir, RBV = ribavirin, RCT = randomized controlled trial, SOF = sofosbuvir, SVR = sustained viral response, SVR12 = SVR at post treatment w eek 12, VLV = velpatasvir

What is the cost-effectiveness of screening for NS5A resistance-associated variants of hepatitis C virus?

No studies on the cost-effectiveness of screening for NS5A resistance-associated variants of hepatitis C virus, were identified.

What are the evidence-based guidelines regarding testing or screening and treatment for NS5A resistance-associated variants of hepatitis C virus?

Two relevant evidence-based guidelines[27,28] with some information on testing or screening and treatment for NS5A resistance-associated variants of HCV were identified. Findings are summarized below and details are provided in Appendix 6, Table A7.

AASLD-IDSA guideline[27]

This American guideline[27] recommended that for treatment-naïve patients with HCV GT 1a infection, who do not have cirrhosis or have compensated cirrhosis and in whom no baseline high fold-changes in NS5A RAVs for EBR are detected, should be treated with a daily fixed-dose combination of EBR (50 mg)/GZR (100 mg) for 12 weeks. (Class I, level A). For treatment-naïve patients with HCV GT 1a infection, who do not have cirrhosis or have compensated cirrhosis and in whom baseline high fold-change in NS5A RAVs for elbasvir are detected, should be treated with an alternate regimen of a daily fixed dose combination of EBR (50 mg)/GZR (100 mg) with weight based RBV for 16 weeks (Class IIa, Level B).

It was recommended that for patients with HCV GT 1a infection who do not have cirrhosis or who have compensated cirrhosis and who failed prior treatment with an HCV protease inhibitor plus PEG-IFN/RBV, and in whom no baseline high fold-change NS5A RAVs for elbasvir are detected, should be treated with a daily fixed-dose combination of EBR (50 mg)/GZR (100 mg) for 16 weeks (Class IIa, Level B).

It was recommended that testing for resistance-associated variants that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors should be conducted for patients with HCV GT 1, regardless of subtype, in whom previous treatment with any HCV NS5A inhibitors has failed, and who have compensated cirrhosis, or have reasons for urgent retreatment (Class IIb, Level C).

It was recommended that testing for resistance-associated variants that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors should be conducted for patients with HCV GT 1, regardless of subtype, in whom previous treatment with HCV protease inhibitor SMV+SOF has failed (no prior NS5A treatment), and who have compensated cirrhosis, or have reasons for urgent retreatment (Class IIb, Level C).

KASL guideline[28]

The Korean guideline[28] recommended that HCV GT 1b patients should be treated with DCV (60 mg) and ASV (200 mg) for 24 weeks and when considering DCV+ASV treatment, patients should be tested for NS5A RAVs L31F/I/M/V and/or Y93H prior to treatment. If for NS5A RAVs L31F/I/M/V and/or Y93H are present, it was recommended that an alternate treatment should be administered, though alternatives were not suggested.

Limitations

The included RCTs and observational studies had different objectives and were not designed to address the research questions relevant for this report. However, the reports contained some relevant data and analyses which have been presented here. It should be noted however, that these analyses had not been specified a priori in the study methods, hence the results of these analyses need to be interpreted with caution.

Not all findings from the analyses were exclusive. Data from Manns et al.[7] study were included in the analysis by McPhee et al.,[15] however results were expressed in different formats. The analyses by Kao et al.[16] and Manns et al.[7] used data from the same RCT but looked at different subgroups, however there was some overlap in the patient groups analyzed.

Most of the studies were on patients with HCV GT 1b infection, who were treated with DCV+ASV. There was sparse information regarding outcomes for HCV GT 1 patients with or without NS5A RAVs who were treated with regimens including LDV, EBR, or VLV. No relevant information regarding outcomes for HCV GT 1 patients with or without NS5A RAVs who were treated with regimens including OMV was identified.
Information on guidance regarding testing or screening and treatment for NS5A RAVs of HCV infection is sparse. Also the available recommendations were mostly based on low level of evidence

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Thirteen relevant studies,[3,6-8,13,15-17,22-26] reported in 14 publications, with analyses relevant for this report and two relevant guidelines[27,28] were identified

The majority of the studies were on HCV GT 1b patients treated with DCV+ASV. In general, for HCV GT 1b infected patients who were treated with DCV+ASV, the proportion of patients achieving SVR12 was lower in patients with the NS5A RAVs compared to those without NS5A RAVs. In one study[26] on HCV GT 1 patients treated with DCV+ASV+BCV, for the GT 1a subtype, the proportion of patients with NS5A RAVs at baseline who achieved SVR12 was less compared to the entire group of patients (with and without NS5A RAVs) and for the GT 1b subtype, the proportion of patients who achieved SVR12 were similar for the patient group with baseline NS5A RAVs and the entire patient group (i.e. with and without NS5A RAVs at baseline). In one study[13] on HCV GT 1b patients treated with DCV+SMV±RBV, the proportion of patients with NS5A RAVs at baseline, who achieved SVR12 was lower compared to those without NS5A RAVs.

There were few studies on regimens including LDV, VLV or EBR and comparing proportion of HCV GT 1 patients, with and without NS5A RAVs at baseline, who achieved SVR12 and definitive conclusions are difficult.

Two relevant evidence-based guidelines[27,28] regarding testing or screening and treatment for NS5A resistance-associated variants of HCV were identified. One guideline[27] recommended that testing for RAVs that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors should be conducted for patients with HCV genotype 1, regardless of subtype, who have compensated cirrhosis or reasons for urgent retreatment, and have failed either previous treatment with any HCV NS5A inhibitor or HCV protease inhibitor (with no prior NS5A treatment). One guideline[28] recommended that patients with HCV GT 1b infection, for whom DCV+ASV treatment is being considered, should be tested for NS5A RAVs prior to treatment initiation.

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ABBREVIATIONS

AASLD	American Association for the Study of Liver Disease
ASV	Asunaprevir
BCV	Beclabuvir
CI	Confidence interval
DAA	Direct-acting antiviral agent
DCV	Daclatasvir
EBR	Elbasvir
FU	Follow-up
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
GZR	Grazoprevir
GT	genotype
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IDSA	Infection Disease Society of America
IFN	Interferon
IU	International units
KASL	Korean Association for the Study of the Liver
LDV	Ledipasvir
LLOQ	lower limit of quantitation
NA	not applicable
NR	not re[ported
NS5A	Non-structural protein 5A
OMV	Ombitasvir
OR	Odds ratio
PCR	Polymerase chain reaction
PEG	Pegylated
RAM	Resistance associated mutation
RAP	Resistance associated polymorphism
RAS	Resistance associated substitution
RAV	Resistance-associated variant
RBV	Ribavirin
RNA	Ribonucleic acid
SD	Standard deviation
SMV	Simeprevir
SOF	Sofosbuvir
SVR	Sustained virological response
SVR4	Sustained virological response at post-treatment week 4
SVR8	Sustained virological response at post-treatment week 8
SVR12	Sustained virological response at post-treatment week 12
TVR	Telaprevir
USA	United States of America
VLV	Velpatasvir

REFERENCES

1. Murakami E, Imamura M, Hayes CN, Abe H, Hiraga N, Honda Y, et al. Ultradeep sequencing study of chronic hepatitis C virus genotype 1 infection in patients treated with daclatasvir, peginterferon, and ribavirin. Antimicrob Agents Chemother [Internet]. 2014 [cited 2016 Jun 6];58(4):2105-12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4023772

2. Premoli C, Aghemo A. Directly acting antivirals against hepatitis C virus: mechanisms of action and impact of resistant associated variants. Minerva Gastroenterol Dietol. 2016 Mar;62(1):76-87.

3. Iio E, Shimada N, Abe H, Atsukawa M, Yoshizawa K, Takaguchi K, et al. Efficacy of daclatasvir/asunaprevir according to resistance-associated variants in chronic hepatitis C with genotype 1. J Gastroenterol. 2016 May 28. [Epub ahead of print].

4. Challacombe L. The epidemiology of hepatitis C in Canada [Internet]. Toronto: CATIE; 2015. [cited 2016 Jun 23]. Available from: http://www.catie.ca/en/fact-sheets/epidemiology/epidemiology-hepatitis-c-canada

5. Myers RP, Shah H, Burak KW, Cooper C, Feld JJ. An update on the management of chronic hepatitis C: 2015 consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol Hepatol [Internet]. 2015 Jan [cited 2016 Jun 21];29(1):19-34. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4334064

6. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014 May 15;370(20):1879-88.

7. Manns M, Pol S, Jacobson IM, Marcellin P, Gordon SC, Peng CY, et al. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: A multinational, phase 3, multicohort study. The Lancet. 2014;384(9954):1597-605.

8. Mizokami M, Dvory-Sobol H, Izumi N, Nishiguchi S, Doehle B, Svarovskaia ES, et al. Resistance analyses of Japanese hepatitis C-infected patients receiving sofosbuvir or ledipasvir/sofosbuvir containing regimens in phase 3 studies. J Viral Hepat. 2016 May 15. [Epub ahead of print].

9. Drugs for chronic hepatitis C infection [Internet]. Ottawa: CADTH; 2015 Apr 10. (Therapeutic review). [cited 2016 Jun 21]. Available from: https://www.cadth.ca/drugs-chronic-hepatitis-c-infection

10. Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection. Updated version [Internet]. Geneva: World Health Organization; 2016 Apr. [cited 2016 Jun 21]. Available from: http://apps.who.int/iris/bitstream/10665/205035/1/9789241549615_eng.pdf?ua=1

11. Rossi LMG, Rahal P. Detection of hepatitis C virus resistant mutants in the era of direct acting antivirals. Am J Infect Dis. 2014;10(4):182-6.

12. Pockros PJ. Direct-acting antivirals for the treatment of hepatitis C virus infection. In: Post TW, editor. UpToDate [Internet]. Waltham (MA): UpToDate; 2016 May 11 [cited 2016 Jun 21]. Available from: www.uptodate.com Subscription required.

13. Zeuzem S, Hézode C, Bronowicki JP, Loustaud-Ratti V, Gea F, Buti M, et al. Daclatasvir plus simeprevir with or without ribavirin for the treatment of chronic hepatitis C virus genotype 1 infection. J Hepatol. 2016 Feb;64(2):292-300.

14. Pawlotsky JM. Hepatitis C virus resistance to direct-acting antiviral drugs in interferon-free regimens. Gastroenterology. 2016 Apr 11. [Epub ahead of print].

15. McPhee F, Suzuki Y, Toyota J, Karino Y, Chayama K, Kawakami Y, et al. High sustained virologic response to daclatasvir plus asunaprevir in elderly and cirrhotic patients with hepatitis C virus genotype 1b without baseline NS5A polymorphisms. Adv Ther [Internet]. 2015 Jul [cited 2016 Jun 2];32(7):637-49. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4522028/pdf/12325_2015_Article_221.pdf

16. Kao JH, Lee YJ, Heo J, Ahn SH, Lim YS, Peng CY, et al. All-oral daclatasvir plus asunaprevir for chronic HCV genotype 1b infection: a sub-analysis in Asian patients from the HALLMARK DUAL study. Liver Int. 2016 Mar 24. [Epub ahead of print].

17. Karino Y, Toyota J, Ikeda K, Suzuki F, Chayama K, Kawakami Y, et al. Characterization of virologic escape in hepatitis C virus genotype 1b patients treated with the direct-acting antivirals daclatasvir and asunaprevir. J Hepatol. 2013 Apr;58(4):646-54.

18. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2016 Jun 2];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

19. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2016 Jun 2];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

20. Brouwers M, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in healthcare. CMAJ [Internet]. 2010 Dec [cited 2016 Jun 2];182(18):E839-E842. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3001530/pdf/182e839.pdf

21. Mizokami M, Yokosuka O, Takehara T, Sakamoto N, Korenaga M, Mochizuki H, et al. Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. Lancet Infect Dis. 2015 Jun;15(6):645-53.

22. Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med. 2015 Dec 31;373(27):2618-28.

23. Zeuzem S, Ghalib R, Reddy KR, Pockros PJ, Ben Ari Z, Zhao Y, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. Ann Intern Med. 2015 Jul 7;163(1):1-13.

24. Wei L, Zhang M, Xu M, Chuang WL, Lu W, Xie W, et al. A phase 3, open-label study of daclatasvir plus asunaprevir in Asian patients with chronic hepatitis C virus genotype 1b infection who are ineligible for or intolerant to interferon alfa therapies with or without ribavirin. J Gastroenterol Hepatol. 2016 Mar 22. [Epub ahead of print].

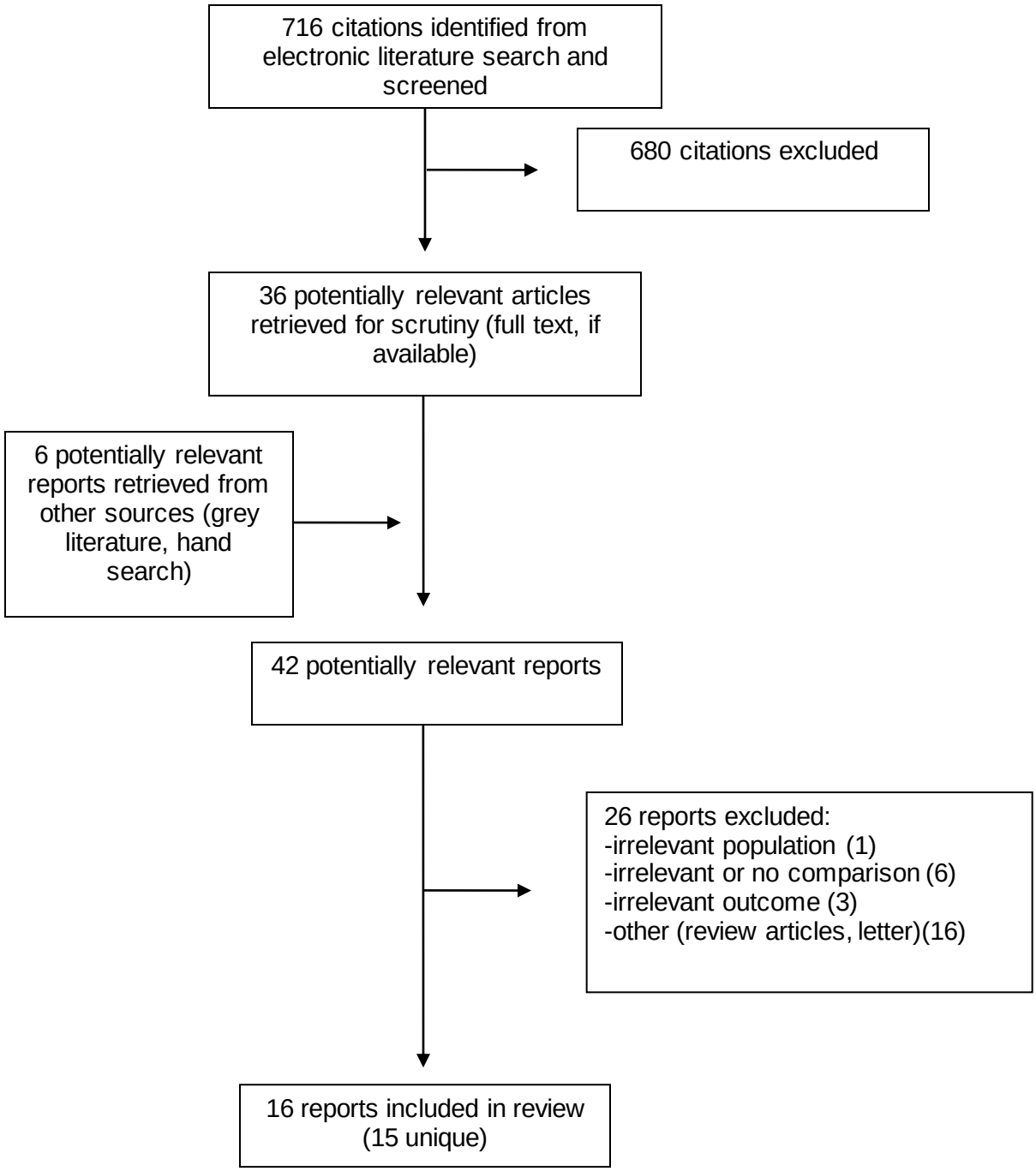
25. Uchida Y, Kouyama JI, Naiki K, Sugawarav K, Inao M, Imai Y, et al. Development of rare RAVs that are extremely tolerant against NS5A inhibitors during daclatasvir/asunaprevir therapy Via a Two-Hit mechanism. Hepatol Res. 2016 Feb 15.

26. Poordad F, Sievert W, Mollison L, Bennett M, Tse E, Bräu N, et al. Fixed-dose combination therapy with daclatasvir, asunaprevir, and beclabuvir for noncirrhotic patients with HCV genotype 1 infection. JAMA. 2015 May 5;313(17):1728-35.

27. American Association for the Study of Liver Diseases, Infectious Diseases Society of America. HCV guidance: recommendations for testing, managing, and treating hepatitis C [Internet]. Alexandria (VA): HCVguidelines.org; 2016 Apr 25. Monitoring patients who are starting hepatitis C treatment, are on treatment, or have completed therapy. [cited 2016 Jun 16]. Available from: http://www.hcvguidelines.org/full-report/monitoring-patients-who-are-starting-hepatitis-c-treatment-are-treatment-or-have

28. Korean Association for the Study of the Liver (KASL). KASL clinical practice guidelines: management of hepatitis C. Clin Mol Hepatol [Internet]. 2016 Mar [cited 2016 Jun 17];22(1):76-139. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4825161

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics[a,b]	Intervention(s)[a]	Comparator(s)[a]	Clinical Outcomes[a]
McPhee,[15] 2015, USA	Analysis with data from 5 phase 2 and 3 studies, pooled	Adults with HCV GT 1b infection,(4 groups: who were (1) treatment naïve, or (2) non responders, or (3) intolerant or ineligible to IFN+RBV treatment or (4) had relapsed) N = 988 Age (range presented as different values for different patient groups) (years): 53.4 (20 to 79) to 61 (45 to 75) Male (%): 37.7 to 52.3 Mean HCV RNA (log_{10} IU/ml):6.4 to 7.1	DCV+ASV Dose: 60 mg DCV once daily with either 200 mg (phase 2 dry tablet formulation) or 100 mg (phase 3 soft-gel formulation) ASV twice daily.	NA	SVR12 (defined as HCV RNA below the LLOQ for the assay used in that study, with or without detectable target.)
Curry,[22] 2015, USA, ASTRAL-4	RCT, open label, multicenter, 3 arms (1:1:1) (patients enrolled from centers in USA, between August 2014 and December 2014) Randomization was stratified by HCV GT	Patients with decompensated cirrhosis caused by chronic HCV GT-1a,1b, 2, 3, or 6 N= 267 (90/87/90) (Patients with GT1a or GT1b: 207 68/ 68/ 71]) Age (mean [range]) (years): 58(42-73)/ 58(40-71)/ 58(46-72)	(1)SOF+VLV for 12 weeks. Dose: fixed dose combination of SOF (400 mg +VLV (100 mg) administered orally once daily	(2)SOF+VLV+RBV for 12 weeks or (3)SOF+VLV for 24 weeks. Dose: fixed dose combination of SOF (400 mg +VLV (100 mg) administered orally once daily. RBV administered orally twice daily	SVR12 (defined as HCV RNA <15 IU per mL)

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics[a,b]	Intervention(s)[a]	Comparator(s)[a]	Clinical Outcomes[a]
		Male (%): 63/ 76/ 70 Mean HCV RNA (log_{10} IU/ml): 6.0/ 5.8/ 5.9 HCV GT1a (%): 56/ 62/ 61 HCV GT1b (%): 20/ 16/ 18			
Iio,[3] 2016, Japan	Observational study, multicenter, 1 arm (patients enrolled from centers in Japan, between September 2014 to October 2015) FU = 12 weeks after treatment	Patients with chronic HCV-GT1b, treatment naïve and treatment experienced N= 641 (336 treatment naïve + 38 treatment experienced) Age (median [range]) (years): 71 (33 to 87) Male (%): 43.5 Mean HCV RNA (log_{10} IU/ml): 6.1 (Note 5.9% had prior treatment with DAA [TVR, SMV or both])	DCV+ASV for 24 weeks. Dose: DCV 60 mg once daily, ASV = 100mg once daily; both drugs were administered orally	NA	SVR12
Kao,[16] 2016,USA, HALLMARK DUAL study	RCT, phase 3, multicenter (patients enrolled from North and South America,	HCV GT 1b infection (3 groups: who were (1) treatment naïve, or (2) non responders, or (3) intolerant and/or	DCV+ASV (for the 3 groups) Dose: 60 mg DCV once daily with	Placebo (only for treatment naïve group, N = 102) Matching placebo	SVR12

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics[a,b]	Intervention(s)[a]	Comparator(s)[a]	Clinical Outcomes[a]
	Europe and Asia). Only Asian patients focus of this analysis Only the treatment naïve patients were randomized 2:1 ([DCV+ASV] vs placebo. The placebo arm further continued in a different study)	ineligible to IFN+RBV treatment N = 153 (Asian patients) Age (mean) (years): 55/ 58/ 59 Male (%): 40/ 56/ 36 HCV RNA ≥3,000,000 IU/ml (% patients) (42%/ 56%/ 61%)	100 mg ASV twice daily, for 24 weeks.		
Karino,[17] 2013, Japan	Observational study, phase 2, open label, 1 arm (patients enrolled in Japan)	Adult patients with HCV GT1b, who were non responders or ineligible/ intolerant to prior IFN+RBV treatment N =21+22 Age (years): 20 to 75 (inclusion criteria) Male (%); NR HCV RNA: ≥10^5 IU/ ml (inc criteria) (Patient details not reported but available in another publication)	DCV+ASV Dose: 60 mg DCV once daily with 100 mg ASV twice daily, for 24 weeks.	NA	SVR
Kowdley,[6] 2014, USA, ION-3 study	RCT, open label, multi center, 3 arm (patients	Patients with chronic HCV-GT1 (80% GT 1a & 20% GT 1b)	(1)LDV+SOF for 8 weeks Dose:	(2)LDV+SOF+RBV for 8 weeks, or (3) LDV+SOF for 12	SVR12 (defined as HCV RNA <25 IU per mL)

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics[a,b]	Intervention(s)[a]	Comparator(s)[a]	Clinical Outcomes[a]
	enrolled from centers in USA, between May 2013 to June 2013) (Includes analysis for NS5A RAV patients)	without cirrhosis, who had not received prior treatment for HCV infection N= 641 (215/216/216 in treatment groups 1/2/3 respectively) Male (%): 60/54/59 Mean HCV RNA (log_{10} IU/ml): 6.5/6.4/6.4	fixed dose combination of SOF (400 mg +LDV (90 mg) administered orally once daily	weeks Dose: fixed dose combination of SOF (400 mg +LDV (90 mg) administered orally once daily. RBV (dose determined according to body weight)administered orally twice daily	
Manns,[7] 2014, multinational, HALLMARK DUAL study	RCT, phase 3, multicenter (patients enrolled from North and South America, Europe and Asia) Only the treatment naïve patients were randomized 2:1 ([DCV+ASV] vs placebo. The placebo arm further continued in a different study)	Adults with HCV GT 1b infection (3 groups: who were (1) treatment naïve, or (2) non responders, or (3) intolerant and/or ineligible to IFN+RBV treatment N = 645 in treatment group Age (mean [range]) in the 3 (years): 55 920 to 79)/ 58 (23 to 77)/ 60 (24 to 77) Male (%): 49/ 54/ 42 HCV RNA ≥800,000 IU/ml (% patients) (74%)	DCV+ASV (for the 3 groups) Dose: 60 mg DCV once daily with 100 mg ASV twice daily, for 24 weeks.	Placebo (only for treatment naïve group, N = 102) Matching placebo	SVR12

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics[a,b]	Intervention(s)[a]	Comparator(s)[a]	Clinical Outcomes[a]
Mizokami,[8] 2016, USA (Mizokami[21] for additional details)	Analysis (from RCT data) RCT, phase 3, open label, multicenter (in Japan)	Adults with HCV GT 1, with or without cirrhosis, and who were treatment naïve or treatment experienced. N =341 Age (years) = 59 Male (%): 42 Mean HCV RNA (log_{10} IU/ml): 6.6	LDV+SOF Dose: Fixed dose combination of DCV (90mg) and SOF (400 mg) once daily for 12 weeks	LDV+SOF+RBV Dose: Fixed dose combination of DCV (90mg) and SOF (400 mg) once daily for 12 weeks and weight based RBV once daily for 12 weeks	SVR12
Poordad,[26] 2015, multinational, UNITY-1 study	Observational, open label, 1-arm, multi center (patients enrolled from centers in USA, Canada, France, and Australia between December 2013 February 2014 to October 2015)	Adults without cirrhosis and who had chronic HCV-GT1, who were treatment naïve (N = 312) or treatment experienced (N = 103) N =415 (GT 1a: 73.3%, GT 1b: 26.7%) Age (median [range]) (years): 55 (19 to 77) Male (%): 57.6 HCV RNA <800,000 IU/ml (18.8%) HCV RNA ≥800,000 IU/ml (81.2%)	DCV+ASV+BCV Dose: fixed dose combination of DCV (30 mg) +ASV (200 mg) + BCV (75 mg) for 12 weeks and followed up to 24 weeks (post-treatment-week 24 ongoing)	NA	SVR12 (post-treatment-week 24 ongoing)
Uchida,[25] 2016, Japan	Obsevational study, 1 arm,	Adults with HCV GT 1b infection.	DCV+ASV	NA	SVR12

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics[a,b]	Intervention(s)[a]	Comparator(s)[a]	Clinical Outcomes[a]
	single center (consecutive patients who had received treatment between September 2014 and January 2015 At Saitama Medical University hospital in Japan)	(included patients with cirrhosis, previous treated hepatocellular carcinoma, treatment naïve, treatment experienced [5.3% had prior treatment with DAAs: SMV or TVR) N =206 Age (median [range]) (years): 71 (23 to 87) Male (%): 44 HCV RNA RNA (log_{10} IU/ml): 6.3	Dose: DCV (60 mg tablet) once daily and ASV (100 mg capsule) twice daily; for 24 weeks		
Wei,[24] 2016, China	Observational, phase 3, open label,1 arm (patients enrolled from China)	Adults with chronic HCV 1b infection, who were INF±RBV ineligible or intolerant N= 159 Age: NR Male (%): 34.6 HCV RNA: ≥800,000 IU/ml (90.6%)	DCV+ASV Dose: DCV (60 mg tablet) once daily and ASV (100 mg capsule) twice daily; for 24 weeks	NA	SVR12, SVR24 (Note: Concordance between the number of patients achieving SVR12 and SVR24 was 100%. Only data for SVR24 was available and is presented in this report)
Zeuzem,[13] 2016, Germany, LEAUGE 1	RCT (phase 2), open label, 2 arm (1:1), Details of	Adults with HCV GT1a or GT1b, who were treatment naïve or non-responders to	(1)DCV+SMV Dose: DCV (30 mg +SMV (150 mg)	(2)DCV+SMV+RBV Dose: DCV (30 mg +SMV (150 mg) + weight	SVR12 (HCV RNA <LLOQ detectable or undetectable at post-treatment

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics[a,b]	Intervention(s)[a]	Comparator(s)[a]	Clinical Outcomes[a]
	patient enrollment and study centers not reported.	prior PEG-INF+RBV treatment. However, only GT 1b group considered for this report as none in the GT 1a group had NS5A RAVs at baseline N= 168 (6 groups by GT, prior treatment & current treatment. GT1b: 147, GT 1a: 21) Age range in GT 1b groups (median[range]): 53(28 to 81 and 59 (20 to 78) Male (%) in GT 1b: 42 to 52 Mean HCV RNA (log_{10} IU/ml): 6.2 to 6.4	administered orally once daily, for 12 weeks	based RBV, administered orally once daily, for 12 weeks	week 12)
Zeuzem,[23] 2015, multinational, C-EDGE study	RCT, blinded and later open label, 2 arm (3:1), multicenter (patients enrolled from centers in USA, Europe, Australia, Scandanavia and Asia)	Adults with HCV GT1, GT4 or GT6 infection; treatment naïve N = 421 (316/105) Age (mean±SD) (years): 52.6± 11.2 (52.2±11.1/ 53.8±11.2) Male (%): 54 (54/53)	(1)Immediate therapy with GZR+ELR Dose: fixed dose combination of GZR (100 mg +EBR (50 mg) administered orally once daily, for 12 weeks	(2)Placebo (Deferred therapy with GZR+ELR [deferred for 4 weeks])	SVR12 (Primary outcome was SVR12 in the immediate therapy group) SVR12 defined as unquantifiable HCV RNA 12 weeks after treatment

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics[a,b]	Intervention(s)[a]	Comparator(s)[a]	Clinical Outcomes[a]
		HCV RNA (geometric mean) (log_{10} IU/ml): 6.4 (6.4/6.4) GT 1a (%): 50 (50/42) GT1b (%): 41 (42/38) GT 4 (%): 6(6/8) GT 6 (%): 3(3/3)			

ASV = asunaprevir, DCV = daclatasvir, EBR = beclabuvir, GT = genotype, GZR = grazoprevir, HCV = hepatitis C virus, IU = international unit, LDV = ledipasvir, NA = not applicable, RBV = ribavirin, RCT = randomized controlled trial, RNA = ribonucleic acid, SOF = sofosbuvir, SVR = sustained viral response, SVR12 = SVR at post treatment week 12, VLV = velpatasvir

[a]Only information relevant for this report is included here
[b]In case of studies with more than one treatment arm, the arms are numbered and patient characteristics are presented sequentially (separated by slash[s] for the individual groups when data are available.

Table A2: Characteristics of Included Guidelines	
Objectives	**Methodology**
AASLD-IDSA,[27] 2016, USA	
Development of guidelines for the optimal screening, management, and treatment for adults with HCV infection in the United States, to provide guidance to healthcare practitioners.	The guideline development panel comprised of experts in the areas of hepatology and infectious disease as well as HCV community representatives. An evidence based review was undertaken. Multiple databases (PubMed, Scopus, EMBASE, and Web of Science) were searched. Conference abstract and presentations were also considered. Classification of the level of the evidence and strength of the recommendation, were based on a modified scale adapted from the American College of Cardiology and the American Heart Association Practice Guidelines. The guideline was internally reviewed by the full panel and then finally reviewed by the AASLD and IDSA Governing Board. Recommendations are updated as new information becomes available
KASL,[28] 2016, Korea	
Development of guidelines for the management of HCV, to provide guidance to physicians and healthcare providers involved in the diagnosis and treatment of HCV	The guideline development committee comprised of hepatologists. A systematic review of the literature was conducted. Multiple databases (PubMed, MEDLINE, KoreaMed, and other databases) searched. GRADE system was used to classify the level of evidence and strength of evidence. The guideline was internally and externally reviewed. Funding for guideline revisions and updating was available

AASLD = American Association for the Study of Liver Disease, GRADE = Grading of Recommendations, Assessment, Development, and Evaluation , HCV = Hepatitis C, IDSA = Infection Disease Society of America , KASL = Korean Association for the Study of Liver disease

APPENDIX 3: Grading of Recommendations and Levels of Evidence

Table A3 Grading of Recommendations and Levels of Evidence

Guideline Society and/or Author, Year, Country, Topic	Recommendation grade and Level of Evidence
AASLD-IDSA,[27] 2016, USA	**Classification of recommendation** **"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 favor of 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" Page: document did not have page numbers **Level of evidence** **"Level A*** Data derived from multiple randomized clinical trials, meta-analyses, or equivalent **Level B*** Data derived from a single randomized trial, nonrandomized studies, or equivalent **Level C** Consensus opinion of experts, case studies, or standard of care" Page: document did not have page numbers "*In some situations, such as for IFN-sparing HCV treatments, randomized clinical trials with an existing standard-of-care arm cannot ethically or practicably be conducted. The US Food and Drug Administration (FDA) has suggested alternative study designs, including historical controls or immediate versus deferred, placebo-controlled trials."
KASL,[28] 2016, Korea	The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system was used for classification of level of evidence and strength of recommendation **Classification of recommendation** Strong (1): "Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost" Weak (2): "Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption" **Level of Evidence** High (A): "Further research is unlikely to change confidence in the estimate of the clinical effect" Moderate (B): "Further research may change confidence in the estimate of the clinical effect" Low (C): "Further research is very likely to impact confidence on the estimate of clinical effect" Note: Level of evidence: Very low (D) was not considered here Pages were not numbered in the guideline document, hence page numbers could not be inserted

AASLD = American Association for the Study of Liver Disease, GRADE = Grading of Recommendations, Assessment, Development, and Evaluation , IDSA = Infection Disease Society of America , KASL = Korean Association for the Study of Liver disease

APPENDIX 4: Critical Appraisal of Included Publications

Table A4: Strengths and Limitations of Clinical Studies

Strengths	Limitations
Pooled Analysis using AMSTAR[18]	
McPhee,[15] 2015, USA	
• Objectives were clearly stated. • Conflict of interest was declared. Authors have industry association	• Unclear if systematic literature search was undertaken • Details of article selection and data extraction were lacking • Characteristics of the individual studies were not presented • Quality assessment of the included studies was not presented. • Unclear if pooling was appropriate • Publication bias was not explored • Study funded by industry
Randomized Studies and Observational Studies using Downs and Black[19]	
Curry,[22] 2015, USA, ASTRAL-4	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described. • Randomized, open label study. Stratification according to HCV GT. Interactive Web Response System (IWRS) was used for randomization and treatment assignment. • Number discontinued or lost to follow up was reported. Discontinuation due to adverse events: 1%/ 5%/ 4% in arms 1, 2 and 3 respectively. • Sample size determinations were provided • Disclosure forms were provided by the authors. Authors have industry association	• The RCT focus was different from the research question being addressed in this report hence randomization and sample size calculation do not apply for this research question. • Unclear if ITT analysis was undertaken • *P*-values were not provided • Generalizability limited to patients with decompensated cirrhosis caused by chronic HCV infection. • Study funded by industry
Iio,[3] 2016, Japan	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described. • Losses to follow up were < 3% • Disclosures were provided by the authors. One author had industry association. Funding	• Not randomized; single arm observational study • Blinding not mentioned • Sample size determinations were not provided • Does not appear to be ITT • *P*-values were not provided • Generalizability limited to study population • Unclear if funded by industry. Partial support for this research was provided by the Japan Agency for Medical Research and Development.
Kao,[16] 2016,USA, HALLMARK DUAL study	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described.	• The RCT focus was different from the research question being addressed in this report hence randomization and sample size calculation do not apply for this research question. • Discontinuation (%): 6/ 16/ 13 (treatment naïve/ non-

Table A4: Strengths and Limitations of Clinical Studies

Strengths	Limitations
• Randomization (only treatment naïve group) by interactive voice response system with a computer generated random allocation sequence • Double-blind • ITT analysis • *P* values provided in some instances • Disclosures were provided by the authors. Authors have industry association	responders/ ineligible or intolerant) • Generalizable is limited to the study population • Study was funded by industry
Karino,[17] 2013, Japan	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described but details were lacking • Disclosures were provided by the authors. Authors have industry association	• Not randomized, open label,1-arm study • Sample size determinations were not mentioned • Findings presented narratively • High discontinuation rate (14%) • *P* values not provided • Generalizability is limited to the study population • Study was funded by industry
Kowdley,[6] 2014, USA, ION-3	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described. • Randomized • Open label • Sample size determinations were mentioned • ITT analysis • Discontinuation ≤ 2% • Disclosures were provided by the authors. Authors have industry association	• The RCT focus was different from the research question being addressed in this report hence randomization and sample size calculation do not apply for this research question. • Open label • *P* values not provided • Generalizability is limited to the study population • Study was funded by industry
Manns,[7] 2014, HALLMARK DUAL	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described. • Randomization (only treatment naïve group) by interactive voice response system with a computer generated random allocation sequence • Patients and investigator sites were blinded to end of week 12 for treatment naïve group, (other 2 groups were open label) • Sample size determinations were mentioned • *P* values reported some times • Disclosures were provided by the authors. Authors have industry association	• The RCT focus was different from the research question being addressed in this report hence randomization and sample size calculation do not apply for this research question. • Unclear if ITT analysis • Discontinuation rates unclear • Generalizable to some extent as this was a multinational study. However, generalizability is limited to the study population • Study was funded by industry

Table A4: Strengths and Limitations of Clinical Studies

Strengths	Limitations
Mizokami,[8] 2016, Japan (for RCT details: Mizokami,[21] 2015, Japan)	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described. • Randomized and treatment allocated using a interactive web response system • ITT analysis • Lost to follow up <1% • Disclosures were provided by the authors. Authors have industry association	• The RCT focus was different from the research question being addressed in this report hence randomization and sample size calculation do not apply for this research question. • *P* values not provided • Generalizability is limited to the study population (i.e patients who had chronic HCV-GT1, in Japan) • Study was funded by industry
Poordad,[26] 2015, multinational, UNITY 1	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described • Sample size determination mentioned • ITT analysis • Discontinuation < 4% • Disclosures were provided by the authors. Authors have industry association	• Not randomized, open label,1-arm study • *P* values not provided • Generalizable to some extent as this was a multinational study. However, generalizability is limited to the study population (i.e patients without cirrhosis and who had chronic HCV-GT1, who were treatment naïve or treatment experienced) • Study was funded by industry
Uchida,[25] 2016, Japan	
• Objectives were clearly stated. • Inclusion and exclusion criteria not applicable as consecutive patients were enrolled • Patient characteristics, interventions and outcomes were described • *P* values provided • Discontinuation reported (10.2%) • Disclosures were provided by the authors. Authors have industry association	• Not randomized, 1-arm study, retrospective analysis • Unclear if patients had discontinued • Unclear if ITT analysis • Generalizability limited to the study population i.e. patients at a single hospital in Japan. However, the study provided real world data • Research grants received from several sources, unclear to what extent there was industry association.
Wei,[24] 2016, China	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described but lacked details • Open label • Number discontinued were reported (9%) • ITT analysis • Disclosures were provided by the authors. Authors have industry association	• Not randomized, 1-arm study • *P* values for the outcomes relevant for this report were not provided • Generalizability is limited to the study population (Asian patients with HCV GT 1b who were intolerant or ineligible for INF±RBV therapy). • Study was funded by industry

Table A4: Strengths and Limitations of Clinical Studies	
Strengths	**Limitations**
Zeuzem,[13] 2016, Germany	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described. • Randomized • Modified ITT analysis conducted (patients who received ≥ 1 dose of study medication were included in analysis) • Disclosures were provided by the authors. Authors have industry association	• The study focus was different from the research question being addressed in this report hence randomization and sample size calculation do not apply for this research question. • Not blinded • *P* values for the outcomes relevant for this report were not provided • Numbers discontinued were reported, and was 13%,15%, 26% 5% in DCV+SMV-tx naïve, DCV+SMV+RBV-tx naive, DCV+SMV-non-responded, DCV+SMV+RBV-non-responder, respectively. • Generalizability is limited to patients with HCV GT 1b who were treatment naïve or non-responders to prior PEG-INF+RBV treatment. • Study was funded by industry
Zeuzem,[23] 2015, multinational, C-EDGE	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described. • Randomized using a central interactive voice response system and computer generated random allocation • Patients, clinical sites and sponsor personnel were blinded. Separate medical team monitoring virologic failure and SAE was unblinded • Number discontinued or lost to follow up was reported. Lost to follow up or discontinuation due to reasons other than virologic failure was 1% • Sample size determination was mentioned • Disclosure forms were provided by the authors. Authors have industry association	• The study focus was different from the research question being addressed in this report hence randomization and sample size calculation do not apply for this research question. • *P* values for the outcomes relevant for this report were not provided • Unclear if ITT, however likely not an issue as lost to follow up & discontinuations were few. • Generalizable to some extent as this was a multinational study. However, generalizability is limited to cirrhotic and noncirrhotic treatment naïve adults with GT1, GT 4 or GT6. Also, generalizability is limited by the exclusion criteria of excluding patients with coinfections/comorbidities (such as decompensated liver disease, hepatocellular carcinoma, HIV, HBV infection) • Study was funded by industry

Table A5: Strengths and Limitations of Guidelines using AGREE II[19]

Strengths	Limitations
AASLD-IDSA,[27] 2016, USA	
• The scope and purpose were clearly stated. • The guideline development group comprised of individuals from relevant areas (hepatolopgy and infectious disease) as well as HCV community representatives • Multiple databases (PubMed, Scopus, EMBASE and Web of Science), were searched. Conference abstracts and presentations were considered. Details of methods used for article selection, data extraction were not available • Recommendations were graded based on a modified scale adapted from the American College of Cardiology and the American Heart Association Practice Guidelines. • Cost implications were discussed to some extent. At the present time, cost-effectiveness analysis are not used to guide recommendations • The guideline was internally reviewed by the full panel and then finally reviewed by the AASLD and IDSA Governing Board • Recommendations were to be updates as new information became available • Panel members are required to disclose their conflict of interest	• Details of methods used for evidence selection and data extraction were lacking. • Organizational barriers were not discussed.
KASL,[28] 2016, Korea	
• The guideline development group comprised of individuals from relevant areas (hepatology) • Multiple databases (PubMed, MEDLINE, KoreaMed, and other databases) searched. It was mentioned that a systematic review was undertaken but details were not provided. • Recommendations were graded using the GRADE system • The guideline was internally and externally reviewed • Funding for the guideline revisions and updating were to be available	• Details of methods used for evidence selection and data extraction were lacking. • Cost implications and organizational barriers were not discussed.

APPENDIX 5: Main Study Findings and Author's Conclusions

Table A6: Summary of Findings of Included Studies

Relevant Study Findings and Author's Conclusions

McPhee,[15] 2015, USA (post hoc analysis - 5 studies pooled, includes HALLMARK DUAL)

Relevant findings:

SVR12 with (DCV+ASV) in patients with HCV, GT-1b and with or without RAPs

Patient category (with or without NS5A RAPs at baseline)	No. of patients	Prevalence of patients with NS5A RAPs (%)	Achieved SVR12 n (%)
With L28M	39	3.0[a]	29 (74.4)
Without L28M	940	NA	813 (86.5)
With R30Q	84	6.7[a]	66 (78.6)
Without R30Q	895	NA	776 (86.7)
With L31F/I/M/V	43	1.8[a]	18 (41.9)
Without L31F/I/M/V	936	NA	824 (88.0)
With Y93H	103	3.9[a]	38 (36.9)
Without Y93H	876	NA	804 (91.8)
With L31F/I/M/V or Y93H	141	5.6[a]	55 (39.0)
Without L31F/I/M/V or Y93H	838	NA	787 (93.9)

[a] Calculated by CADTH reviewer

SVR12 with (DCV+ASV) in various subgroups of patients with HCV, GT-1b and with or without RAPs

Patient group	NS5A polymorphism at baseline	Proportion of patients achieving SVR12 (%)		
		Japan	Korea and Taiwan	Non-Asian country
All	With L31F/I/M/V and/or Y93H	39.7	37.5	38.6
	Without L31F/I/M/V or Y93H	95.4	91.7	93.5
Treatment naïve[a]	With L31F/I/M/V and/or Y93H	33.3	75.0	53.8
	Without L31F/I/M/V or Y93H	92.8	97.1	97.0
Previous non-responders[a]	With L31F/I/M/V and/or Y93H	35.7	20.0	28.6
	Without L31F/I/M/V or Y93H	90.2	8.9	92.4
Ineligible or intolerant[a]	With L31F/I/M/V and/or Y93H	45.2	28.6	39.1
	Without L31F/I/M/V or Y93H	96.6	89.2	91.4
< 65 years	With L31F/I/M/V and/or Y93H	39.5	36.4	42.0
	Without L31F/I/M/V or Y93H	93.6	90.2	92.9
≥ 65 years	With L31F/I/M/V and/or Y93H	40.0	40.0	14.3
	Without L31F/I/M/V or Y93H	99.0	96.2	96.2
With cirrhosis	With L31F/I/M/V and/or Y93H	50.0	45.5	52.9
	Without L31F/I/M/V or Y93H	100.0	91.7	91.5
Without cirrhosis	With L31F/I/M/V and/or Y93H	39.4	20.0	32.5
	Without L31F/I/M/V or Y93H	95.1	91.7	94.3

[a] Includes patients with and without NS5A variants and also refers to previous treatment with PEGinf+RBV

Table A6: Summary of Findings of Included Studies

Relevant Study Findings and Author's Conclusions

Prevalence of baseline NS5A polymorphism in patients with HCV, GT-1b

NS5A polymorphism type	Prevalence (%) of NS5A polymorphism in		
	Japan N = 374	Korea or Taiwan N = 125	Non-Asian countries N = 489
L28M	7.2	4.8	1.4
R30Q	11.5	9.6	6.1
L31F/I/M/V	4.3	2.4	4.9
Y93H	15.0	10.4	7.2
L31F/I/M/V or Y93H	18.4	12.8	11.7

Authors' Conclusions

"Pooled data from clinical studies of DCV/ ASV for chronic HCV GT-1b infection show that the most significant baseline correlate of SVR so far observed is the presence of pre-therapy DCV RAPs at NS5A amino acids L31 and/or Y93H. In the absence of these NS5A RAPs, very high rates of SVR12, between 90% and 100%, were achieved, irrespective of older age, cirrhosis, prior experience of pegIFN/RBV, or baseline HCV RNA level." Page 647

Curry,[22] 2015, USA, ASTRAL-4

Relevant findings:

SVR12 with (SOF+VLV±RBV) in patients with HCV, GT-1

Treatment	Proportion of patients (%) achieving SVR12	
	With NS5A RAVs	Without NS5A RAVs
SOF+VLV (12 week)	80	96
SOF+VLV+RBV (12 week)	100	98
SOF+VLV (24 week)	90	98

Authors' Conclusions

"Treatment with sofosbuvir–velpatasvir with or without ribavirin for 12 weeks and with sofosbuvir–velpatasvir for 24 weeks resulted in high rates of sustained virologic response in patients with HCV infection and decompensated cirrhosis." Page 2618

Iio,[3] 2016, Japan

Relevant findings:

SVR with (DCV+ASV) in patients with HCV, GT-1b

Response category	Patient category	No. of patients	Achieved SVR12 n (%)
SVR12	All	625	543 (86.9)
	Without NS5A-93H mutation at baseline	590	521 (88.3)
	With NS5A-93H mutation at baseline	25	12 (48.0)
SVR8	All	641	568 (88.6)
	Without NS5A-93H mutation at baseline	603	542 (89.9)
	With NS5A-93H mutation at baseline	25	13 (52.0)
SVR4	All	641	574 (89.5)
	Without NS5A-93H mutation at baseline	603	547 (90.7)
	With NS5A-93H mutation at baseline	25	14 (56.0)

Authors' Conclusions

"History of SMV therapy and pre-existing NS5A Y93H were associated with virological failure of DCV/ASV therapy, resulting in the emergence of multiple RAVs. Patients with RAVs at baseline should be assessed

Table A6: Summary of Findings of Included Studies

Relevant Study Findings and Author's Conclusions
to optimize future DAA therapies." Page 1 & 2 of 10
Kao,[16] 2016,USA, HALLMARK DUAL study

Relevant findings:

SVR12 with (DCV+ASV) in Asian patients with HCV, GT-1b

Patient category	No. of patients	Prevalence of patients with NS5A RAVs n (%)	Achieved SVR12 n (%)
All	153	18 (11.8)	128 (83.7)
Treatment naïve[a]	52	4 (7.7)	48 (92.3)
Previous non-responders[a]	45	5 (11.1)	36 (80.0)
Ineligible, intolerant or both[a]	56	9 (16.1)	44 (78.6)
With NS5A-Y93H or NS5A-L31M/V RAV at baseline	18	18 (11.8)	7 (38.9)
With no NS5A-Y93H or NS5A-L31M/V RAV at baseline	135	NA	90.1%

Multivariate regression analysis of baseline factors showed that NS5A RAVs (at positions L31 or Y93) were negative predictors of SVR12.

Population	Comparison	SVR12	
		OR (95% CI)	*P* value
Asian	NS5A resistance (absent vs present)	19.64 (4.72 to 81.75)	<0.0001
Non-Asian	NS5A resistance (absent vs present)	17.34 (8.62 to 34.91)	<0.0001

Authors' Inference

"Baseline RAVs were strong predictors of virologic response in both Asian and non-Asian cohorts. However, despite the presence of ``NS5A-Y93H RAVs, six of 15 Asian patients achieved SVR12" Page. 7

Karino,[17] 2013, Japan

Relevant findings:

Results, pertaining to SVR for HCV, GT-1b patients with and without NS5A variants present at baseline, were presented graphically and partially described in the text. Two groups of patients were assessed: (1) those who were ineligible, intolerant or both to PEG-INF & RVB treatment (N= 21) and (2) those who were non-responders to PEG-INF & RVB treatment (N = 21). Viral breakthrough and post treatment relapses were observed in the ineligible and/or intolerant and not in the non-responder group. "NS5A-Y93H was identified as the predominant polymorphism at baseline in all three patients with viral breakthrough and in two of the four patients with relapse. However, three null responders and two ineligible/intolerant patients also had a pre-existing NS5A-Y93H polymorphism and all achieved SVR, making the significance of Y93H alone, for response in the broader patient population, difficult to assess." Page 651.

Note: The prevalence of NS5A-Y93H observed in this study was 23% (10/43), higher than that generally observed. Global prevalence of NS5A-Y93H was estimated to be 4%, based on data from the Los Alamos database and several unpublished DCV studies.

Authors' Conclusions

"A loose association with a baseline NS5A polymorphism on virologic outcome was observed; however, further data from larger studies are required." Page 653

Table A6: Summary of Findings of Included Studies

Relevant Study Findings and Author's Conclusions

Kowdlay,[6] 2014, USA, ION-3 study

Relevant findings:

SVR12 with (SOF+LDV±RBV) in patients with HCV, GT-1

Treatment	Patient type	Total no. of patients in the group	Proportion of patients with SVR12 n (%)
SOF+LDV for 8 weeks	All patients this treatment group	215	202 (94.0)
SOF+LDV+RBV for 8 weeks	All patients this treatment group	216	201 (93.1)
SOF+LDV for 12 weeks	All patients this treatment group	216	206 (95.4)
Any of the above treatment	Patients with NS5A RAV at baseline	116	104 (90)

Authors' Conclusions

"Ledipasvir–sofosbuvir for 8 weeks was associated with a high rate of sustained virologic response among previously untreated patients with HCV genotype 1 infection without cirrhosis. No additional benefit was associated with the inclusion of ribavirin in the regimen or with extension of the duration of treatment to 12 weeks." Page. 1879

Manns,[7] 2014, HALLMARK DUAL study

Relevant findings:

SVR12 with (DCV+ASV) in patients with HCV, GT-1b

Patient category	No. of patients	Prevalence of patients with NS5A RAVs n (%)	Achieved SVR12 n (%)
Treatment naïve[a]	203	NR	182 (90)
Previous non-responders[a]	205	NR	168 (82)
Ineligible or intolerant[a]	235	NR	192 (82)
With NS5A-L31 RAV at baseline	27	27 (5)	11 (41)
With NS5A-Y93 RAV at baseline	48	48 (8)	18 (38)

[a]Includes patients with and without NS5A variants and also refers to previous treatment with PEGinf+RBV
RAV = resistance associated variant

Multivariate regression analysis of baseline factors showed that NS5A RAVs (at positions L31 or Y93) were negative predictors of SVR12.

Comparison	SVR12	
	OR (95% CI)	*P* value
NS5A-Y93H (absent vs present)	13.69 (6.80 to 27.55)	<0.0001
NS5A-L31M/V (absent vs present)	15.03 (5.71 to 39.57	<0.0001

Authors' Inference:

"Patients who did not achieve SVR12 with daclatasvir plus asunaprevir (16%) had a higher frequency of baseline NS5a variants at position L31 and Y93 than did those who achieved SVR12; however, some patients who had these baseline variants still achieved SVR12" Page 1603

Table A6: Summary of Findings of Included Studies

Relevant Study Findings and Author's Conclusions

Mizokami,[8] 2016, USA

Relevant findings:

SVR12 with (LDV+SOF±RBV) in patients with HCV, GT-1a and1b and with RAVs

NS5A RAVs at baseline		No. of patients with NS5A RAV	HCV genotype	Achieved SVR12 n (%)
Single	L31M	8	1b	8 (100)
	L3H	1	1b	1 (100)
	L31F	1	1b	1 (100)
	L31V	1	1b	1 (100)
	Y93H	59	1b	58 (98)
	Q30R	1	1a	1 (100)
Multiple	L31I, Y93N, Y93C	1	1a	1 (100)
	L31I, Y93H	1	1b	1 (100)
	Y93S, Y93N, Y93H	1	1b	1 (100)
	Y93F, Y93H	2	1b	2 (100)

SVR12 with (LDV+SOF) or (LDV+SOF+RBV) in patients with HCV, GT-1 and with or without NS5A RAVs

Treatment	NS5A RAV present	Number of patients	Patients achieving SVR12 n (%)
Overall	yes	76	75 (98.7)
	no	265	263 (99.2)
LDV+SOF	yes	42	42 (100)
	no	171	171 (100)
LDV+SOF+RBV	yes	170	168 (98.8)
	no	24	23 (97.1)

SVR12 with (LDV+SOF) or (LDV+SOF+RBV) in various subgroups of patients with HCV, GT-1 and with NS5A RAVs

Patient group	Treatment	Number of patients	Patients achieving SVR12 n (%)
Treatment naive	Overall	46	45 (97.8)
	LDV+SOF	22	22 (100)
	LDV+SOF+RBV	24	23 (95.8)
Treatment experienced[a]	Overall	30	30 (100)
	LDV+SOF	10	10 (100)
	LDV+SOF+RBV	20	20 (100)

[a]Patients had previously received treatment

Prevalence of baseline NS5A RAVs in patients with HCV, GT-1b

NS5A RAV	Prevalence (%) of NS5A RAVs
L31M	2.4
L31F	0.3
L31I	0.3
Y93H	17.9

Table A6: Summary of Findings of Included Studies

Relevant Study Findings and Author's Conclusions

Authors' Conclusions

"The presence of baseline NS5A RAVs did not impact treatment outcome in GT1 Japanese patients treated with LDV/SOF for 12 weeks." Page 1

Poordad,[26] 2015, multinational, UNITY-1

Relevant findings:

SVR12 with (DCV+ASV+BCV) in patients with HCV, GT-1

HCV GT	NS5A polymorphism present at baseline	Patients achieving SVR 12, n/N (%)[a]		
		Treatment naïve patients (N = 312)	Treatment experienced (N = 103)	All patients (N = 415)
GT 1a	M28L/I/T/V	12/17 (71)	8/9 (89)	20/26 (77)
	Q30H/R	0/5	1/1 (100)	1/6 (17)
	L31M	2/2 (100)	2/2 (100)	4/4 (100)
	Y93C/H	1/2 (50)	0	1/2 (50)
	M28, Q30, L31, or Y93[b]	15/23 (65)	10/11 (91)	25/34 (74)
GT 1b	L28M/V	1/1 (100)	1/1 (100)	2/2 (100)
	R30Q	3/3 (100)	1/1 (100)	4/4 (100)
	L31I/M	3/3 (100)	1/1 (100)	4/4 (100)
	Y93H	6/6 (100)	3/3 (100)	9/9 (100)
	L28, R30, L31, or Y93[b]	12/12 (100)	5/5 (100)	17/17 (100)
GT 1a	With and without NS5A polymorphism at baseline	206/229 (90.0)	64/75 (85.3)	270/304 (88.8)
GT1b		81/83 (97.6)	28/28 (100.0)	109/111 (98.2)

[a]n/N = (number of patients with SVR12)/(total number of patients) for the particular patient group
[b]This group includes patients with ≥ 1NS5A RAVs at baseline

Authors' Conclusions

"In this open-label, nonrandomized, uncontrolled study, a high rate of SVR12 was achieved in treatment-naive and treatment-experienced noncirrhotic patients with chronic HCV genotype 1 infection who received 12 weeks of treatment with the oral fixed-dose regimen of daclatasvir, asunaprevir, and beclabuvir." Page. 1728

Uchida,[25] 2016, Japan

Relevant findings:

SVR12 with (DCV+ASV) in patients with HCV, GT-1b and with or without NS5A RAVs

NS5A RAVs present at baseline	Number of patients	Patients achieving SVR12 n (%)
None	132	125 (94.7)
NS5A-L31M	6	5 (83.3)
NS5A-Y93H	22	13 (59.1)
NS5A-R30Q/H/L	53	41 (77.4)

Baseline NS5A RAVs in various HCV, GT-1b patient groups receiving treatment with DCV+ASV

NS5A RAVs present at baseline	Total patients (N = 206)	Patients achieving SVR12 (N = 180)	Patients not achieving SVR12 (N = 26)
Y93H	22 (10.7)	13 (7.2)	9 (34.6)
L31M	6 (2.9)	5 (2.8)	1 (3.8)
R30Q/H/L	53 (25.7)	41 (22.8)	12 (46.2)

Table A6: Summary of Findings of Included Studies

Relevant Study Findings and Author's Conclusions

Multivariate logistic regression analysis of baseline factors showed that NS5A RAVs (Y93H and R30Q/H/L mutations) were negative predictors of SVR12.

Comparison	SVR12	
	OR (95% CI)	*P* value
Y93H (absent[<1%] vs present [≥1%])	8.03 (2.83 to 22.74)	<0.001
R30Q/G/L (absent vs present)	3.49 (1.40 to 8.69)	0.007
Note: Although virologic failure occurred in all the patients who had received triple therapy with simeprevir, previous antiviral therapies, including ribavirin and/or IFN/Peg-IFN therapies, were not identified as a factor affecting SVR12 in the multivariate analysis." Page 5		

Authors' Conclusions

"NS5A-R30Q/H/L and NS5A-Y93H mutations at baseline determined the therapeutic efficacy of dual oral therapy with daclatasvir/asunaprevir, but rare NS5A-RAVs developed frequently in patients with previous simeprevir treatment. Such RAVs may develop in a two-hit manner, with simeprevir altering the quasispecies of HCV strains in the NS5A regions, leading to the emergence of HCV strains with NS5A-P29del and NS5A-P32del during exposure to daclatasvir/asunaprevir." Page 1

Wei,[24] 2016, China

Relevant findings:

SVR24 with (DCV+ASV) in patients with HCV, GT-1b and with or without NS5A RAVs

NS5A RAV present at baseline	Number of patients	Patients achieving SVR24 n (%)
yes	19	8 (42.1)
no	139	137 (98.6)

Note: Concordance between the number of patients achieving SVR12 and SVR24 was 100%. Only data for SVR24 was available and is presented above

Prevalence of baseline NS5A RAVs in patients with HCV, GT-1b

NS5A RAV	Prevalence (%) of NS5A RAVs
Y93H or L31M	11.9 (Of the 19 patients with NS5A RAVs, NS5A-Y93H was found in 9, 3, and 6 patients from mainland China, Korea and Taiwan respectively and NS5A-L31M was found in 1 patient from mainland China)

Authors' Conclusions

"Daclatasvir plus asunaprevir achieved a SVR24 rate of 91.2%, rising to 98.6% in patients without baseline NS5A RAVs, and was generally well tolerated in interferon (±ribavirin)-ineligible or - intolerant patients with genotype 1b infection from mainland China, Korea, and Taiwan." Page 1 of manuscript

Table A6: Summary of Findings of Included Studies

Relevant Study Findings and Author's Conclusions

Zeuzem,[13] 2016, Germany

Relevant findings:

SVR12 with (DCV+SMV±RBV) in patients with HCV, GT-1b and with or without NS5A RAVs

Patient category: with or without NS5A polymorphisms at baseline	No. of patients	Achieved SVR12 n (%)
With L28, R30, L31, or Y93 polymorphism	29	16 (55.2)
Without L28, R30, L31, or Y93 polymorphism	107	97 (90.7)
With L31 or Y93 polymorphism	18	8 (44.4)
Without L31 or Y93 polymorphism	118	105 (89.0)
With L28M polymorphism	2	1 (50.0)
Without L28M polymorphism	134	112 (83.6)
With R30L/Q/S polymorphism	11	7 (63.6)
Without R30L/Q/S polymorphism	125	106 (84.8)
With L31M/V polymorphism	7	2 (28.6)
Without L31M/V polymorphism	129	111 (86.0)
With Y93H polymorphism	13	6 (46.2)
Without Y93H plymorphism	123	107 (87.0)

Authors' Conclusions

In conclusion, the efficacy and safety of DCV + SMV, with or without RBV, was demonstrated in treatment-naive patients and null responders with genotype 1b infection. DCV + SMV was effective alone or in combination with RBV and with a 12- week treatment duration. SVR12 rates were higher in patients without NS5A polymorphisms at baseline." Page. 299

Zeuzem,[23] 2015, multinational, C-EDGE study

Relevant findings:

SVR12 with (EBR+GZR)) in patients with HCV, GT-1b or GT 1a and with or without NS5A RAVs

HCV genotype	NS5A RAV present at baseline	Number of patients	Patients achieving SVR24 n (%)
GT 1a	yes	19	11 (58%)
	no	135	133 (99%)
GT 1b	yes	18	17 (94)
	no	112	112 (100)

Prevalence of NS5A RAVs

At baseline, NS5A RAVs were identified in 19 of 154 (i.e. 12%) GT 1a infected patients.
At baseline, NS5A RAVs were identified in 18 of 130 (i.e. 14%) GT 1b infected patients.

Authors' Conclusions

"Grazoprevir-elbasvir achieved high SVR12 rates in treatment-naïve cirrhotic and noncirrhotic patients with genotype 1, 4, or 6 infection. This once daily all-oral, fixed combination regimen represents a potent new therapeutic option for chronic HCV infection." Page 1

ASV = asunaprevir, DCV = daclatasvir, GT = genotype, HCV = hepatitis C virus, LDV = ledipasvir, NS5A = non-structural protein 5A, RAV = resistance associated variance, RBV = ribavirin, SMV = semiprevir, SOF = sofosbuvir, SVR = sustained virologic response

APPENDIX 6: Guidelines and Recommendations

Table A7: Summary of Guidelines and Recommendations

AASLD-IDSA,[27] 2016, USA

Recommendations

HCV GT 1a

For HCV GT 1a treatment naïve patients with without cirrhosis

"Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis and in whom no baseline high fold-change NS5A RAVs[§] for elbasvir are detected.
Rating: Class I, Level A"

For HCV GT 1a treatment naïve patients with compensated cirrhosis

"Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis and in whom no baseline high fold-change NS5A RAVs[§] for elbasvir are detected.
Rating: Class I, Level A"

For HCV GT 1a treatment naïve patients without cirrhosis - Alternative

"Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based RBV for 16 weeks is an Alternative regimen for patients with HCV genotype 1a infection who do not have cirrhosis but have baseline high fold-change NS5A RAVs[§] for elbasvir.
Rating: Class IIa, Level B"

For HCV GT 1a treatment naïve patients with compensated cirrhosis - Alternative

"Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based RBV for 16 weeks is an Alternative regimen for treatment-naïve patients with HCVgenotype 1a infection who have compensated cirrhosis and have baseline high fold-change NS5A RAVs[§] for elbasvir.
Rating: Class IIa, Level B"

HCV GT 1

For GT 1 HCV nonstructural protein (NS3) protease inhibitor (teleprevir, boceprevir, or simeprevir) plus PEG-IFN/RBV treatment experienced patients without cirrhosis

"Daily fixed-dose combination elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who do not have cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/RBV has failed. Genotype 1a patients who have baseline high fold-change NS5A RAVs[§] for elbasvir should have this treatment extended to 16 weeks.
Rating: Class IIa, Level B"

For GT 1 HCV nonstructural protein (NS3) protease inhibitor (teleprevir, boceprevir, or simeprevir) plus PEG-IFN/RBV treatment experienced patients with compensated cirrhosis

"Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based RBV for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have

Table A7: Summary of Guidelines and Recommendations

compensated cirrhosis, in whom a prior treatment with an HCV protease inhibitor plus PEG-IFN/RBV has failed. Genotype 1a patients who have baseline high fold-change NS5A RAVs[§] for elbasvir should have this treatment extended to 16 weeks.
Rating: Class IIa, Level B"

For GT 1 Simeprevir plus sofosbuvir treatment experienced patients

"Deferral of treatment is recommended, pending availability of data for patients with HCV genotype 1, regardless of subtype, in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed, who do not have cirrhosis, and do not have reasons for urgent retreatment.
Rating: Class IIb, Level C"

" Testing for resistance-associated variants that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended for patients with HCV genotype1, regardless of subtype, in whom prior treatment with the HCV protease inhibitor SMV+SOF has failed (no prior NS5A treatment), who have compensated cirrhosis,[‡] or have reasons for urgent retreatment. The specific drugs used in the retreatment regimen should be tailored to the results of this testing as described below.

When using nucleotide-based (eg, sofosbuvir) dual DAA therapy a treatment duration of 24 weeks is recommended, and weight-based RBV, unless contraindicated, should be added.

If available, nucleotide-based (eg, sofosbuvir) triple or quadruple DAA regimens may be considered. In these settings treatment duration ranges from 12 weeks to 24 weeks […], and weight-based ribavirin, unless contraindicated, are recommended.
Rating: Class IIb, Level C"

For HCV GT 1 NS5A inhibitor treatment experienced patients

"Deferral of treatment is recommended, pending availability of data for patients with HCV genotype 1, regardless of subtype, in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed, who do not have cirrhosis, and do not have reasons for urgent retreatment.
Rating: Class IIb, Level C"

" Testing for resistance-associated variants that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended for patients with HCV genotype 1, regardless of subtype, in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed, and who have compensated cirrhosis,[‡] or have reasons for urgent retreatment. The specific drugs used in the retreatment regimen should be tailored to the results of this testing as described below.

When using nucleotide-based (eg, sofosbuvir) dual DAA therapy a treatment duration of 24 weeks is recommended, and weight-based RBV, unless contraindicated, should be added.

If available, nucleotide-based (eg, sofosbuvir) triple or quadruple DAA regimens may be considered. In these settings treatment duration ranges from 12 weeks to 24 weeks […], and weight-based ribavirin, unless contraindicated, are recommended.
Rating: Class IIb, Level C"

([§] Includes G1a polymorphisms at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

[‡]For decompensated cirrhosis, please refer to the appropriate section. (http://www.hcvguidelines.org/printpdf/161

There w as no information w ith respect to NS5A so not described here.)

Table A7: Summary of Guidelines and Recommendations
KASL,[28] 2016, Korea
Recommendation "Patients infected with HCV genotype 1b with or without cirrhosis should be treated with daily daclatasvir (60 mg) and asunaprevir (200 mg) for 24 weeks. Patients infected with HCV genotype 1b in whom treatment with daclatasvir and asunaprevir is considered must be tested for NS5A RAVs L31F/I/M/V and/or Y93H prior to treatment. Patients with NS5A RAVs L31F/I/M/V and/or Y93H should be treated with an alternative regimen (A1)."
AASLD = American Association for the Study of Liver Disease, IDSA = Infection Disease Society of America, KASL = Korean Association for the Study of the Liver

APPENDIX 7 : Additional References of Potential Interest

Study did not meet inclusion criteria (as study population included > 10% patients who had prior treatment with DAA)

Ogawa E, Furusyo N, Yamashita N, Kawano A, Takahashi K, Dohmen K, et al. Effectiveness and safety of daclatasvir plus asunaprevir for HCV genotype 1b patients aged 75 and over with or without cirrhosis. Hepatol Res. 2016 May 3. [Epub ahead of print]