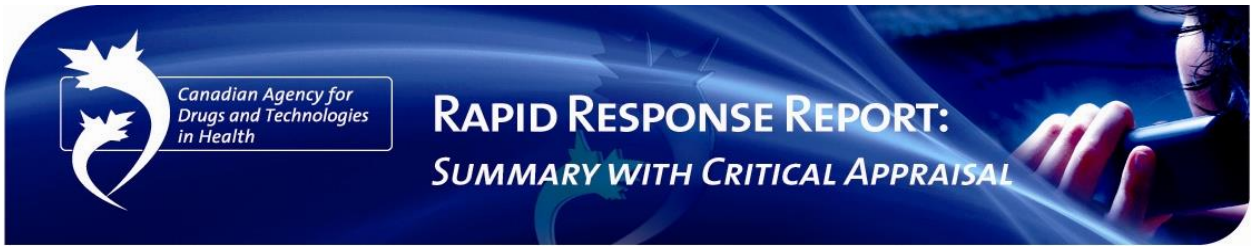

TITLE: Re-treatment for Patients with NS5A Resistant-Associated Variants of Hepatitis C Virus: A Review of Clinical Effectiveness

DATE: 28 July 2016

CONTEXT AND POLICY ISSUES

Hepatitis C virus (HCV) is a major cause of chronic liver disease, with an estimated 130 to 150 million people have chronic HCV infection, globally.[1] In 2010, more than 500,000 deaths worldwide were attributed to infection by HCV.[2] According to a 2015 factsheet published by the Canadian AIDS Treatment Information Exchange (CATIE), an estimated 220,697 to 245,987 Canadians were living with chronic hepatitis C at the end of 2011, and 10,180 HCV diagnoses were reported to the Public Health Agency of Canada in 2012, representing 29.3 cases of HCV per 100,000 Canadians.[3]

The goal of HCV treatment is to achieve sustained virological response (SVR), defined as having a negative or undetectable HCV RNA test result 12 to 24 weeks after the end of treatment.[4] Until recently, HCV treatment was based on therapy with interferon (IFN) and ribavirin (RBV), which required weekly injections for 48 weeks. The cure rate for this therapy is approximately 50%, but causes frequent and sometimes life-threatening adverse reactions.[1] Interferon-free direct-acting antiviral (DAA) agents-based regimens have become the current standard of care for HCV therapy.[5] They work by inhibiting enzymes that are essential for HCV replication such as NS3-4A proteases, NS3 helicase, and HCV replication proteins NS5B, and NS5A.[2] Treatments with DAA agents have resulted in high efficacy with SVR rates of more than 90%.[6] However, these drugs fail to eliminate the HCV infection in 1% to 7% of patients.[6] HCV drug-resistant variants are detected in most patients who do not achieve viral eradication.

Resistance-associated variants (RAVs) affect the nucleotide sequence coding for proteins on which different DAA drugs act.[6] Therefore, HCV RAVs may reduce susceptibility to antivirals, patients who carry RAVs may be at risk of disease progression, and the variants may be transmitted from person to person.[7] NS3-4A RAVs tend to disappear after treatment discontinuation, whereas NS5A and NS5B variants persist longer.[7] NS5A RAVs developed during treatment can persist even 3 years after treatment discontinuation, potentially affecting retreatment (also known as “salvage” therapy) of the relapsed patient with the same DAA-class.[8] Retreatment options for HCV patients with NS5A RAVs who have failed previous NS5A

inhibitor therapy are not well defined. This review aims to summarize the evidence on the clinical effectiveness of retreatment choices for patients with NS5A RAVs who failed on previous NS5A inhibitor therapy.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of re-treatment in patients with NS5A resistance-associated variants of hepatitis C virus who have failed on treatment with NS5A inhibitors?

KEY FINDINGS

One low quality study[9] showed that 12 weeks therapy with a combination regimen of sofosbuvir (SOF) and simeprevir (SIM) was an effective retreatment in chronic HCV GT 1 or 4 patients who had failed a previous daclatasvir (DCV)-based regimen. The SVR12 rate in patients with NS5A RAVs was 84.6%, whereas the overall SVR12 was 87.5%. Another low quality study[10] found that retreatment with a combination of ledipasvir (LDV) and SOF for 12 weeks was effective retreatment in HCV-infected patients with early-stage hepatic fibrosis who had previously failed a short-course (4 or 6 weeks) of combination therapy containing LDV/SOF. The SVR12 in patients with NS5A RAVs was 89.7% whereas the overall SVR12 was 91%. A third low quality study[11] showed that the addition of ribavirin (RBV) to a combination therapy with LDV and SOF for 24 weeks was effective retreatment for patients who had failed 12 weeks initial treatment with LDV/SOF combination alone. The SVR12 in patients with NS5A RAVs was 86% whereas the overall SVR12 was 89%.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, Ovid Embase, 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 retrieval by publication 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 June 29, 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 genotypes 1 to 6, including subtypes 1a and 1b, who have failed on treatment with regimens containing NS5A inhibitors (elbasvir, daclatasvir, ombitasvir, ledipasvir and velpatasvir)
Intervention	Longer treatment duration with regimens containing NS5A inhibitors (with or without ribavirin), adding drugs, or switching treatment regimens in patients with NS5A resistance-associated variants
Comparator	Longer treatment duration with regimens containing NS5A inhibitors (with or without ribavirin), or switching treatment regimens in patients without NS5A resistance-associated variants
Outcomes	Treatment response (SVR12)
Study Designs	Health technology assessments, Systematic Reviews and/or /Meta-Analyses, Randomized Controlled Trials, Non-Randomized Studies

HCV = Hepatitis C virus; SVR = sustained virological response

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 as they did not provide adequate information to conduct critical appraisal. Additional references of potential interest are provided in appendix 5.

Critical Appraisal of Individual Studies

The quality of the included studies was assessed using the Downs and Black checklist.[12] Summary scores were not calculated; rather, a review of the strengths and limitations of each included study were described narratively. The strengths and limitations of the individual studies are summarized in Appendix 3.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 350 citations were identified in the literature search. Following screening of titles and abstracts, 329 citations were excluded and 21 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of the 23 potentially relevant articles, 20 publications were excluded as they did not provide adequate information (i.e., review articles, conference abstracts, editorials), while three publications[9-11] met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Study Design

The three included studies[9-11] had a non-randomized, open-label, non-comparative design. The studies by Hézode et al.[9] and Wilson at al[10] were single-center studies whereas the study by

and Copper et al.[11] was conducted at nine sites. Hézode at al[9] described their study as a "real-world" study involving patients from clinical practice and without the usual restrictions of a clinical trial. Wilson et al.[10] reported outcomes of a separate arm of an eight-arm phase 2a study sponsored by the National Institute of Allergy and Infectious Diseases (NIAID),[13] whereas the study by Cooper et al.[11] was a sub-study of the ION-4 study.[14] The NIAID study was an interventional study to assess the safety, tolerability, and efficacy of treatment of several selective HCV nucleotide NS5B, NS5A, non-nucleotide NS5B and NS3 inhibitors in different patient groups, including naïve and treatment-experienced patients. Each study arm had a unique focus, differing from the others in either the intervention(s) of interest or the study population. The ION study was a phase 3, multicenter, interventional study to investigate the efficacy and safety of LDV 90 mg /SOF 400 mg fixed-dose combination in patients with chronic genotype 1 (GT-1) or GT-4 HCV and HIV-1 co-infection.

Country of Origin

The study by Hézode et al.[9] was conducted in France, and the studies by Wilson at al[10] and Copper et al.[11] were conducted in the USA. All the studies[9-11] were published in 2016.

Patient Population

The study by Hézode et al.[9] included a total of 16 patients with chronic HCV infection who had relapsed after previous treatment with DCV-based regimen. The mean age of the patients was 54.9 years and most (81%) of them were male. Eleven of the patients (68.8%) were infected with HCV GT-1a, whereas three (18.8%) had HCV GT-1b and two (12.5%) had HCV GT-4. At baseline of retreatment, 14 patients (87.5%) had HCV RNA >800,000 IU/mL and NS5A RAVs were observed in 12 (75.0%) of the 16 patients. Nine patients had cirrhosis and 7 had severe fibrosis. No patient had decompensated cirrhosis and/or Child-Pugh B or C score.

The study by Wilson et al.[10] included 34 patients with HCV GT-1 and early-stage liver fibrosis who previously failed four to six weeks of therapy with LDV/SOF combination plus one or both of two experimental drugs (GS-9669 and/or GS-9451). The mean age of the patients was 58.9 years, and they were predominantly male (82.3%) and black (82.3%). Twenty-six of the patients (76.5%) were infected with HCV GT-1a, and eight had HCV GT-1b. At the baseline for retreatment median HCV viral load was 1.3×10^6 IU/mL, and 29 (85.3%) of the patients had NS5A RAVs. The majority (97.1%) of patients had early-stage liver disease (stage 0–2).

The study by Cooper et al.[11] enrolled nine HCV/HIV co-infected patients who had relapsed after 12 weeks treatment with LDV/SOF combination. The mean age of the patients was 57.0 years, and they were predominantly male (77.8%) and all black (100%). The mean HCV RNA at the re-treatment baseline was 6.4 $\log_{10}$ IU/mL. Seven patients (77.8%) were infected with HCV GT-1a, two (22.2%) had HCV GT-1b, and two (22.2%) had cirrhosis. NS5A RAVs were detected in seven (77.8%) of the patients.

Interventions and Comparators

In the study by Hézode et al.,[9] the patients were retreated with a combination of once-daily SOF (400-mg) and SIM (150-mg) without RBV for 12 weeks. The previous treatment regimens were DCV + pegylated (Peg)-IFN + RBV (for 13 patients), or DCV + Peg-IFN + asunaprevir (ASV) + RBV (for 3 patients). Thus the retreatment approach switched therapy from NS5A inhibitor-based regimen to a combination of NS5B inhibitor (SOF) and a protease inhibitor

(SIM). The mean time from the end of the previously failed treatment to the initiation of retreatment was 31.5 ± 11.8 months. All 16 patients completed the 12-week retreatment course, and 12 weeks of post-retreatment follow-up were available for all patients.

In the study by Wilson et al.,[10] the patients were retreated with a LDV/SOF fixed-dose combination for 12 weeks. Thus the retreatment used the same combination NS5A/NS5B inhibitors as in the initial treatment, but extended the duration of therapy from four or six weeks to 12 weeks. The doses used were not specified. The mean time from virologic failure in the initial failed therapy to the initiation of retreatment was 25.1 weeks. There was 12 weeks of post-retreatment follow-up.

In the study by Cooper et al.,[11] the patients were retreated with a once daily fixed-dose combination of LDV/SOF (actual dose not specified) plus weight-based RBV (1000 mg in patients with a body weight of <75 kg, and 1200 mg in patients with a body weight of ≥75 kg) in a divided dose for 24 weeks. Thus the retreatment added RBV to the same combination NS5A/NS5B inhibitors used in the initial treatment, but the duration of therapy was extended from 12 weeks to 24 weeks. The median time from virologic failure in the primary study to initiation of retreatment was 40 days. The duration of post-retreatment follow-up was not specified.

Outcomes

The primary efficacy endpoint in all the included studies[9-11] was SVR12, defined as sustained virologic response 12 weeks after completion of treatment (in this case retreatment). Plasma HCV RNA levels were measured using the HCV Assay.[9,10] Secondary efficacy endpoints in the studies by Hézode et al.[9] and Wilson et al.[10] included the proportion of patients with unquantifiable HCV viral load at specified time points during and after treatment. Based on assessments during the re-treatment period, Hézode et al.[9] classified patients as rapid responders (HCV RNA undetectable at week 4) early responders (HCV RNA undetectable at week 8), or late responders (HCV RNA was detectable at weeks 4 and 8, but undetectable at week 12. In all the studies[9-11] patients were assessed for safety. Safety endpoints included frequency and severity of adverse events (AEs), discontinuations due to AEs, and changes in clinical laboratory values.

Summary of Critical Appraisal

All three included studies[9-11] clearly described the objectives of study and the main outcomes measured. They also described the characteristics of patients included in the studies, the interventions of interest, and the main findings.

In the study by Hézode et al.,[9] the "real-world" approach which included patients from routine clinical practice had less restrictive inclusion criteria than regular clinical trials and thus was expected to result in a more diverse study population. However, the criteria for inclusion and exclusion were not adequately described and the potential for selection bias cannot be ruled out. The study[9] did not include any patients with decompensated cirrhosis (Child-Pugh score B or C patients) and most of the included patients (68.8%) were infected with HCV GT 1a, with only three patients infected with HCV GT-1b (19%) and two patents infected with HCV GT-4. Therefore, the generalizability of the study findings to patients with decompensated cirrhosis or those infected with HCV genotypes that were not tested is uncertain.

The study by Wilson et al.[10] included patients who had relapsed after four to six weeks of treatment with LDV/SOF,[10] and they were retreated with the same drugs for 12 weeks. However, it was not reported whether the dose(s) of LDV/SOF in the initial therapy was/were maintained or adjusted during retreatment. Thus, it is unknown if the successful retreatment was due solely to the extended duration of therapy. It is unknown if the findings are generalizable in HCV infected patients who relapse after a longer duration of treatment than four or six weeks. The consensus guideline from the Canadian Association for the Study of the Liver recommends that LDV/SOF should be given for eight weeks in non-cirrhotic, treatment-naïve patients with HCV GT-1, and extending the therapy to 12 weeks can be considered where baseline HCV RNA ≥6million IU/mL.[15] In cirrhotic, treatment-naïve patients with HCV GT-1, the guideline recommends that treatment with LDV/SOF be given for 12 weeks.[15]

In the retreatment period of the study by Cooper et al.,[11] HCV/HIV co-infected patients who relapsed after 12 weeks treatment with LDV/SOF, maintained the HIV antiretroviral regimens they received during the initial treatment, thus minimizing the confounding effect of the HIV co-treatment. All the patients in this study[11] were black and infected with HCV GT-1(GT 1a, n = 7; GT 1b n =2). Thus generalizability of study findings in patients infected with untested HCV genotypes is uncertain.

All of the included studies[9-11] were non-randomized, open-label studies, with small sample sizes. Thus by design they had a higher potential for bias than randomized studies, and their small sample sizes increased the potential that their findings could be due to chance. In all, only two NS5A inhibitors (DCV and LDV) were involved in the included studies making it uncertain whether the findings of could be generalizable in HCV infected patients with NS5A RAVS who failed therapy with other NS5A inhibitors.

The study by Wilson et al.[10] was a non-industry sponsored study reviewed and approved through a peer-review process and study management. Thus the potential of influence from competing interest was reduced. Some authors in the studies by Hézode et al.[9] and Cooper et al.[11] declared association with industry as advisors, consultants, speakers, employees and stock holders, and/or recipients of research grants.

Summary of Findings

What is the clinical effectiveness of re-treatment in patients with NS5A resistance-associated variants of hepatitis C virus who have failed on treatment with NS5A inhibitors?

The literature search for this review found three low quality studies that assessed and reported re-treatment outcomes for HCV infected patients with NS5A RAVSs who had failed previous therapy containing NS5A inhibitors. Additional references of potential interest are provided in appendix 5.

One study[9] (n =16) found that 14 of 16 (87.5%) HCV patients who had failed to achieve SVR on previous therapy containing DCV achieved SVR12 following 12 weeks retreatment with a combination of SOF and SIM (i.e. NS5B inhibitor and a protease inhibitor combination); without RBV. Eleven of 13 patients (84.6%) who had NS5A RAVs (Q30E/R/K, L30S, L31M, andY93C/H) at retreatment baseline achieved SVR12. One of the two patients who failed to achieve SVR12 had Q30K and the other had L31M substitutions as the dominant viral populations at retreatment baseline, which persisted 12 weeks after retreatment.

Apart from SVR12, the study reported that all the patients (n=16) achieved HCV RNA below the lower limit of quantification (LLOQ) by the end of treatment, with no on-treatment virological failure. The LLOQ was defined as HCV RNA <12 IU/mL. HCV RNA was undetectable in 10 patients (62.5%) by week-4 (rapid responders) and in one patient by week-8 (early responder). The 5 (31.3%) remaining patients were classified as late responders because they had detectable HCV RNA at weeks 4 and 8, but not at week-12. All rapid and early responders achieved SVR12 whereas three of five late responders achieved SVR12. The two late responders who relapsed had cirrhosis and were infected with HCV GT 1a.

One study[10] (n=34) found that 91.2% of chronic HCV GT-1 patients who had previously failed short-course (four or six weeks duration) of combination therapy containing LDV/SOF achieved SVR12 after retreatment with LDV/SOF for 12 weeks. Prior to retreatment, 85.3% (29 of 34) patients had NS5A RAVs (K24R, M28T, Q30H/R/L/T, L31M/V/I, and Y93H/N). Twenty-six of 29 NS5A RAV patients (89.7%) who had NS5A RAVs prior to retreatment achieved SVR12. The patient who experienced viral relapse had an L31M NS5A RAV at baseline and developed a Y93H NS5A RAV in addition to maintaining the L31M at relapse after short-course therapy.[10] Two of the 29 patients with NS5A RAVs prior to retreatment withdrew from the study after day 0 and were lost to follow-up.

One study[11] (n=9), found that 88.8% (8 of 9) HCV/HIV co-infected patients who relapsed after receiving 12 weeks treatment with LDV/SOF achieved SVR12 after re-treatment with LDV/SOF plus RBV for 24 weeks. Six (85.7%) of seven patients who had NS5A RAVs (L31M/V/I, H58D, and Y93N/H) at retreatment baseline achieved SVR12 after re-treatment.

All the patients in this study[11] (n=9) had undetectable HCV RNA (defined as HCV RNA <25 IU/mL) by week 4 of re-treatment. There was no patient who experienced virologic breakthrough, and no patient was nonresponsive to the retreatment. The patient who did not achieve SVR12 experienced virologic relapse 4 weeks after retreatment. Although the patient was reported to be adherent to the study drugs as measured by pill count at study visits, he had developed a viral population of >99% NS5A RAV L31M by the time of relapse to the primary treatment, and was observed to have L31M (98%) and L31V (2%) at relapse following retreatment.

Retreatment regimens in the included studies[9-11] were safe and well tolerated, with generally mild side effects and no discontinuations due to adverse events. The study by Hézode et al.[9] had no grade 3 or 4 AEs, serious AEs (SAEs) or grade 3 or 4 laboratory abnormalities. Thirty patients (88.2%) in the study by Wilson et al.[10] experienced AEs, most of which were mild in severity, with the most common being grade-1 constipation (5.9%). While on study medications, hyperglycemia was detected in one patient (2.9%) with a history of type 2 diabetes mellitus, and two patients (5.9%) developed grade 3 cholesterol elevations, one of whom had an elevated cholesterol measurement at baseline. There were no grade 4 laboratory abnormalities.[10] In the study by Cooper et al.,[11] four patients (44.4%) required modification or interruption of their RBV dose. The details of these dose modifications/interruptions were not provided.

Limitations

A major limitation of this review was that the literature search did not find any methodologically rigorous studies that met the inclusion criteria. The included studies[9-11] had small sample sizes and they were all open-label in design. Further, selection of patients who participated in the studies was not adequately described. Two studies[10,11] in which patients were retreated for

extended treatment duration with the same drugs as were used in the previous therapy they failed did not specify whether the doses in the initial therapy were maintained or adjusted during the retreatment. In all, patients who were retreated had failed only two NS5A inhibitors (DCV and LDV). Thus it is unknown if patients who fail other NS5A inhibitors could be successfully retreated using the same intervention strategies described in the included studies of this review.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

This review included three studies in which different strategies were employed for successful retreatment of HCV infected patients who had failed a previous treatment with a NS5A inhibitor-based therapy. In one low quality study,[9] HCV patients who had failed a DCV-based regimen were switched to a combination therapy with SOF plus SIM for 12 weeks which resulted in SVR12 rates of 84.6% and 87.5% in patients with NS5A RAVs and the overall study population, respectively. In another low quality study[10] HCV patients who had previously failed 4 or 6 weeks therapy with a regimen containing LDV/SOF were retreated with LDV/SOF combination for 12 weeks achieved SVR12 rates of 89.7% and 91.2% in patients with NS5A RAVs and in the overall study population, respectively. A third low quality study[11] showed that the addition of RBV to a combination therapy with LDV and SOF for 24 weeks was effective retreatment for patients who had failed 12 weeks initial treatment with LDV/SOF combination alone. The SVR12 rates in this study[11] were 85.7% and 88.8% in patients with NS5A RAVs and in the overall study population, respectively. The retreatment regimens in all the studies[9-11] were safe and well tolerated.

In general, the evidence from these studies[9-11] suggests that patients with NS5A RAVs who have failed on previous treatment with NS5A inhibitors could be successfully retreated with a combination of drugs selected from different classes of DAA other than the initial drug, or by using the initial drugs for an extended duration of therapy with or without RBV. However, the small sample sizes and low quality of the included studies preclude a definitive conclusion.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

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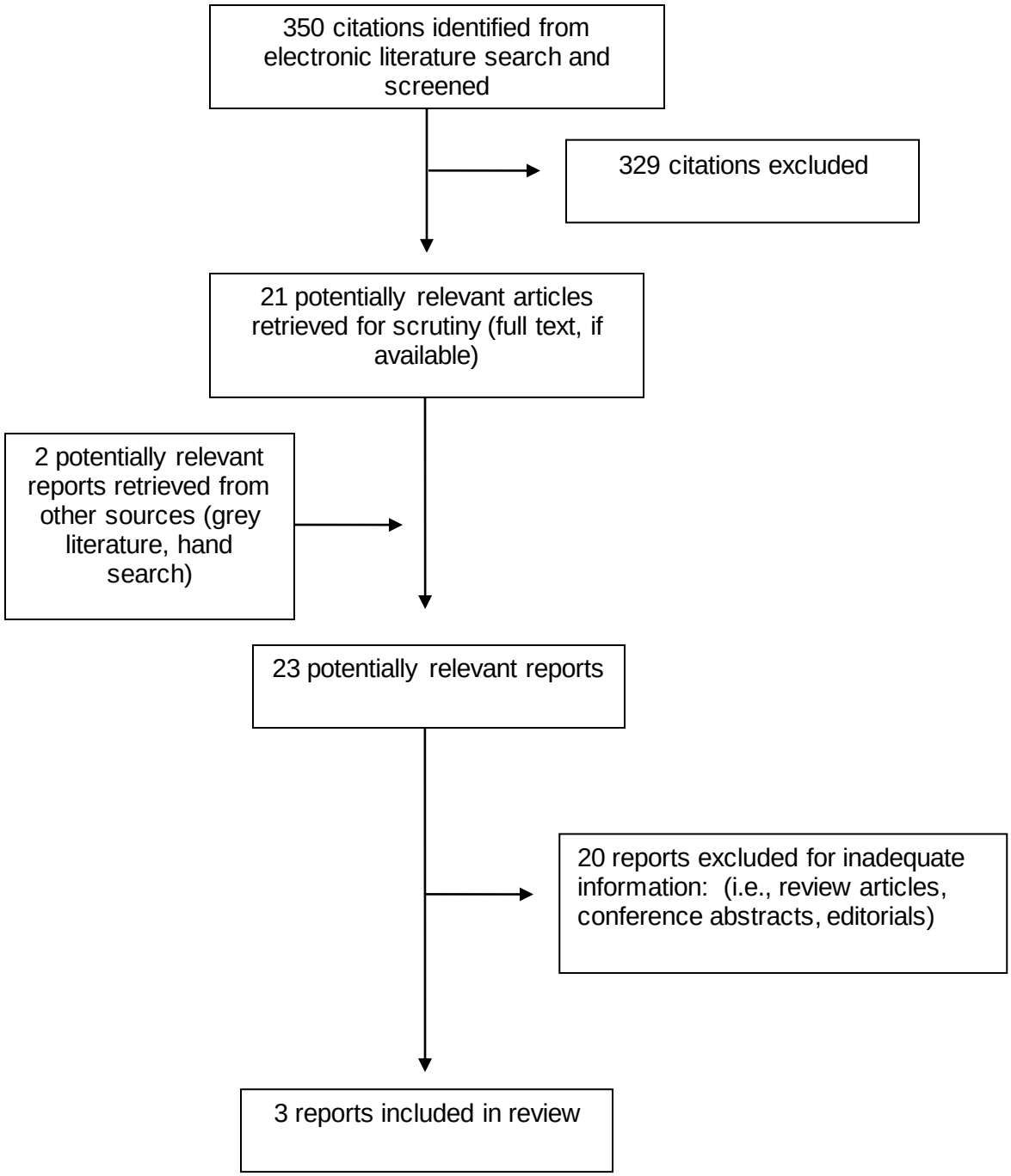
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Hézode, 2016[9] France	A single-center "real-world" intervention study.	Sixteen patients (mean age 54 years) who had failed to achieve SVR on NS5A-based therapy with DCV + Peg-IFN + RBV (n = 13) or DCV +Peg-IFN+ ASV + RBV (n = 3) They had advanced fibrosis or compensated cirrhosis, and the median baseline HCV-RNA level was 1.38 3 10^6 IU/mL	SOF 400-mg capsule once-daily plus SIM 150-mg capsule once-daily for 12 weeks, with 12 weeks of post-retreatment follow-up. Mean time from the end of failed therapy to the initiation of retreatment was 31.5 ± 11.8 months	N/A	The primary endpoint was SVR12. On-treatment response was also assessed
Wilson 2016,[10] USA	One arm of the 8-arm phase 2a, open-label NIAID study [a]	34 patients with HCV (genotype-1) and early-stage liver fibrosis who previously failed 4 or 6 weeks of LDV/SOF. Twenty-nine patients (85%) had NS5A-resistant variants prior to retreatment.	LDV/SOF for 12 weeks, with 12 weeks of post-retreatment follow-up. Mean time initial treatment failure to initiation of retreatment was 25.1 weeks (range 5–32 weeks).	N/A	The primary endpoint was SVR12
Cooper, 2016[11] USA	An open-label, re-treatment sub-study of the ION study [b] conducted at nine sites	Nine black HIV/HCV co-infected patients (mean age 57 years) who relapsed after treatment with LDV/SOF for 12 weeks.	LCD/SOF plus RBV for 24 weeks. Post retreatment follow-up duration was not specified. The median time treatment failure to initiation of retreatment 40 days (range, 34–70 days)..	N/A	SVR12 and safety

ASV = asunaprevir; HCV = hepatitis C virus; HIV = human immunodeficiency virus; DCV = daclatasvir; LDV = ledipasvir; N/A = not applicable; NIAID = National Institute of Allergy and Infectious Diseases; Peg-IFN = pegylated interferon; RBV = ribavirin; SOF =

sofosbuvir; SVR = sustained virologic response; SVR12 = SVR 12 weeks after completion of therapy; USA = United States of America.

[a] The NIAID study was a phase 2, non-randomized multi-arm (A-H), open-label interventional study to assess the safety, tolerability, and efficacy of treatment of several selective HCV nucleotide NS5B, NS5A, non-nucleotide NS5B and NS3 inhibitors in different patient groups, including naïve and treatment experienced patients. Each study arm had a unique focus, being different in either the intervention(s) of interest or the study population. Sponsored by National Institute of Allergy and Infectious Diseases[13]

[b] The ION study was a phase 3, multicenter, open-label interventional study to investigate the efficacy and safety of Ledipasvir 90 mg /sofosbuvir 400 mg fixed-dose combination for 12 weeks in patients with chronic genotype 1 or 4 HCV and HIV-1 co-infection. Sponsored by Gilead Sciences[14]

APPENDIX 3: Critical Appraisal of Included Publications

Table A2: Strengths and Limitations of Included Study using link to the Downs and Black Checklist[12]

Strengths	Limitations
Hézode, 2016[9]	
• The objectives of the study and the main outcomes were clearly described • The interventions of interest and main findings, as well as the characteristics of patients included in the study were clearly described. • The "real-world" approach which included patients from routine clinical practice has less restrictive inclusion criteria than regular clinical trials and thus was expected to result in a more diverse study population.	• The study was described as "real-world" study which included patients from routine clinical practice. Although this approach is expected to have a less restrictive inclusion criteria resulting in a diverse study population, selection bias cannot be ruled out in the absence of a mechanism to determine which patients could be included or excluded. • With a sample size of 16 patients and without a sample size calculation, it is uncertain whether the study was adequately powered to detect meaningful differences. • Patients with decompensated cirrhosis (Child-Pugh score B or C patients) were excluded, and most of the included patients (68.8%) were infected with HCV GT 1a. Adding these to the small sample size and the fact that only patients who failed past daclatasvir-based treatment were included, a wider application of the findings is uncertain. • Four of the 11 authors had some form of association with industry and had acted as advisors, consultants or speakers, and/or received research grants.
Wilson, 2016[10]	
• The objectives of the study and the main outcomes were clearly described • The interventions of interest and main findings, as well as the characteristics of patients included in the study were clearly described. • This was a non-industry sponsored study in which the sponsor (the Regulatory Compliance and Human Participants Protection Branch of NIAID) reviewed and approved the study through a peer-review process and study management. Thus the potential of influence from competing interest was reduced.	• This was a non-randomized, non-comparative, single-center, open-label, phase 2a trial with 34 participants. With no sample size calculation, there is uncertainty to whether the study was adequately powered to detect meaningful differences. • Patients included in the study predominantly (82.4%) black (African American) and male (82.4%), thus it remains uncertain whether findings are generalizable to female and non-black populations. However, the efficacy outcome (SVR12) was objectively determined through assays not likely to be

	affected by sex and race. • The included patients had relapsed after 4 to 6 weeks of treatment with LDV/SOF plus either one or both of two investigational drugs in a primary study (the SYNERGY study). It is unknown if the findings will be generalizable in HCV patients who relapse on other treatments and at different times.
Cooper, 2016[11]	
• The objectives of the study and the main outcomes were clearly described • The interventions of interest and main findings, as well as the characteristics of patients included in the study were clearly described. • Patients continued on the same HIV antiretroviral regimens as in the primary (ION) study, thus minimizing the confounding effect of the HIV co-treatment.	• With a sample size of nine patients, and without a sample size calculation, it is uncertain whether the study was adequately powered to detect meaningful differences. • All the patients were black, infected with HCV GT-1(GT 1a, n = 7; GT 1b n =2) who failed past ledipasvir/sofosbuvir combination treatment. Thus generalizability of study findings in patients with untested HCV genotypes and/or those who failed on a different NS5A agent is uncertain. • It is unknown whether the dose of ledipasvir/sofosbuvir fixed-dose combination was the same in the retreatment as that used in the primary treatment in which the patients relapsed. • This study was sponsored by industry and the authors had association with industry as advisors, consultants, speakers, employees and stock holders, and/or recipients of research grants.

ASV = asunaprevir; HCV = hepatitis C virus; HIV = human immunodeficiency virus; DCV = daclatasvir; LDV = ledipasvir; N/A = not applicable; NIAID = National Institute of Allergy and Infectious Diseases; Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response; SVR12 = SVR 12 weeks after completion of therapy; USA = United States of America

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A3: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Hézode, 2016[9]	
• Re-treatment resulted in overall SVR12 rate of 87.7% (14 of 16 patients). The SVR12 rat in patients with NS5A RAVs was 84.6% (11 of 13 patients). • All 16 patients achieved HCV RNA below LLOQ (defined as <12 IU/mL) by the end of treatment. • Rapid response (defined as HCV RNA < LLOQ at week 4) was observed in 62.5% of the patients. • The two patients who did not achieve SVR12 relapsed by the 4th week after the end of re-treatment. They were both infected by HCV-GT 1a and they had cirrhosis. NS5A and NS3 protease RAVs were detected in both patients at baseline.	• "In conclusion, these real-life findings suggest high efficacy, good tolerance, and feasibility of a combination regimen of SOF and SIM in patients infected with chronic HCV GT 1 or 4 infection who have failed a previous DCV-based regimen. The study shows that patients who achieved rapid or early responses were more likely to achieve SVR than those achieving late responses." "These results support the concept of retreating NS5A inhibitor failures with SOF combined with SIM and provide a signal as to which patient profiles could require longer duration of therapy and or addition of RBV. Such patients may include those with cirrhosis and/or pre-existing RAVs."[9] page 1815 • "However, the most difficult-to-cure patients may need more than 12 weeks of treatment and/or the addition of RBV."[9] page 1809
Wilson, 2016,[10]	
• The SVR12 rate was 91.2% (31 of 34 patients) after retreatment. One patient (2.9%) relapsed. • The SVR12 in patients with NS5A RAVs was 89.7% (27 of 29 patients)	• "Our data do suggest, however, that the presence of RAVs identified here do not preclude successful retreatment with some or all of the drugs used in the initial regimen."[10] Page 284 • "In summary, our data support that retreatment with LDV/SOF is a safe, effective, and tolerable option for HCV-infected patients with early-stage hepatic fibrosis who have previously failed short-course combination DAA therapy containing LDV/SOF."[10] Page 284, 287 • "In patients who previously failed short-course combination DAA therapy, we demonstrate a high SVR rate in response to 12 weeks of LDV/SOF, even for patients with NS5A resistance-associated variants."[10] Page 280

Table A3: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
Cooper, 2016[11]	
• The overall SVR rate was 88.8% (eight of the nine patients, while the SVR rate among patients who had NS5A RAVs was 85.7% (six of seven patients). • All patients had HCV RNA <25 IU/mL by week 4 of retreatment (target not detected). • No patients experienced virologic breakthrough or nonresponse.	• "The addition of ribavirin to ledipasvir/sofosbuvir in this re-treatment substudy may account for the improved SVR outcome in our study; however, the small sample size precludes definitive conclusion" "This high SVR12 rate was achieved in patients harboring high fold-change NS5A RAVs and provides proof of concept for retreatment strategies in patients failing NS5A regimens."[11] page 3 • "These results suggest an effective salvage therapy for patients for whom direct-acting antiviral treatment has failed."[11] page 1

DAA = direct-acting antiviral agent; EOT = end of treatment; HCV = hepatitis C virus; ITT = intention-to-treat; LDV = ledipasvir; LLOQ = lower limit of quantification; N/A = not applicable; RAVs = resistance-associated variants; SOF = sofosbuvir; SVR = sustained virologic response

APPENDIX 5: Additional References of Potential Interest

Conference abstracts excluded for inadequate information to conduct critical appraisal

1. Lawitz E, Flamm S, Yang JC, Pang PS, Zhu Y. Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks. J Hepatol. 2015;62 Suppl 2:S192.

2. Poordad F, Bennett M, Sepe TE. Retreatment of HCV genotype 1 DAA-failures with ombitasvir/paritaprevir/r, dasabuvir, and sofosbuvir [abstract]. Hepatology. 2015;62(6):1392A.