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Screening for Hepatitis C Virus Infection in Adolescents and Adults: A Systematic Review Update for the U.S. Preventive Services Task Force

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Structured Abstract

Background: Prior reviews on hepatitis C (HCV) infection screening and treatment used by the U.S. Preventive Services Task Force (USPSTF) to inform its 2013 recommendation found interferon-containing antiviral therapies associated with sustained virologic response (SVR) rates of 68 percent to 78 percent and an association between SVR after antiviral therapy and improved clinical outcomes. Interferon-containing regimens were associated with a high rate of harms. Since the prior reviews, interferon-containing antiviral therapies have been replaced by all-oral direct acting antiviral (DAA) regimens.

Purpose: To systematically review the evidence on screening for HCV infection in asymptomatic adults and adolescents, including effects of DAA regimens and interventions to prevent mother-to-child transmission.

Data Sources: We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, Ovid MEDLINE and ClinicalTrials.gov through February 2019, manually reviewed reference lists, and conducted literature surveillance through November 22, 2019.

Study Selection: Randomized controlled trials (RCTs), non-randomized trials, and cohort studies of HCV screening, antiviral therapy, and interventions to prevent mother-to-child transmission of HCV infection on SVR and clinical outcomes; and cohort studies on the association between an SVR after antiviral therapy versus no SVR and clinical outcomes. Treatment studies focused on populations without cirrhosis who are more likely to be asymptomatic and identified by screening.

Data Extraction: One investigator abstracted data, and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF.

Data Synthesis (Results): No study evaluated the benefits of HCV screening versus no screening, or the yield of repeat versus one-time screening. Previously reviewed studies found that HCV screening might be associated with negative psychological and social consequences, but had important methodological limitations; no new studies were identified. One new study found similar diagnostic yield of risk-based and birth cohort screening, but it was retrospective and assumed perfect implementation of risk-based screening. Ten trials reported improvements in some quality of life and functional outcomes following DAA treatment compared with prior to treatment, but differences were small, studies were open-label, and there was no non-DAA comparison group. Forty-nine trials found DAA regimens associated with pooled SVR rates that ranged from 95.5 percent to 98.9 percent across genotypes; rates of serious adverse events (1.9%) and withdrawal due to adverse events (0.4%) were low. Seven trials reported SVR rates in adolescents with DAA therapy similar to those observed in adults. An SVR after antiviral therapy was associated with decreased risk of all-cause mortality (13 studies, pooled hazard ratio [HR] 0.40, 95% confidence interval [CI] 0.28 to 0.56), liver mortality (4 studies, pooled HR 0.11, 95% CI, 0.04 to 0.27), cirrhosis (4 cohorts in 3 studies, pooled HR 0.36, 95% CI, 0.33 to 0.40), and hepatocellular carcinoma (20 studies, pooled HR 0.29, 95% CI, 0.23 to 0.38) versus

no SVR, after adjustment for potential confounders. New evidence on interventions to reduce the risk of mother-to-infant transmission was limited and did not change the conclusion from the prior review that no intervention has been clearly demonstrated to reduce risk.

Limitations: Most DAA trials were not randomized and did not have a non-DAA comparison group, almost all DAA trials relied on SVR as the main efficacy outcome, observational studies varied in how well they adjusted for confounders, and few studies evaluated the effectiveness of DAA regimens in adolescents.

Conclusions: The USPSTF previously determined that HCV screening is highly accurate. Currently recommended all-oral DAA regimens are associated with very high SVR rates (95.5% to 98.9% across genotypes) and few harms relative to older antiviral therapies. An SVR after antiviral therapy is associated with improved clinical outcomes compared with no SVR, after adjusting for potential confounders. Direct evidence on the benefits of HCV screening remains unavailable, and direct evidence on the effects of antiviral therapy on clinical outcomes remains limited but indicates improved long-term outcomes.

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Chapter 1. Introduction and Background

Purpose

The purpose of this report is to systematically review the evidence on screening for hepatitis C virus (HCV) infection in asymptomatic adults and adolescents without known liver enzyme abnormalities. This report updates prior (2013) U.S. Preventive Services Task Force (USPSTF) reviews on screening for HCV infection[1,2] and prenatal screening,[2,3] and a comparative effectiveness review on antiviral treatments.[4,5] Although prior reports focused on benefits and harms of screening and treatment in adults, this report expands the population to include adolescents. For treatments, this report focuses on currently recommended direct acting antiviral (DAA) therapies and interventions to potentially reduce risk of mother-to-child transmission. It will be used by the USPSTF to update its 2013 recommendation on screening for HCV infection in adults and potentially inform a new recommendation on HCV screening in adolescents.

In 2013, the USPSTF recommended screening for HCV infection in adults at high risk for infection and recommended offering one-time screening for HCV infection in adults born between 1945 and 1965 ("birth cohort" screening) (**B Recommendation)**.[6] This recommendation represented a change from the prior (2004) USPSTF recommendation, which found insufficient evidence to recommend for or against HCV screening in adults at high risk for infection (**I recommendation**); the 2004 USPSTF recommendation did not address birth cohort screening and recommended against HCV screening in persons not at increased risk (**D recommendation**).[7] The USPSTF did not issue a recommendation specifically on prenatal HCV screening, but noted that antiviral therapies were contraindicated during pregnancy and found inadequate evidence that labor management and breastfeeding strategies in HCV-infected persons are effective at reducing risk for mother-to-child transmission.

The basis for the change in the 2013 USPSTF recommendation was evidence that newer antiviral therapies are more effective than prior therapies in achieving the intermediate outcome of sustained virologic response (SVR) and evidence showing that SVR after antiviral therapy is associated with improved clinical outcomes (all-cause and liver-related mortality and hepatocellular carcinoma [HCC]), with few serious treatment-related harms that generally resolve after treatment discontinuation.[6] The USPSTF also considered the prevalence of HCV infection in high-risk persons (e.g., ≥50% in persons who inject drugs [PWID]) and in persons born between 1945 and 1965 (3% to 4%), and modeling studies that indicated cost-effectiveness of the birth cohort screening strategy.[8,9] The USPSTF found few serious adverse events with liver biopsy performed for the diagnostic evaluation of persons with HCV infection and noted that fewer biopsies were being performed due to the availability of accurate noninvasive tests for evaluating liver fibrosis. The USPSTF had previously found that screening tests are highly accurate for diagnosing HCV infection (overall sensitivity 94% and specificity 97%).[7]

Condition Background

Condition Definition

HCV is a single-stranded, positive-sense ribonucleic acid (RNA) virus of the family Flaviviridae. HCV infection can range from mild and self-limited to a serious, lifelong illness that can result in cirrhosis, liver failure, and HCC.[10] In most cases (78% to 85%), acute HCV leads to chronic HCV.[10] HCV is primarily acquired by exposures to infected blood, with injection drug use the strongest risk factor. In the United States, approximately 70 to 77 percent of HCV infections are caused by genotype 1 (subtypes 1a or 1b), 13 to 16 percent by genotype 2, 12 percent by genotype 3, and less than 5 percent by genotypes 4, 5, or 6 combined.[11,12]

Prevalence and Burden of Disease/Illness

HCV is the most common chronic bloodborne pathogen in the United States. The number of U.S. residents with past or current HCV infection (positive for anti-HCV antibody) is estimated at 4.1 million (range 3.4 million to 4.9 million); of these, an estimated 2.4 million (range 2.0 million to 2.8 million) are currently infected, defined as having HCV detectable in the blood (viremia).[10,13,14] Approximately three-quarters (78% to 85%) of those who test positive for anti-HCV antibody have chronic infection;[10,15] those with anti-HCV antibody but no viremia are considered to have cleared the infection. The estimated prevalence of chronic HCV infection during the years 2013 to 2016 was approximately 1.0 percent (95% confidence interval [CI], 0.8 to 1.1%).[16] Persons born between 1945 and 1965 comprise approximately 27 percent of the U.S. population but account for approximately three-quarters of all HCV infection,[16] and are at 6.0- to 9.5-fold increased risk of having HCV infection compared with younger adults.[17,18] Males are at increased risk for HCV infection compared with females (odds ratio [OR] 1.6, 95% CI, 1.1 to 2.4), and non-Hispanic black persons are at increased risk compared with 62 other races/ethnicities (OR 1.6, 95% CI, 1.1 to 2.3), excluding American Indian/Alaska Natives.[18] American Indian/Alaska Natives, who are often not included in national seroprevalence surveys, have higher HCV-related mortality than non-Hispanic black persons.[19] Reported cases of acute HCV infection increased approximately 3.5-fold from 2010 through 2016.[20] After adjusting for under-ascertainment and under-reporting, an estimated 41,200 (95% CI, 32,600 to 140,600) new HCV infections occurred in the United States in 2016.[20] The increase in acute HCV incidence has most impacted young, white PWID living in non-urban areas.[21-23]

Data also indicate an increase in the number of reproductive aged women (15 to 44 years of age) with HCV infection.[24,25] An estimated 29,000 females with HCV infection give birth annually in the United States, resulting in 1,700 cases of infected infants.[25] Trends in HCV epidemiology, prevalence, and incidence are discussed in more detail in Contextual Question 1.

Etiology and Natural History

HCV infection is a leading cause of complications from chronic liver disease. The number of deaths due to HCV infection ranged from 18,650 to 19,629 from 2012 to 2015 (4.9 to 5.0 deaths/100,000) and decreased to 18,153 in 2016 (4.5 deaths/100,000).[20] Despite likely underestimation, HCV-related mortality exceeds mortality associated with 60 other nationally notifiable infectious conditions combined.[26] According to the Centers for Disease Control and Prevention, of every 100 persons infected with HCV, approximately 60-70 will develop chronic liver disease, 5 to 20 will develop cirrhosis over a period of 20 to 30 years, and 1 to 5 will die from the consequences of liver cancer or cirrhosis.[27] HCV without cirrhosis is associated with worse quality of life and symptoms (e.g., fatigue) compared with not having HCV infection.[28-32] Other extrahepatic manifestations of HCV infection include mixed cryogloblinemias, non-Hodgkin lymphoma, type II diabetes mellitus and insulin resistance, cardiovascular disease, and renal disease.[33]

The natural course of chronic HCV infection varies. Some patients with chronic HCV infection have only mild liver disease after decades of infection or never develop histologic evidence of liver disease.[34] In other patients, inflammation and fibrosis of the liver may progress to cirrhosis, which can lead to end-stage liver disease or HCC. In persons with cirrhosis due to HCV infection, the annual incidence of HCC is 1 to 4 percent.[35] Once cirrhosis develops, patients have a much higher risk of death, and some may benefit from liver transplantation. Until recently, chronic HCV was the leading indication for liver transplantation in the United States.[36,37] The number of HCV-related liver transplants in the United States declined from a peak of 1,905 in 2014 to 1,535 in 2016.[36] Well-established predictors of advanced fibrosis in those with chronic HCV infection include older age at infection, longer duration of infection, male sex, concomitant HIV or hepatitis B virus (HBV) infection, and greater alcohol use.[34,38,39] Other factors that may be associated with increased risk of fibrosis include insulin resistance, hepatic steatosis, higher viral load, and the presence of certain human leukocyte antigen (HLA) class II polymorphisms. Once a person develops advanced (METAVIR stage 3) fibrosis, the risk of progression to cirrhosis is around 10 percent per year.[40]

Estimating the proportion of patients in the general population with HCV infection who progress to cirrhosis is difficult because the time of acquisition is often unclear and important endpoints often do not occur until after decades of infection; in addition, reasons for the variability in progression are not completely understood.[41] Six retrospective cohort studies of HCV-infected adults with known time of infection (based on an identified exposure, often to contaminated blood products during young adulthood) reported cirrhosis in 0 to 10 percent of patients after at least 10 years of followup.[29,42-48] Studies of community cohorts estimate cirrhosis in an average of 7 percent of persons after 20 years of HCV infection, with rates about twice as high in clinical and referral cohorts.[38,49] One study of females infected by contaminated batches of anti-D immunoglobulin in 1980 found that approximately 14 percent of those who remained viremic had cirrhosis after 35 years.[50] Other studies suggest that progression to cirrhosis may accelerate after 20 years of chronic infection.[47,51]

Mother-to-child (vertical) transmission is believed to be the main route of HCV infection acquisition in children. In a meta-analysis of the risk of vertical HCV infection, the pooled

transmission rate was 5.8 percent among females with HCV monoinfection and 10.8 percent among those with HCV/HIV coinfection.[52]

Risk Factors

HCV is primarily acquired via percutaneous exposures to infected blood. The strongest risk factor for HCV infection is injection drug use. The prevalence of HCV infection in PWID varies widely depending on age, duration of injection drug use, and other factors (such as availability and use of needle exchange programs).[53] Recent surveys of active PWID indicate that approximately one third of those aged 18 to 30 years are HCV-infected. Older PWID typically have a higher prevalence (approximately 70% to 90%) of HCV infection.[27] Although large population-based studies[54-56] report independent associations between HCV infection and some high-risk sexual behaviors (multiple sexual partners, unprotected sex, and/or sex with a person infected with HCV infection or using injection drugs), the efficiency of transmission via sexual contact appears to be low; high-risk sexual behaviors may be a marker for unacknowledged drug use or other risk factors. Transfusions prior to 1992 are a risk factor for HCV infection but are no longer an important source of infection due to the implementation of effective screening programs for donated blood.[57,58]

Rationale for Screening/Screening Strategies

Screening for HCV infection in asymptomatic adults who have no history of liver disease or known liver enzyme abnormalities may identify infected patients at earlier stages of disease, before they develop serious or irreversible liver damage. Studies estimate that around 50 percent (range 43 to 72%) of persons in the United States with chronic HCV infection are unaware of their status.[18,57-60] Antiviral treatment, has become increasingly effective at achieving sustained aviremia (clearance of HCV infection). Screening for HCV infection might also help prevent transmission by decreasing high-risk injection drug use and other risky behaviors in those who test positive or through successful treatment of HCV,[61] and could identify those who might benefit from hepatitis A or HBV vaccinations, alcohol cessation counseling, identification and management of extrahepatic manifestations, or other interventions. Screening is an important component of the National Academies of Sciences, Engineering, and Medicine report on eliminating HCV as a public health problem by the year 2030.[62] Shorter-term goals of the National Viral Hepatitis Action Plan are to increase the proportion of persons aware of their positive HCV infection status to 66 percent and to decrease the number of HCV-related deaths by 25 percent by the year 2020.[63]

Although prenatal HCV infection could identify infected females, a challenge is the lack of antiviral therapies proven to be effective for reducing risk of perinatal transmission and approved for use in pregnancy.[1] Older antiviral therapies were contraindicated in pregnancy due to teratogenic risks. Due to the lack of data on safety of newer DAA regimens during pregnancy and breastfeeding, clinical practice guidelines do not recommend antiviral therapy during pregnancy.[64,65] However, even in the absence of antiviral therapy proven to be safe and effective during pregnancy, identification of HCV infection during pregnancy could facilitate decision

making around the management and use of interventions during labor and delivery or in the perinatal period that might reduce risk of perinatal transmission, and identify females who could benefit from antiviral treatment later and infants who should be tested for HCV infection. A potential alternative strategy for preventing mother-to-child transmission is identification and treatment of HCV infection prior to pregnancy.[24]

Interventions/Treatment

The goal of antiviral treatment for chronic HCV infection is to prevent the long-term health complications associated with HCV infection, such as cirrhosis, hepatic decompensation, and liver cancer. However, it is extremely difficult to design and carry out clinical trials long and large enough to provide direct evidence related to these outcomes. The SVR rate, typically defined as the proportion of patients who experience a decline in HCV RNA to undetectable levels 12 or 24 weeks following completion of antiviral treatment, is the standard marker of successful treatment in clinical trials. Most studies now focus on SVR at 12 weeks. Long-term recurrence of hepatitis C viremia occurs in less than one percent of patients with an SVR at 12 or 24 weeks of therapy; therefore, an SVR is considered equivalent to a cured infection.[66-68] Studies have consistently found an association between achieving an SVR after antiviral therapy and reductions in mortality, liver failure, and cancer, though such analyses are susceptible to residual confounding.[69-72]

A major advance in antiviral treatment for HCV infection has been the development and adoption of all-oral DAA regimens without interferon. Such regimens are associated with substantially higher SVR rates than previous antiviral regimens, shorter duration of treatment (8 to 12 weeks instead of 24 to 48 weeks), and improved tolerability.[73] SVR rates with older antiviral regimens are shown in **Table 1**. DAA regimens are highly effective for HCV genotype 1 infection, the most common genotype in the United States and historically associated with lower SVR rates when treated with interferon-only regimens.

Given the rapid pace of development for HCV antiviral therapies, guidance for antiviral therapy for HCV is rapidly evolving (**Tables 2** and **3**).[74] Several newer DAA regimens are pangenotypic,[75] meaning that they are effective across all common genotypes, and most currently recommended regimens do not require use of ribavirin. Whereas antiviral therapy was previously reserved for patients with more advanced fibrosis, the American Association for the Study of Liver Disease (AASLD) and the Infectious Diseases Society of America (IDSA) now recommend treatment for all patients with chronic HCV, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy.[65] The U.S. Food and Drug Administration (FDA) recently approved three HCV regimens for children 12 to 17 years of age (**Table 4**).[76,77] Although HCV antiviral therapy has traditionally most frequently been administered in specialty settings, studies have demonstrated similar SVR rates without any negative impacts on safety in community-based and primary care settings.[78,79]

Recommendations regarding the diagnostic workup and pretreatment assessment for HCV are also evolving. Whereas liver biopsy was previously recommended in all patients with HCV

infection in order to determine the severity of fibrosis, the AASLD-IDSA guideline currently also recommends blood tests or transient elastography as noninvasive options for fibrosis assessment.[65,74,80,81] Given the availability of noninvasive tests to stage HCV infection, rates of biopsy have declined substantially, though precise data on current biopsy rates are lacking.

Current Clinical Practice/Recommendations of Other Groups

U.S.-based screening guidelines are summarized in **Table 5**. All are consistent in recommending HCV screening in persons born between 1945 and 1965 and in persons with risk factors for HCV infection. Data on rates of birth cohort screening are limited, though a study of U.S. veterans found an increased rate of testing in this age group compared with other age groups.[82]

Guidelines from the European Association for the Study of the Liver (EASL)[83] and the World Health Organization (WHO)[84] are generally consistent with the above screening guidance. In 2017, the Canadian Task Force on Preventive Health Care recommended against screening for HCV in adults not at elevated risk (including persons born between 1945 and 1965 or other birth cohorts).[85] The Canadian recommendation was based on the reasoning that most persons with HCV infection have risk factors that can be identified using risk-based guidelines. However, the Canadian Association for the Study of the Liver recommends screening of high-risk persons and persons born between 1945 and 1975.[86]

The CDC[87] and the American College of Obstetricians and Gynecologists[88] recommend offering HCV screening to pregnant people with risk factors.

Chapter 2. Methods

Key Questions and Analytic Framework

This systematic review followed a standard protocol in accordance with USPSTF procedures.[89] The scope and Key Questions (KQs) for this report were determined by the USPSTF and informed by evidence gaps identified from the prior reviews.[1-3,5,90] Three additional contextual questions on recent epidemiologic trends in HCV infection, modeling analyses, and behavioral effects of current antiviral therapies were requested by the USPSTF. The KQs and Contextual Questions are shown below. Investigators created an analytic framework incorporating the KQs and outlining the patient populations, interventions, outcomes, and potential adverse effects, as well as the direct and indirect pathways from screening to health outcomes (**Figure 1**).

Key differences between this report and the prior reviews are inclusion of adolescents in addition to adults; evaluation of new all-oral, DAA regimens. We also removed previously reviewed questions on harms of liver biopsy, given its reduced role in evaluation of patients with HCV infection, and on effects of counseling or immunizations in persons with HCV infection, given limited evidence and likely small magnitude of effects relative to antiviral treatments. This report focuses on effects of treatments in populations more likely to be identified by screening (i.e., asymptomatic and without advanced liver disease), and excludes poor quality studies (e.g., cohort studies that did not perform statistical adjustment) that were included in prior USPSTF reviews. We did not re-review the diagnostic accuracy of HCV screening, which the prior review found to be highly accurate.[91]

Key Questions

1a. Does screening for HCV infection in pregnant and nonpregnant adolescents and adults without known abnormal liver enzyme levels reduce HCV-related mortality and morbidity or affect quality of life?
1b. Does prenatal screening for HCV infection reduce risk of vertical transmission of HCV infection?
2. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?
3. What is the yield (number of new diagnoses per tests performed) of one-time versus repeat screening or alternative screening strategies for HCV infection, and how does the screening yield vary in different risk groups?
4. What are the harms of screening for HCV infection (e.g., anxiety and labeling)?
5. What are the effects of interventions during labor and delivery or the perinatal period on risk of vertical transmission of HCV infection?
6. What is the effectiveness of currently recommended antiviral treatments in improving health outcomes in patients with HCV infection?*
7. What is the effectiveness of currently recommended antiviral treatments in achieving a SVR in patients with HCV infection?*
8. What are the harms of currently recommended antiviral treatments?*

9. What is the association between experiencing SVR following antiviral treatment and reduction in risk of HCV-related adverse health outcomes?

* Subpopulations of interest for KQs 6, 7, and 8 include those defined by age, race/ethnicity, sex, drug use, receipt of medications for treatment of opioid use disorder, stage of disease, HCV genotype, and pregnancy status (including nonpregnant women of childbearing age).

Contextual Questions

Three Contextual Questions were also requested by the USPSTF to help inform the report. Contextual Questions are addressed by narratively summarizing key evidence; they are not reviewed using systematic review methodology.

1. Based on population level estimates, what are recent trends in the epidemiology, prevalence, and incidence of HCV infection in the United States, including in primary care settings, over the past 5 to 10 years?
2. What are the effects of different risk- or prevalence-based methods for screening for HCV infection in modeling studies?
3. What is the effect of antiviral treatments on behavioral outcomes?

Search Strategies

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through February 8, 2019), and Ovid MEDLINE (1946 through February 8, 2019) for relevant studies. Search strategies are available in **Appendix A1**. We also searched ClinicalTrials.gov for ongoing studies, and reviewed the reference lists of relevant review articles and studies meeting inclusion criteria. We also carried forward studies in the prior USPSTF report that met inclusion criteria for this update.[2,90] Ongoing surveillance was conducted to identify major studies published since February 2019 that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on November 22, 2019 and identified no studies affecting review conclusions.

Study Selection

Two reviewers independently evaluated each study to determine its inclusion eligibility based on predetermined inclusion and exclusion criteria developed for each KQ (**Appendix A2**).

The target population for screening was asymptomatic, pregnant and nonpregnant adolescents (ages 12 to 17 years) and adults without prior HCV infection. For treatment, the target population was persons with HCV infection likely to be identified by screening. However, no trial enrolled screen-detected patients, and trials did not report presence of symptoms. To evaluate patients more likely to be asymptomatic and identified by screening, we restricted

inclusion of antiviral treatment studies to those in which up to 20 percent of participants had cirrhosis at baseline. For antiviral regimens with few studies meeting this threshold and for studies on the association between SVR after antiviral therapy and clinical outcomes, we permitted a threshold up to 25 percent. We included studies of patients previously treated with interferon-based therapy (interferon or pegylated interferon with or without ribavirin) or boceprevir or telaprevir with pegylated interferon and ribavirin, because data indicate similar SVR rates in these treatment-experienced compared with treatment-naive patients.[73] Included interventions were HCV screening and alternative screening strategies; mode of delivery, labor management strategies, and breastfeeding practices; currently recommended (including alternative) DAA regimens for evaluation of clinical outcomes, SVR rates and harms; and DAA regimens or interferon-based treatment for evaluation of mortality and long-term clinical outcomes.[74] For analysis of SVR rates, we included studies in which ribavirin or dasabuvir was not used as recommended (e.g., ombitasvir / paritaprevir / ritonavir / dasabuvir that omitted ribavirin for genotype 1a infection or used ribavirin for genotype 1b infection, or did not include dasabuvir for genotype 1 infection) (**Tables 2** and **3**), because SVR rates were similar to recommended regimens with these variations, but performed sensitivity analyses without them. For analysis of adverse events, we restricted inclusion to trials in which ribavirin was administered as recommended. DAA regimens were restricted to recommended doses and durations. We excluded trials that focused on persons coinfected with HIV or HBV infection, transplant patients, or with advanced renal disease.

For KQs on screening and treatment, we included randomized trials. For questions on screening, perinatal (labor and delivery or breastfeeding) interventions, effects of DAA regimens on clinical outcomes, and the association between SVR after antiviral therapy and clinical outcomes, we also included cohort studies that reported risk estimates adjusted for potential confounders. We included trials of current DAA regimens versus placebo, an older antiviral regimen, or another DAA regimen (including regimens not currently recommended). We also included trials of DAA regimens without one of these comparisons, because there were few comparative trials. Clinical trials were defined as studies in which patients were prospectively allocated to treatment by the study investigator using pre-defined inclusion criteria and followup methods. Included outcomes were mortality, morbidity (e.g., cirrhosis, hepatic decompensation, liver transplant, extrahepatic manifestations of HCV infection), quality of life, HCV transmission, harms (e.g., labeling, anxiety, drug-related and treatment-related harms), screening yield (number of new diagnoses per tests performed), and perinatal transmission. We restricted inclusion to English-language articles, and we excluded studies published only as abstracts. Studies of non-human subjects were excluded, and studies had to report original data. The selection of literature is summarized in the literature flow diagram (**Appendix A3**), and **Appendix A4** provides a list of included studies. **Appendix A5** lists excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

We constructed evidence tables summarizing the data from each study. One investigator abstracted details about the study design, patient population, setting, interventions, analysis, followup, and results. A second investigator reviewed abstracted data for accuracy. Two investigators independently applied criteria developed by the USPSTF[89] to rate the quality of

each study as good, fair, or poor (**Appendix A6**). Discrepancies were resolved through a consensus process. In accordance with the USPSTF Procedure Manual, we excluded studies rated poor quality due to important methodological shortcomings that severely undermine their reliability;[89] this applied to studies utilized in the prior USPSTF review that were rated poor quality and were excluded in the current report.

Data Synthesis

We performed a random effects meta-analysis to summarize the proportion of patients experiencing SVR and adverse events with current DAA regimens. We used a generalized linear mixed effects model with a logit link, allowing the inclusion of studies in which the proportion of patients with the event were 0 percent or 100 percent. We combined arms of comparable interventions within the same study so each study was represented once in a meta-analysis, in order to avoid overweighting. For SVR, we performed separate analyses for each genotype (1 through 6); for adverse events, results were pooled across genotypes. For SVR and adverse events, analyses were stratified according to DAA regimen. Subgroup and sensitivity analyses were performed on geographic settings (United States or Europe, multinational, or other), fibrosis stage (cirrhosis excluded or some [up to 20% of patients] with cirrhosis), prior treatment status (naïve or experienced to interferon-based therapies, boceprevir or telaprevir), and quality. For SVR, we performed sensitivity analysis by excluding studies in which ribavirin or dasabuvir was not used as recommended. For analyses of adverse events, we excluded trials of ribavirin-containing regimens except for ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin, which is recommended for genotype 1b infection.

We also performed a random effects meta-analysis of adjusted hazard ratios (HRs) of SVR after antiviral therapy versus no SVR on clinical outcomes (mortality, liver-related mortality, cirrhosis, and HCC) using a linear mixed effects model. In some cases the adjusted HR for SVR versus no SVR had to be calculated from other estimates (e.g., from adjusted HRs for SVR and no SVR vs. no treatment). In these situations we calculated the adjusted HR for SVR versus no SVR based on the HRs for SVR versus no treatment and no SVR versus no treatment and their reported CIs, assuming a correlation of 0 between the two HRs. Because HRs are typically positively correlated, this assumption results in more conservative (i.e., wider) CIs for the calculated HR. Subgroup analysis were performed on duration of study (5 years or less vs. more than 5 years), geographic setting (United States/Europe vs. Asia) and whether the study had full adjustment of confounding variables (age, sex, fibrosis stage and genotype) or did not adjust for one or more of these populations. We also performed sensitivity analysis by excluding studies with potential overlapping populations in order to ensure that results were not sensitive to double counting of patients.

For all meta-analyses, statistical heterogeneity was assessed using the variance parameter of the random effects, the Cochran Q-test and I^2 statistic.[92] For pooled proportions of SVR and adverse events, the Cochran Q-test and I^2 statistic were based on the Freeman-Tukey double arcsine transformed proportions.[93] All meta-analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA.) and forest plots were created using Stata/SE 14.0 (StataCorp, College Station, TX).

We also conducted random effects meta-analysis on adverse events with DAA regimens versus placebo and DAA regimens versus telaprevir / pegylated interferon / ribavirin using RevMan 5.3.5 (the Nordic Cochrane Centre, Copenhagen). Analyses were stratified by DAA regimen. There were too few trials evaluating these comparisons to conduct additional sensitivity or subgroup analyses

We assessed the aggregate internal validity (quality) of the body of evidence for each KQ ("good", "fair", "poor") using methods developed by the USPSTF, based on the number, quality and size of studies, consistency of results between studies, and directness of evidence in the Summary of Evidence.[89] We determined aggregate internal validity using the totality of evidence (new studies identified for the update plus studies carried forward from the prior USPSTF report).

Expert Review and Public Comment

The draft research plan was posted for public comment from September 21 to October 18, 2017. In response to public comments, the USPSTF modified the research plan before finalizing to clarify the following: screening settings include emergency departments and settings that offer integrated services for primary care and behavioral health care; subpopulations of interest include drug use, persons using medication-assisted therapies, and nonpregnant women of childbearing age; morbidity outcomes include extrahepatic manifestations of HCV infection, such as depression and diabetes; health outcomes include perinatal HCV transmission; and the population for antiviral treatment includes persons with a METAVIR fibrosis stage of 0 to 3. The USPSTF also added a KQ on the yield of repeat HCV screening and revised Contextual Question 3 to address the effects of antiviral treatment on both positive and negative behaviors pertaining to HCV risk.

A draft version of this report was reviewed by content experts, USPSTF members, Agency for Healthcare Research and Quality Medical Officers, and collaborative partners. Reviewer comments were presented to the USPSTF during its deliberations and subsequently addressed in revisions of this report when appropriate. Additionally, a draft of this report was posted for public comment on the USPSTF Web site from August 27, 2019 to September 23, 2019. Comments were received from 11 commenters during this public comment period; minor editorial changes were made to the report based on these comments, but no changes were made to the results or conclusions.

Chapter 3. Results

A total of 7,170 new references from electronic database searches and manual searches of recently published studies were reviewed, and 700 full-text papers were evaluated for inclusion. We included a total of 97 studies (reported in 94 publications). Eighty-four studies were newly identified as part of this update, and 13 were carried forward from the previous review. Included studies and quality ratings are described in **Appendix B**.

Key Question 1a. Does Screening for HCV Infection in Pregnant and Nonpregnant Adolescents and Adults Without Known Abnormal Liver Enzyme Levels Reduce HCV-Related Mortality and Morbidity or Affect Quality of Life?

As in the prior USPSTF review, no study directly assessed effects of HCV screening versus no screening on clinical outcomes such as HCV-related mortality and morbidity or quality of life.

Key Question 1b. Does Prenatal Screening for HCV Infection Reduce Risk of Vertical Transmission of HCV Infection?

As in the prior USPSTF review, no study assessed effects of prenatal HCV screening versus no screening on risk of vertical transmission of HCV infection.

Key Question 2. What Is the Effectiveness of Different Risk- or Prevalence-Based Methods for Screening for HCV Infection on Clinical Outcomes?

As in the prior USPSTF review, no study directly assessed the effectiveness of different risk- or prevalence-based methods for HCV screening on clinical outcomes.

Key Question 3. What Is the Yield (Number of New Diagnoses per Tests Performed) of One-Time vs. Repeat Screening or Alternative Screening Strategies for HCV Infection, and How Does the Screening Yield Vary in Different Risk Groups?

Summary

- The prior USPSTF review included five studies that found screening strategies that targeted multiple risk factors associated with sensitivities of more than 90 percent and

numbers needed to screen to identify one case of HCV infection of less than 20. More narrowly targeted screening strategies were associated with numbers needed to screen of less than two, but missed up to two-thirds of infected patients.

- One new study found that applying risk-based guidelines perfectly would result in 24.7 percent of the population tested and 82 percent of HCV cases identified (number needed to screen 14.6), compared with 45 percent of the population tested and 76 percent of HCV cases identified with birth cohort screening (number needed to screen 28.7), but assumed perfect implementation of risk-based testing.

Evidence

The prior USPSTF review included five poor quality studies[94-98] that found screening strategies that targeted multiple risk factors associated with sensitivities of more than 90 percent and numbers needed to screen to identify one case of HCV infection of less than 20.[2] More narrowly targeted screening strategies were associated with numbers needed to screen of less than two, but missed up to two-thirds of infected patients.

One new study that retrospectively applied screening criteria to patients in the 2003 to 2006 National Health and Nutrition Examination Survey (NHANES) database compared the yield of risk-based HCV screening (based on then-current AASLD guidelines) versus birth cohort screening.[99] It found that applying risk-based guidelines perfectly would result in 24.7 percent of the general population tested and identify 82 percent of the HCV exposed population, with a number needed to screen to identify one case of HCV infection of 14.6. Applying the birth cohort strategy would result in 45 percent of the general population tested and identify 76 percent of the HCV exposed population, with a number needed to screen to identify one case of 28.7. Although this analysis suggests that the two strategies would identify a similar proportion of HCV infected persons, it would require perfect implementation of risk-based testing, which has not occurred in actual practice.

No study evaluated the yield of one-time versus repeat screening, the yield of alternative screening strategies in different risk groups, or the yield of currently recommended screening (i.e., 1945 to 1965 birth cohort plus risk-based screening) versus expanded screening strategies. Studies that modeled effects of alternative screening strategies are addressed in Contextual Question 2.

Key Question 4. What Are the Harms of Screening for HCV Infection (e.g., Anxiety and Labeling)?

The prior USPSTF review included five studies[31,100-103] of persons with HCV infection that suggested potential negative psychological and social effects of screening, but the quality of evidence was assessed as poor due to small sample sizes and methodological shortcomings, included no unscreened comparison group, reliance on retrospective recall, and poorly defined outcomes.[2] All of the studies were conducted in the context of treatment with older interferon-

containing regimens. No new study meeting inclusion criteria evaluated harms associated with HCV screening.

Key Question 5. What Are the Effects of Interventions During Labor and Delivery or the Perinatal Period on Risk of Vertical Transmission of HCV Infection?

Summary

- Five observational studies (four included in the prior USPSTF review) found no clear association between the mode of delivery and risk of mother-to-infant transmission of HCV infection, after adjustment for potential confounders.
- One observational study included in the prior USPSTF review found prolonged (longer than 6 hours) rupture of membranes associated with increased risk for HCV transmission versus less prolonged (6 hours or less) rupture after adjusting for maternal demographic characteristics, HCV RNA level, intravenous drug use, and smoking status during pregnancy (adjusted OR 9.3, 95% CI, 1.5 to 180).[104] No new study evaluated this association.
- One observational study included in the prior USPSTF review found internal fetal monitoring associated with increased risk of mother-to-infant transmission of HCV infection versus external monitoring, after adjustment for maternal demographic characteristics, HCV viral load, intravenous drug use history, and smoking status in pregnancy (adjusted OR 6.7, 95% CI, 1.1 to 35.9).[104] No new study evaluated this association.
- Three observational studies (two included in the prior USPSTF review) found no clear association between breastfeeding and risk of mother-to-infant transmission of HCV infection after adjustment for potential confounders; in the two good quality studies adjusted OR estimates were close to 1.[105-107]

Evidence

Mode of Delivery

The prior USPSTF review[2] included 14 observational studies in 16 publications (sample sizes of 56 to 1,034 mother-infant pairs) that found no clear association between the mode of delivery (vaginal vs. cesarean delivery) and risk of mother-to-infant transmission of HCV.[104-106,108-120] Twelve studies found no statistically significant association between the mode of delivery and risk of HCV transmission;[104-106,109-112,114-120] most estimates were imprecise, and findings were inconsistent, with point estimates that favored vaginal delivery in some studies and cesarean delivery in others. Most of the studies included in the prior review did not meet inclusion criteria for the current review: eight were rated poor quality[109,111-113,116-120] and ten did not conduct multivariate analyses.[109-120] No study reported baseline characteristics according to mode of delivery or matched women on key potential confounders.

Restricting inclusion to the four studies (total 1,717 mother-infant pairs) in the prior review that met current inclusion criteria (fair or good quality and multivariate analysis performed) resulted in a similar conclusion of no clear association between the mode of delivery and risk of HCV transmission (**Table 6**, **Appendix B Table 1**).[104-106,108] One of the studies was conducted in the United States[104] and the other three in Europe. Although one fair quality study (424 mother-infant pairs) found elective cesarean associated with decreased risk of HCV transmission versus vaginal delivery or emergent (after onset of labor) cesarean after adjusting for HIV status and breastfeeding (adjusted OR 0.0, 95% CI, 0.0 to 0.87),[105] the other three studies, including two good quality studies,[104,106] found no association between the mode of delivery and HCV transmission risk. One good quality study (1,034 mother-infant pairs) found no statistically significant association between the mode of delivery and risk of HCV transmission, though there was a trend towards higher risk with elective cesarean versus vaginal or emergent (after onset of labor) cesarean, after adjusting for infant sex, prematurity, and breastfeeding status (adjusted OR 1.59, 95% CI, 0.88 to 2.86),[106] and another good quality study (181 mother-infant pairs) found no association between the mode of delivery (elective cesarean, emergent cesarean or vaginal) and risk of mother-to-infant transmission in univariate analysis; mode of delivery was excluded from the multivariate model.[104] The fourth, fair quality study (78 mother-infant pairs) found no association between cesarean (not specified as elective or emergent) versus vaginal delivery and risk of transmission (data not reported).[108]

One additional Italian study (1,301 mother-infant pairs) not included in the prior USPSTF review also found no statistically significant association between the mode of delivery (cesarean vs. vaginal delivery) and risk of mother-to-infant transmission of HCV infection (adjusted OR 0.83, 95% CI, 0.65 to 1.08). Cesarean deliveries were not specified as elective or emergent[107] (**Table 6**, **Appendix B Tables 1-3**). The study was rated good quality (**Table 6; Appendix B Table 4**).

Rupture of Membranes

Evidence on the association between duration of rupture of membranes during labor and risk of HCV transmission is limited. The prior USPSTF review included one good quality United States cohort study (189 mother-infant pairs) that found prolonged rupture (longer than 6 hours) of membranes associated with increased risk for HCV transmission versus less prolonged rupture (6 hours or less) after adjusting for maternal demographic characteristics, HCV RNA level, intravenous drug use, and smoking status during pregnancy (adjusted OR 9.3, 95% CI, 1.5 to 180)[104] (**Table 7**; **Appendix B Tables 1-3**). However, there were only 7 cases of perinatal HCV infection, and the estimate was very imprecise. A smaller (63 mother-infant pairs) Australian study[116] included in the prior USPSTF review found that mean duration of membrane rupture was longer in mothers in whom HCV transmission occurred compared with those in whom transmission did not occur, but did not meet current inclusion criteria because it did not attempt to adjust for potential confounders and was rated poor quality. We identified no new studies on the association between the duration of rupture of membranes and risk of HCV transmission that met inclusion criteria.

Fetal Monitoring

Evidence on the association between use of fetal monitoring methods during labor and risk of HCV transmission is limited. The prior USPSTF review included one good quality U.S.-based study (188 mother-infant pairs) that found internal fetal monitoring associated with increased risk of mother-to-infant transmission of HCV infection versus external monitoring, after adjustment for maternal demographic characteristics, HCV viral load, intravenous drug use history, and smoking status in pregnancy (adjusted OR 6.7, 95% CI, 1.1 to 35.9)[104] (**Table 8; Appendix B Tables 1-3**). However, there were only 7 cases of perinatal HCV infection and the estimate was imprecise. Although the prior USPSTF review included two other studies on the association between fetal monitoring and risk of HCV transmission, neither met current inclusion criteria because they did not report adjusted risk estimates.[112,114] One of the studies[112] did not compare internal fetal monitoring to no internal monitoring and the other study[114] found no association between internal fetal monitoring and transmission risk (relative risk [RR] 1.24, 95% CI, 0.70 to 2.2). We identified no new studies on the association between the use of fetal monitoring methods and risk of HCV transmission that met inclusion criteria.

Breastfeeding

The prior USPSTF review[2] included 14 observational studies[104-106,109,111,115-124] (total of 2,971 mother-infant pairs) that found no association between breastfeeding by women infected with HCV and risk of transmission to infants. No study reported a statistically significant association, though some estimates were very imprecise due to few cases of HCV transmission. Most of the studies included in the prior review did not meet inclusion criteria for the current review: ten were rated poor quality,[108-114,116-120] and twelve did not conduct multivariate analyses.[104,108-120]

Restricting the analysis to the two studies[105,106] in the prior review that meet current inclusion criteria (fair or good quality and multivariate analysis performed) resulted in a similar conclusion of no association between breastfeeding and risk of HCV transmission (**Table 9**; **Appendix B Tables 1-3**).[104-106,108] One large (1,034 mother-infant pairs) European study found no association between breastfeeding by HCV-infected women without HIV infection and risk of HCV transmission to infants (followed until at least 18 months of age), after adjusting for infant sex, prematurity, and mode of delivery (adjusted OR 0.92, 95% CI, 0.50 to 1.70). A fair quality European study (414 mother-infant pairs) also found no association between breastfeeding and risk of HCV transmission to infants (duration of followup 24 months), after adjusting for HIV status (5% of mothers were HIV-infected) and mode of delivery (adjusted OR 1.52, 95% CI, 0.35 to 5.12). Although the point estimate was consistent with increased risk associated with breastfeeding, the estimate was imprecise.

One additional good quality Italian cohort study[107] (1,281 mother-infant pairs) not included in the prior systematic review also found no association between breastfeeding and risk of HCV transmission to infants, after adjusting for maternal HCV viral load, HIV status (14% of mothers were HIV-infected), injection drug use, and mode of delivery (adjusted OR 0.95, 95% CI, 0.58 to 1.40) (**Table 9**; **Appendix B Tables 1-4**). Duration of followup was 24 months.

Key Question 6. What Is the Effectiveness of Currently Recommended Antiviral Treatments in Improving Health Outcomes in Patients With HCV Infection?

Summary

Adults

- The prior review included no randomized trials or observational studies on the effects of then-current antiviral regimens on long-term (e.g., more than 2 years) clinical outcomes; no new randomized trial evaluated effects of current DAA regimens on long-term clinical outcomes.
- Ten new trials reported quality of life and functional outcomes before and after treatment with a current DAA regimen.
    - A pooled analysis of four trials found sofosbuvir / velpatasvir associated with an average improvement of 5.5 to 6.1 points (0 to 100 scale) on 26 measures related to quality of life or function at 24 weeks (12 weeks post-treatment) in persons without cirrhosis.
    - A pooled analysis of three trials found sofosbuvir / ledipasvir associated with small but statistically significant improvements from baseline to 24 weeks (12 weeks post-treatment) on multiple quality of life and functional domains in persons with no to mild fibrosis at baseline.
    - Three trials of DAA regimens not included in the pooled analyses (two trials of ombitasvir / paritaprevir / ritonavir / dasabuvir and one trial of elbasvir / grazoprevir) found DAA use associated with small changes from baseline to 12 weeks post-treatment on the 36-Item Short Form Health Survey (SF-36) physical (improvement 0.5 to 1.4 points) or mental component (improvement 2.5 to 3.0 points) summary scales (0 to 100 scale).
- Thirty-one trials reported mortality 12 to 36 weeks following completion of therapy with a DAA regimen. Twenty-one trials reported no deaths; in the other ten trials, there were 17 deaths (0.4% [17/3,848] overall).
- Three large (n=34,206; 17,836; and 6,850) cohort studies evaluated the association between use of DAA regimens, interferon-based treatment, and no antiviral therapy and risk of cardiovascular events and HCC.
    - One retrospective study (n=34,206) found DAA therapy and interferon-based therapy each associated with similarly decreased risk of cardiovascular events relative to no therapy (incidence per 1,000 person-years 16.3 for DAA therapy, 23.5 for interferon-based therapy, and 30.4 for no therapy; $p<0.001$ for DAA therapy or interferon-based therapy vs. no therapy).
    - One study (n=17,836) found no difference between interferon-based treatment versus DAA therapy in risk of HCC (incidence rate per 1,000 person-years of followup 7.48 vs. 7.92; $p=0.72$); both regimens were associated with lower incidence of HCC than no therapy.

- One study (n=6,850) found no difference between DAA therapy versus no antiviral therapy and risk of HCC (adjusted HR 1.02, 95% CI, 0.40 to 2.61) among persons without known cirrhosis at baseline after 33 months followup; effects on all-cause mortality favored DAA therapy, but the difference was not statistically significant (adjusted HR 0.74, 95% CI, 0.43 to 1.28).

Adolescents

- Three trials of DAA therapy in adolescents found quality of life improved from baseline based on Pediatric Quality of Life Inventory scores.
- Three short-term trials of DAA regimens in adolescents reported no deaths.

Evidence

Adults

The prior review identified no randomized trials or observational studies on the effects of then-current antiviral regimens (triple therapy with telaprevir or boceprevir, pegylated interferon, and ribavirin or dual therapy with pegylated interferon and ribavirin) for chronic HCV infection on long-term (more than 2 year) clinical outcomes.[5,90] Two trials in the prior review reported short-term mortality with triple therapy versus dual therapy, but events were few and estimates were imprecise, with no clear differences.[125,126] There were a total of 9 deaths in over 1,700 persons across the two trials.

No new randomized trial evaluated effects of current DAA regimens on long-term clinical outcomes. Randomized trials of older (non-DAA) antiviral therapy versus no antiviral therapy that evaluated long-term clinical outcomes did not meet inclusion criteria because they enrolled persons with cirrhosis at baseline,[127-132] utilized non-standard therapy (indefinite treatment with interferon),[133] or were rated poor quality (not clearly randomized).[134]

Ten trials reported quality of life and functional outcomes before and after receipt of current DAA regimens; seven trials were included in two pooled analyses[135,136] and three additional trials (reported in 2 publications) not in the pooled analyses also reported these outcomes (**Appendix B Tables 5, 10 and 11**).[137,138] One trial of sofosbuvir / velpatasvir that reported quality of life and functional outcomes was included in a pooled analysis and is not reported separately here.[139,140] The trials were all open-label and none reported comparisons of DAA therapy versus placebo or non-DAA therapy.

Thirty-one trials (in 28 publications)[139,141-167] reported short-term mortality with current DAA regimens (**Appendix B Tables 10 and 11**). A multicenter prospective cohort study conducted in France[168] and two retrospective cohort studies[169,170] based on a national Veterans Affairs (VA) database, Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES), evaluated the association between treatment with a DAA regimen versus no treatment and other clinical outcomes (cardiovascular outcomes and HCC) after adjusting for potential confounders (**Appendix B Table 5**).

Quality of Life and Function

Ten trials reported quality of life and functional outcomes before and after treatment with a current DAA regimen **(Appendix B Tables 5, 10, and 11)**. Seven trials were included in two post-hoc pooled analyses: one analysis[135] included three trials (n=1,005) of sofosbuvir / ledipasvir and one analysis[136] included four trials (n=1,701) of sofosbuvir / velpatasvir. The trials varied with regard to whether antiviral therapy was administered with or without ribavirin. Two additional trials (reported in 1 publication, n=309 and 148) of ombitasvir / paritaprevir / ritonavir / dasabuvir (with or without ribavirin)[137] and one additional trial of elbasvir / grazoprevir (n=129) also reported quality of life or function.[138] All studies used an open-label design, and the quality of life and functional measures assessed in the trials differed. In addition, the trials included in the pooled analyses lacked a non-DAA regimen comparison group.

A pooled analysis of four trials found sofosbuvir / velpatasvir associated with an average improvement of 5.5 to 6.1 points on 26 measures related to quality of life or function at 24 weeks (12 weeks post-treatment) in persons without cirrhosis.[136] Changes from baseline were not statistically significant. Findings were similar when the regimen was administered with or without ribavirin. The average improvement was based on 26 outcomes derived from the SF-36, the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), the Chronic Liver Disease Questionnaire-HCV version (CLDQ-HCV), and the Work Productivity Activity Index: Specific Health Problem (WPAI-SHP) measures, standardized to a 0 to 100 scale.

A pooled analysis of three trials found sofosbuvir / ledipasvir associated with statistically significant improvements from baseline to 24 weeks (12 weeks post-treatment) on multiple quality of life and functional domains in persons with no to mild fibrosis at baseline.[135] Estimates were similar when sofosbuvir / ledipasvir was administered with or without ribavirin. Mean differences were less than 3 points on the 0 to 100 SF-36 physical and mental component summary scales, 10 to 11 points on the 0 to 160 FACIT-F scale, 0.5 to 0.6 points on the CLDQ-HCV, less than 0.1 point on the 0 to 1 WPAI-SHP scales, and 0.04 to 0.05 points on the six-dimensional health state short-form (SF-6D) health utility scale; the latter measure was derived from the SF-36 instrument.

Three trials not included in pooled analyses also reported small improvements in some measures of quality of life or function.[137,138] Two trials found ombitasvir / paritaprevir / ritonavir / dasabuvir associated with small changes from baseline to 12 weeks post-treatment on the SF-36 physical (improvement 0.5 to 1.4 points) or mental component (improvement 2.5 to 3.0 points) summary scales.[137] Estimates were similar when the regimen was administered with or without ribavirin and among treatment-naïve and -experienced patients. In both trials, there were no statistically significant differences between the DAA regimen versus telaprevir / pegylated interferon / ribavirin on the SF-36 (differences –1.1 to –1.5 points on the mental component and –1.3 to +0.9 points on the physical component summary scales). Changes from baseline following treatment with ombitasvir / paritaprevir / ritonavir / dasabuvir on the WPAI-SHP scale were also very small. Another trial found elbasvir / grazoprevir use associated with small but statistically significant improvements from baseline in SF-36 mental and physical component scores (mean change of 2 points each).[138] There was no effect of elbasvir / grazoprevir on patient fatigue, based on FACIT-F scale score.

Mortality

Thirty-one trials (in 28 publications; n=21 to 558; total N=3,848) reported mortality 12 to 36 weeks following completion of therapy with a DAA regimen (**Appendix B Tables 10 and 11**).[139,141-167] The trials were not designed or powered to assess mortality, and 21 studies reported no deaths. There were 17 deaths in the remaining ten studies (0.4% overall). The regimens evaluated in these trials were sofosbuvir / velpatasvir (8 deaths in 884 patients; 0.9%),[139,146,147,150] ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin (4 deaths in 187 patients; 2%),[149,162] grazoprevir / elbasvir (2 deaths in 732 patients; 0.3%),[164,166] glecaprevir / pibrentasvir (2 deaths in 1,172 patients; 0.2%),[167] and sofosbuvir / daclatasvir (one death in 115 patients; 0.9%).[167] Ten of the 17 deaths were reported in three trials that enrolled persons reporting recent injection drug use (26% to 66% at baseline) or use of opioid substitution therapy (3% to 85% at baseline).[149,150,167]

Other Clinical Outcomes

Three large, fair-quality cohort studies evaluated the association between antiviral treatment versus no treatment and clinical outcomes (cardiovascular events, HCC, or all-cause mortality).[168-170] Two studies[169,170] were conducted using the VA ERCHIVES database, and one study[168] was conducted in France.

Two large (n=17,836 and 34,206), retrospective analyses of VA patients evaluated the association between use of DAA regimens, interferon-based treatment, and no antiviral therapy and risk of cardiovascular events and HCC (**Appendix B Tables 5 and 6**).[169,170] The studies included primarily male (3 to 4% female), HCV-infected veterans. Mean age ranged from 54 to 62 years; approximately 20 percent of the population had cirrhosis at baseline. One study found DAA therapy and interferon-based therapy each associated with decreased risk of cardiovascular events, including acute myocardial infarction, congestive heart failure, and stroke (incidence rate per 1,000 person-years of followup: 16.3 for DAA therapy, 23.5 for interferon-based therapy, and 30.4 for no therapy; $p<0.001$ for DAA therapy vs. no therapy and for interferon-based therapy vs. no therapy).[169] The proportion of patients with at least 5 years followup was 82% for interferon-based therapy, 3.7% for DAA therapy, and 43% for no therapy (mean followup not reported). The other study found no difference between interferon-based treatment versus DAA therapy in risk of HCC (incidence rate per 1,000 person-years of followup 7.48 vs. 7.92; $p=0.72$).[170] Both types of antiviral therapy regimens were associated with lower incidence of HCC than no therapy (incidence rate per 1,000 person years 10.90). The mean duration of followup was 7.4 years for persons treated with interferon-based therapy and 1.1 years for persons treated with DAA therapy (mean not reported for untreated patients).

A third, smaller (n=6,850) study conducted in France found no difference between DAA therapy versus no antiviral therapy in risk of HCC (adjusted HR 1.02, 95% CI, 0.40 to 2.61) in persons not known to have cirrhosis at baseline after a median of 33 months followup.[168] Effects on all-cause mortality favored DAA therapy, but the difference was not statistically significant (adjusted HR 0.74, 95% CI, 0.43 to 1.28). There were too few events to estimate effects on liver-related mortality or decompensated cirrhosis. Some differences between this analysis and the VA studies described above include availability of results for the subgroup of persons without

cirrhosis at baseline, a much higher proportion of female patients (approximately 50%), restriction to DAA therapy, prospective design, and similar duration of followup in treated and untreated patients.

No study evaluated effects of treatment with DAA regimens on risk of HCV transmission.

Adolescents

Data on health outcomes associated with DAA regimens in adolescents is available from one fair quality, open-label trial[171] and post-hoc, before-after analyses of two other fair quality trials (**Appendix B Tables 7 and 8**).[172,173] The studies included a total of 200 patients, mean age was 14 to 15 years, the proportion of females ranged from 40 to 63 percent, and patients did not have known cirrhosis. The studies utilized ledipasvir and sofosbuvir in adolescents with genotype 1 infection,[172] sofosbuvir and ribavirin in adolescents with genotype 2 or 3 infection,[173] and glecaprevir / pibrentasvir in patients with genotype 1, 2, 3 or 4 infection.[171] Quality of life was assessed based on change from baseline on the Pediatric Quality of Life Inventory.[174] The Pediatric Quality of Life Inventory comprises four domains: Physical, Emotional, Social and School Functioning, and the total score is determined by averaging the scores from each of the four domains. In adolescents with genotype 1 infection treated with ledipasvir and sofosbuvir, caregiver-reported total quality of life scores were significantly improved from baseline at 24 weeks post-treatment (0-100 scale; mean change 5.2 points; p=0.009). However, there was no significant change in patients' self-reported total scores (mean change 1.9 points; p=0.12). Only the Emotional Functioning domain was rated as significantly improved from baseline by both caregivers (mean change 9.32 points, p<0.001) and patients (mean change 3.66, p=0.04).[172] In adolescents with genotype 2 or 3 infection treated with sofosbuvir and ribavirin, scores improved on the self-reported Social Functioning score by 4.8 points (p=0.02) and on the parent-proxy-reported School Functioning score by 13.0 points (p=0.0065). Adolescents treated with glecaprevir / pibrentasvir also experienced a small improvement in total quality of life score (mean change 2.3 points) though the statistical significance (p-value not reported) and timing of the assessment in this study is unclear.

Three studies of DAA regimens (sample sizes 30 to 100; total N=182) reported no deaths, but were not designed to assess long-term clinical outcomes (duration of followup ≤48 weeks; **Appendix B Tables 7 and 8**). Two of the studies evaluated DAA regimens FDA-approved for use in adolescents (ledipasvir and sofosbuvir[175] and sofosbuvir and ribavirin[173]) and one study evaluated a DAA regimen currently recommended for use in adults but not FDA-approved for use in adolescents (sofosbuvir and daclatasvir[176]).

Key Question 7. What Is the Effectiveness of Currently Recommended Antiviral Treatments in Achieving a SVR in Patients With HCV Infection?

Summary

Adults

- The prior review found triple therapy with telaprevir or boceprevir associated with higher likelihood of SVR than dual therapy with pegylated interferon and ribavirin in persons with genotype 1 infection. SVR rates were 68 percent to 72 percent with triple therapy and 38 percent to 46 percent with dual therapy.
- One new randomized trial found sofosbuvir / velpatasvir associated with very high likelihood of SVR versus placebo in persons with mixed genotype (1, 2, 4, 5, or 6) infection (99% vs. 0%, RR 231.6, 95% CI, 14.6 to 3,680).[139] Across genotypes, the SVR rate with sofosbuvir / velpatasvir ranged from 97 percent to 100 percent.
- Two new randomized trials found ombitasvir / paritaprevir / ritonavir / dasabuvir (with or without ribavirin) associated with increased likelihood of SVR versus telaprevir / pegylated interferon / ribavirin in persons with genotype 1 infection who were treatment-naïve (98% vs. 80%, RR 1.22, 95% CI, 1.08 to 1.37) or who had previously received interferon therapy (99% vs. 66%, RR 1.50, 95% CI, 1.22 to 1.85).[137]
- Forty-nine new trials found current DAA regimens associated with pooled SVR rates that ranged from 95.5 percent to 98.9 percent:
    - Genotype 1 infection (32 trials): Pooled SVR 97.7 percent (95% CI, 96.6% to 98.4%, I^2=82%)
    - Genotype 2 infection (5 trials): Pooled SVR 98.9 percent (95% CI, 97.5% to 99.5%, I^2=4%)
    - Genotype 3 infection (6 trials): Pooled SVR 95.5 percent (95% CI, 91.6% to 97.7%; I^2=66%)
    - Genotype 4 infection (10 trials): Pooled SVR 98.2 percent (95% CI, 94.7% to 99.4%; I^2=50%)
    - Genotype 5 infection (4 trials): Pooled SVR 96.0 percent (95% CI, 88.3% to 98.7%; I^2=0%)
    - Genotype 6 infection (5 trials): Pooled SVR 98.2 percent (95% CI, 95.4% to 99.3%, I^2=0%).
    - Mixed genotype 1 to 6 (2 trials): Pooled SVR 95.4% (95% CI, 89.4% to 98.1%; I^2=0%).
- SVR estimates were consistent in analyses stratified by DAA regimen, study quality, inclusion of persons with cirrhosis at baseline, and geographic setting; and when analyses were restricted to trials that utilized ribavirin as recommended or to treatment-naïve patients.
- SVR estimates were similar in trials that stratified patients according to age (17 trials, primarily using a 55- or 65-year threshold), sex (17 trials), race or ethnicity (11 trials), or treatment-experience (five trials).

Adolescents

- Seven new trials (total N=348) reported SVR rates of 97 percent to 100 percent with DAA regimens in adolescents with HCV infection.
    - Four trials evaluated DAA regimens currently recommended and FDA-approved for use in adolescents (ledipasvir / sofosbuvir, sofosbuvir / ribavirin or glecaprevir / pibrentasvir) and three trials evaluated DAA regimens currently recommended for adults but not FDA-approved for use in adolescents.
    - Results were consistent across genotypes and in treatment-naïve and -experienced patients.

Evidence

Adults

The prior review found higher SVR rates in persons with HCV genotype 1 infection treated with triple therapy with telaprevir or boceprevir plus pegylated interferon and ribavirin than with dual therapy with pegylated interferon and ribavirin.[5,90] Findings were consistent for a 48-week boceprevir regimen (2 trials, SVR rates 70% vs. 38%, RR 1.8, 95% CI, 1.6 to 2.1),[126,177] a 24-week, fixed-duration telaprevir regimen (3 trials, SVR rates 68% vs. 46%, RR 1.5, 95% CI, 1.3 to 1.8),[178-180] and a 24- or 48-week, response-guided telaprevir regimen (1 trial, SVR rate 72% vs. 44%, RR 1.6, 95% CI, 1.4 to 1.9).[125] The prior review also included 5 trials of dual therapy with pegylated interferon and ribavirin for genotype 2 or 3 infection that reported pooled SVR rates of 78 percent (95% CI, 67% to 88%) for 24 weeks of treatment and 68 percent (56% to 78%) for 12 to 16 weeks of therapy.[181-184] None of the studies in the prior review evaluated current DAA regimens.

Forty-nine new trials (in 44 publications) reported effects of current DAA treatment regimens on SVR in patients with HCV infection (**Table 10**; **Appendix B Tables 10 and 11**).[137,139,141-167,185-199] Sample sizes ranged from 20 to 706 (total N=10,181), mean age ranged from 45 to 68 years, and the proportion of female participants ranged from 18 to 64 percent. Twenty-four trials (in 20 publications) were multinational (primarily United States, Australia and/or Europe),[137,139,143,144,149,150,155,158,160,164,166,167,185-189,191,196,198] 11 (in 10 publications) were conducted in the United States and/or Canada,[146,147,153,154,157,161,190,192-194] eight in Asia,[145,151,152,156,163,165,197,199] two in France,[141,142] two in Egypt,[162,195] and one each in Brazil,[159] and New Zealand.[148] The eight trials conducted in Asia did not report race. In the other studies, among those that reported race, the majority of participants were white (range 60 to 100%)[139,141,142,146,147,153-155,157,158,160-162,166,185-188,190-194] with the exception of one study conducted in New Zealand in which 16 percent of participants were white[148] and one study conducted primarily in Asian countries in which 28% of participants were white.[164] Twenty-one trials (in 19 publications) enrolled patients with genotype 1 infection,[137,145,149,151-156,159-161,163,167,185-188,190-194,197] one trial genotype 2,[147,199] three trials genotype 3,[147,157,158,167] three trials genotype 4,[141,162,189,195,200] one trial each for genotypes 5[142,143] and 6,[143,148] and nine trials mixed genotypes (three trials genotypes 1 through 6;[146,150,165] one trial genotypes 1, 2, 4 and 6;[139] two trials genotypes 2 through 6;[144,196] two trials genotypes 1, 4 and 6;[166,198] and one trial genotypes 1 and

4[164]). Thirty-one trials (in 28 publications) excluded patients with cirrhosis[137,144,146,147,154,155,159-162,167,186,188-194,196,197,199] or reported results in the subgroup of patients without cirrhosis.[139,147,149,150,164,165,185,198] For trials that enrolled patients with cirrhosis, inclusion was restricted to trials in which the proportion of patients with cirrhosis was less than 20 percent, with the exception of one trial of grazoprevir / elbasvir that had a slightly higher proportion (22%).[166] All trials excluded patients with HBV infection. Five trials (in 4 publications) enrolled patients with a history of receiving methadone or buprenorphine for opioid use disorder.[149,150,167,192] The other trials excluded patients with recent or current substance use or did not describe substance use.

Thirteen trials (in 11 publications) evaluated ombitasvir / paritaprevir / ritonavir / dasabuvir, with or without ribavirin,[137,149,151,155,162,186-189,191,192] ten trials ledipasvir / sofosbuvir,[141,142,145,148,156,163,185,190,193,195] eight trials (in 6 publications) glecaprevir / pibrentasvir,[143,167,194,196,197,199] seven trials (in 6 publications) sofosbuvir / velpatasvir,[139,146,147,150,158,165] six trials elbasvir / grazoprevir,[144,152,160,164,166,198] four trials daclatasvir / sofosbuvir.[157,159,161,167] and three trials simeprevir / sofosbuvir.[153,154,159] One trial compared a current DAA regimen versus placebo,[139] two trials (reported in one publication) compared a current DAA regimen versus a regimen with telaprevir,[137] and two trials (reported in one publication) compared a current DAA regimen versus an older, not currently recommended, DAA regimen.[147] Five other trials randomized patients to a DAA regimen versus placebo with delayed DAA therapy, but only reported SVR rates following active treatment.[151,152,164,166,187] The other trials did not compare a current DAA regimen to placebo or an older antiviral regimen. The duration of treatment was 12 weeks in all trials except for seven trials (in 5 publications)[143,167,196,197,199] which evaluated 8 or 12 weeks of glecaprevir / pibrentasvir and two trials which evaluated 8 or 12 weeks of ledipasvir / sofosbuvir.[191,193] Fourteen trials (in 12 publications) evaluated the same DAA regimen with and without ribavirin;[137,144,154,158,160,161,185,186,188,191,193,194] of these, six trials (in 4 publications[137,186,188,191]) evaluated ombitasvir / paritaprevir / ritonavir / dasabuvir, two trials[185,193] ledipasvir / sofosbuvir, two trials[144,160] elbasvir / grazoprevir, and one trial each evaluated simeprevir / sofosbuvir,[154] sofosbuvir / velpatasvir,[158] glecaprevir / pibrentasvir,[194] and daclatasvir / sofosbuvir.[161] Twenty-one trials did not vary duration of treatment or use of ribavirin.[141,142,145,146,148-150,153,155-157,159,162-165,189,190,192,195,198] Thirty-two trials (in 30 publications) enrolled treatment-naïve populations or reported results stratified according to prior treatment status,[137,141,142,144-146,149,151-153,155-157,159-167,185,188-191,193,195,198] five trials only enrolled treatment-experienced patients,[137,154,158,186,194] and 11 trials (in 10 publications) enrolled a mix of treatment-naïve and -experienced patients but did not stratify results according to treatment status.[139,143,147,148,150,187,192,196,197,199] In trials of mixed populations, the proportion of treatment-naïve patients ranged from 52 to 95 percent. SVR was measured 12 weeks after the end of treatment in all trials except for one trial that assessed SVR at 14 weeks post-treatment[166] and four trials (in 3 publications) that reported 12- and 24-week post-treatment SVR rates.[167,191,192] In the latter trials, 12- and 24-week SVR rates were identical or very similar.

Twenty-seven trials (in 24 publications[137,139,144,146,147,151-154,158-161,166,167,185-191,193,194]) had multiple DAA treatment arms, and 22 trials (in 21 publications[141-143,145,148-150,155-157,162-165,167,192,195-199]) were single-arm studies (**Appendix B Tables 10 and 11**). Among the trials with multiple treatment arms, 20 (in 18 publications[137,144,146,147,153,154,158-161,167,185,186,189-191,193,194]) used an open-label design. In the open-label trials, treatment allocation was random in 11 trials (in 9

publications[137,147,153,159,167,185,186,190,194]); in the other trials patients were allocated to treatment based on genotype (4 trials[144,146,160,161]), prior treatment status (1 trial[191]), or clinical characteristics (e.g., fibrosis stage).[154,158,189,193] Thirteen trials were rated good quality,[137,139,141,146,152,159,162,164,166,187-189,191] and the remainder were rated fair quality. Frequent methodological limitations included unclear randomization or enrollment methods (e.g., unclear if the trial enrolled consecutive patients meeting inclusion criteria, or a random sample). Loss to followup was low across all trials (range 0 to 3%). All of the trials were industry-funded.

SVR Rates in Comparative Trials

DAA Regimen vs. Placebo

One randomized trial (n=706) compared sofosbuvir / velpatasvir versus placebo in persons with HCV infection (genotypes 1, 2, 4, 5, or 6; **Table 11**).[139] Genotype 1 infection was present in 53 percent of patients, 32 percent of patients had previously received interferon therapy, and 19 percent had cirrhosis at baseline. Sofosbuvir / velpatasvir was associated with an SVR rate of 99 percent (618/624), compared with no cases of SVR among 116 patients randomized to placebo (RR 231.6, 95% CI, 14.6 to 3680). Across genotypes, the SVR rate with sofosbuvir / velpatasvir ranged from 97 percent to 100 percent.

DAA Regimen vs. Telaprevir-Containing Regimen

Two randomized trials (reported in one publication) compared ombitasvir / paritaprevir / ritonavir / dasabuvir (with or without ribavirin) for 12 weeks versus telaprevir (12 weeks) / pegylated interferon / ribavirin (24 or 48 weeks) for genotype 1 infection (**Table 11**).[137] One trial (n=311) enrolled treatment-naïve patients, and the other (n=148) enrolled patients previously treated with pegylated interferon and ribavirin. In treatment- naïve patients, ombitasvir / paritaprevir / ritonavir / dasabuvir was associated with increased likelihood of SVR versus telaprevir / pegylated interferon / ribavirin (98% vs. 80%, RR 1.22, 95% CI, 1.08 to 1.37). SVR rates were similar in genotype 1a patients who received ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin (97%) and genotype 1b patients who received the same regimen with or without ribavirin (98 to 99%). In the other trial, ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin was associated with increased likelihood of SVR versus telaprevir / pegylated interferon / ribavirin in treatment-experienced patients (99% vs. 66%, RR 1.50, 95% CI, 1.22 to 1.85). SVR rates were similar for genotype 1a (100%) and 1b (99%) infection.

DAA Regimen vs. Non-Recommended DAA Regimen

Two randomized trials (reported in one publication) compared sofosbuvir / velpatasvir for 12 weeks versus sofosbuvir / ribavirin for 24 weeks.[147] One trial (n=269) enrolled patients with genotype 2 infection (14 to 15% prior interferon therapy, 14% cirrhosis) and one trial (n=280) enrolled patients with genotype 3 infection (26% prior interferon therapy and 29 to 30% cirrhosis; results reported for non-cirrhosis subgroup). Sofosbuvir / velpatasvir was associated with increased likelihood of SVR for genotype 2 infection (99% vs. 94%, RR 1.06, 95% CI, 1.01 to 1.11) and for genotype 3 infection (non-cirrhosis subgroup, 97% vs. 87%, RR 1.11, 95% CI, 1.05 to 1.18).

Pooled SVR Rates by Genotype

Genotype 1

Thirty-two trials (total N=6,055) reported SVR rates associated with seven different DAA regimens in persons with genotype 1 infection.[137,139,145,146,149,151-156,159-161,163-167,185-188,190-194,197,198] Across DAA regimens, the pooled SVR rate was 97.7 percent (95% CI, 96.6% to 98.4%; I^2=82%) (**Figure 2**). Although statistical heterogeneity was present, the SVR rate was 91 percent or higher in all of the trials. The most frequently evaluated regimen was ombitasvir / paritaprevir / ritonavir, with or without dasabuvir or ribavirin (11 trials).[137,139,149,151,155,186,188,191,192] The pooled SVR rate with this regimen was 93.7 percent (95% CI, 89.0% to 96.5%; I^2=77%) for genotype 1a infection (5 trials), 98.2 percent (95% CI, 96.4% to 99.1%; I^2=68%) for genotype 1b infection (8 trials), and 93.2 percent (95% CI, 87.0% to 96.6%, I^2=27%) for non-subtyped genotype 1 infection (2 trials). Ledipasvir / sofosbuvir was evaluated in six trials,[145,156,163,185,190,193] with a pooled SVR rate of 99.4 percent (95% CI, 95.2% to 99.9%, I^2=89%), and elbasvir / grazoprevir was evaluated in five trials[152,160,164,166,198] with pooled SVR rate of 96.7 percent (95% CI, 95.0% to 97.8%; I^2=55%). Four other antiviral regimens were evaluated in two or three trials each; pooled SVR rates ranged from 95.7 percent to 99.0 percent for these regimens (**Table 12**).

Results were similar for trials rated good quality (pooled SVR 97.2%, 95% CI, 95.2% to 98.4%) or fair quality (pooled SVR 97.9%, 95% CI, 96.7% to 98.7%), for trials that excluded patients with cirrhosis (pooled SVR 97.1%, 95% CI, 95.7% to 98.1%) or included some (less than 20% of sample) patients with cirrhosis (pooled SVR 98.7%, 95% CI, 97.1% to 99.4%), and when the analysis was restricted to trials conducted in the United States and Canada (pooled SVR 96.6%, 95% CI, 93.1% to 98.4%) (**Table 12**). Results were also similar when the analysis was restricted to trials that used ribavirin as recommended or did not omit dasabuvir in combination with ombitasvir / paritaprevir / ritonavir (pooled SVR 98.3%, 95% CI, 97.4% to 98.9%) or when the analysis was restricted to treatment-naïve patients (pooled SVR 97.4%, 95% CI, 96.1% to 98.3%).

Genotype 2

Five trials (total N=526) reported SVR rates associated with two different DAA regimens in persons with genotype 2 infection (pooled SVR 98.9%, 95% CI, 97.5% to 99.5%; I^2=4%) (**Figure 3**).[139,147,165,196,199] Three trials evaluated sofosbuvir / velpatasvir (pooled SVR 99.6%, 95% CI, 97.6% to 99.95%, I^2=0%),[139,147,164] and two trials evaluated glecaprevir / pibrentasvir (pooled SVR 97.9%, 95% CI, 95.0% to 99.1%, I^2=0%).[196,199] Estimates were similar when trials were stratified according to quality, geographic setting, or enrollment of some patients with cirrhosis (**Table 12**). SVR rates were also similar in trials that were restricted to treatment-experienced patients[164,196,199] or enrolled a mix of treatment-naïve and treatment-experienced patients;[139,147] one mixed population trial reported an SVR of 100% (95% CI, 95.4% to 100%) in the subgroup of treatment-naïve patients.[139]

Genotype 3

Six trials (total N=742) reported SVR rates associated with three different DAA regimens in persons with genotype 3 infection (pooled SVR 95.5%, 95% CI, 91.6% to 97.7%; I^2=66%) (**Figure 4**).[146,147,157,158,165,167] Estimates were similar for sofosbuvir / velpatasvir (4 trials; pooled SVR 95.6%, 95% CI, 87.1% to 98.6%; I^2=82%)[146,147,158,165] sofosbuvir / daclatasvir (2 trials; pooled SVR 96.4%, 95% CI, 93.0% to 98.2%, I^2=0%),[157,167] and glecaprevir / pibrentasvir (one trial, SVR 94.9%, 95% CI, 90.2% to 97.8%).[167]

The SVR rate was higher in five trials that excluded patients with cirrhosis (pooled SVR 96.4%, 95% CI, 94.6% to 97.5%) than in one trial[165] that included some patients with cirrhosis (SVR 85.7%, 95% CI, 76.5% to 91.7%; p for interaction=0.01). Results were similar when trials were stratified according to study quality or when the analysis was restricted to trials conducted in the United States or Canada (**Table 12**). Results were also similar when the analysis excluded results from one trial[158] of sofosbuvir / velpatasvir plus ribavirin (ribavirin is not required with this regimen; pooled SVR 95.2%, 95% CI, 91.4% to 97.3%) and when the analysis was restricted to treatment-naïve patients (pooled SVR 96.1%, 95% CI, 94.5% to 97.3%) (**Table 12**).

Genotype 4

Ten trials (total N=485) reported SVR rates associated with five different DAA regimens in persons with genotype 4 infection (pooled SVR 98.2%, 95% CI, 94.7% to 99.4%; I^2=50%) (**Figure 5**).[139,142,144,162,164,166,189,195,196,198] Estimates were similar for elbasvir / grazoprevir (4 trials, pooled SVR 97.3%, 95% CI, 83.2% to 99.6%, I^2=0%),[138,144,164,166,198] ombitasvir / paritaprevir / ritonavir with ribavirin (2 trials, pooled SVR 98.7%, 95% CI, 72.7% to 99.95%; I^2=88%),[162,189] and ledipasvir / sofosbuvir (2 trials, pooled SVR 98.4%, 95% CI, 93.7% to 99.6%, I^2=25%)[142,195] (**Table 12**). One trial each evaluated sofosbuvir / velpatasvir (SVR 100%, 95% CI, 95.9% to 100%)[139] and glecaprevir / pibrentasvir (SVR 93.5%, 95% CI, 82.1% to 98.6%).[196]

Results were similar when the analysis was restricted to trials that were rated good quality (pooled SVR 96.5%, 95% CI, 86.5.0% to 99.2%), when trials were stratified according to whether they were restricted to patients without cirrhosis (pooled SVR 98.3%, 95% CI, 94.4% to 99.5%) or included some patients with cirrhosis (pooled SVR 99.1%, 95% CI, 91.2% to 99.9%), and when trials were stratified according to geographic setting (**Table 12**). Results were also similar when the analysis was restricted to treatment-naïve patients (pooled SVR 98.3%, 95% CI, 94.5% to 99.5%).

Genotype 5

Four trials (total N=75) reported SVR rates associated with three different DAA regimens in patients with genotype 5 infection (pooled SVR 96.0%, 95% CI, 88.3% to 98.7%; I^2=0%; **Figure 6**).[139,141,143,196] Estimates were similar for glecaprevir / pibrentasvir (2 trials, pooled SVR 96.0%, 95% CI, 76.4% to 99.4%; I^2=0%),[143,196] ledipasvir / sofosbuvir (1 trial, SVR 95.2%, 95% CI, 76.2% to 99.9%),[141] and sofosbuvir / velpatasvir (1 trial, SVR 96.6%, 95% CI, 82.2% to 99.9%).[139] Estimates were similar when trials were stratified according to study quality,

inclusion of patients with cirrhosis, and geographic setting (**Table 12**). Results were also similar when the analysis was restricted to treatment-naïve patients (pooled SVR 95.6%, 95% CI, 83.9% to 98.9%).

Genotype 6

Five trials (total N=229) reported SVR rates associated with three different DAA regimens in persons with genotype 6 infection (pooled SVR 98.2%, 95% CI, 95.4% to 99.3%, I^2=0%) (**Figure 7**).[139,143,148,165,196] Estimates were similar for glecaprevir / pibrentasvir (2 trials, pooled SVR 97.2%, 95% 89.4% to 99.3%; I^2=42%),[143,196] sofosbuvir / velpatasvir (2 trials, pooled SVR 99.2%, 95% CI, 94.9% to 99.9%; I^2=0%)[139,165] and ledipasvir / sofosbuvir (1 trial, SVR 96.0%, 95% CI, 79.6% to 99.9%).[148] Results were similar when analyses were stratified according to quality, enrollment of some patients with cirrhosis, and geographic setting (**Table 12**). Results were also similar when the analysis was restricted to treatment-naïve patients (pooled SVR 98.4%, 95% CI, 89.6% to 99.8%).

Mixed Genotypes

Two trials (total N=108) reported SVR rates associated with sofosbuvir / velpatasvir in persons with mixed genotype 1 to 6 infections (pooled SVR 95.4%, 95% CI, 89.4% to 98.1%; I^2=0%) (**Figure 8**).[146,150] Both trials were restricted to patients without cirrhosis. In one trial[146] patients were treatment-naïve, and in the other trial prior treatment status was not reported.[150]

Subgroup Analyses

Nineteen trials (in 18 publications) reported analyses stratified according to demographic characteristics.[139,145,147,149,150,152,156,157,164-167,185-187,190,191,198] SVR rates were similar when patients were stratified according to age in 17 trials, according to sex in 17 trials, and according to race or ethnicity in 11 trials (**Table 13**). One trial found SVR rates were slightly higher in persons with body mass index (BMI) less than 30 kg/m^2 versus 30 kg/m^2 or more (97% vs. 92%) and in persons with diabetes versus no diabetes (100% vs. 96%).[187]

Nine trials found SVR rates were similar when analyses were stratified according to whether patients were treatment-experienced or treatment-naïve.[151-153,155,159,163,165,167,198] Five trials (in 4 publications)[149,150,167,192] of patients with current or recent use of methadone or buprenorphine for opioid use disorder reported SVR rates ranging from 89 to 100 percent. The other trials excluded patients with current or recent opioid use or did not report opioid use status.

Adolescents

Seven trials evaluated the effects of DAA regimens on SVR in adolescents with HCV infection (**Appendix B Tables 7** and **8**).[171,173,175,176,201-203] Sample sizes ranged from 30 to 100 (total N=348), mean age ranged from 12 to 15 years, and the proportion of female participants ranged from 35 to 66 percent. Four studies[171,173,175,203] were multinational (primarily conducted in the United States, Europe and/or Australia), and three were conducted in Egypt.[176,201,202] In the four multinational studies, the majority (75% or more) of participants were white.[171,173,175,203] The

three Egyptian studies[176,201,202] enrolled genotype 4 patients, one multinational study enrolled patients with genotype 1,[175] and three multinational studies enrolled mixed genotypes.[171,173,203] Patients with cirrhosis were excluded in two trials and cirrhosis/fibrosis stage inclusion criteria was not reported in a third trial. In the other four trials, enrollment of patients with cirrhosis was permitted, but two of these did not conduct liver biopsy or other testing for cirrhosis at baseline. Fibrosis stage was F0-F1 in 68 to 96 percent of the population in five studies;[171,176,201-203] fibrosis stage was unknown in over half of participants in the other two studies. The proportion of treatment-naïve patients ranged from 66 to 100 percent. In the six trials that included treatment-experienced patients, prior HCV treatment was interferon with or without ribavirin in three trials[171,202,203] and was unclear in three trials.[173,175,176] Four trials evaluated DAA regimens currently recommended and FDA-approved for use in adolescents: ledipasvir and sofosbuvir (2 trials),[175,202] sofosbuvir and ribavirin (1 trial)[173] and glecaprevir / pibrentasvir (1 trial).[171] Three trials evaluated DAA regimens currently recommended for adults but not FDA-approved for use in adolescents: sofosbuvir and daclatasvir (2 trials)[176,201] and ombitasvir / paritaprevir / ritonavir / dasabuvir and weight-based ribavirin (one trial).[203] One study was rated good quality,[176] and the others fair quality, primarily due to unclear patient enrollment methods (**Appendix B Table 9**).

SVR was assessed at 12-weeks post-treatment. Therapy was administered for 12 weeks in all trials with the exception of sofosbuvir / ribavirin which was administered for 12 (genotype 2) or 24 (genotype 3) weeks in one trial, and glecaprevir / pibrentasvir which was administered for 8 weeks for 94 percent of the study population in one trial.[171] Across all studies, the rate of SVR ranged from 97 to 100 percent (**Table 14; Appendix B Tables 7** and **8**). Results were similar for specific genotypes (genotype 1 [N=31]: 98% to 100%; genotype 2 [N=13]: 100%; genotype 3 [N=39]: 97%; and, genotype 4 [N=7]: 98 to 100%), though the number of adolescents with genotype 2 or 4 infection was very small. In two studies, SVR rates were 98 percent to 100 percent for both treatment-naïve and treatment-experienced patients.[175,203]

Key Question 8. What Are the Harms of Currently Recommended Antiviral Treatments?

Summary

- The prior review found triple therapy with boceprevir or telaprevir plus pegylated interferon and ribavirin or dual therapy with pegylated interferon and ribavirin associated with high rates of adverse events:
    - Serious adverse events: Pooled rates 8.5 to 16 percent
    - Withdrawal due to adverse event: Pooled rates 12 to 15 percent
    - Fatigue: Pooled rates 51 to 64 percent
    - Influenza-like symptoms: Pooled rates 19 to 40 percent
    - Depression: Pooled rates 19 to 22 percent
    - Headache: Pooled rates 42 to 52 percent
    - Myalgia: Pooled rates 18 to 26 percent
- The prior review found triple therapy with boceprevir associated with increased risk of thrombocytopenia (3.8% vs. 1.4%, RR 3.2, 95% CI, 1.4 to 2.8) and neutropenia (33% vs.

18%, RR 1.8, 95% CI, 1.5 to 2.3) versus dual therapy, and telaprevir associated with increased risk of anemia (52% vs. 39%, RR 1.3, 95% CI, 1.1 to 1.3). Triple therapy with telaprevir was also associated with increased risk of rash versus dual therapy (49% vs. 35%, RR 1.4, 95% CI, 1.1 to 1.7) and boceprevir with increased risk of dysgeusia (35% vs. 13%, RR 2.5, 95% CI, 2.0 to 3.2).

- Four new randomized trials found current DAA regimens associated with slightly increased risk of any adverse event versus placebo (pooled RR 1.12, 95% CI, 1.02 to 1.24, I^2=46%; adjusted risk difference [ARD] 8%, 95% CI, 2% to 15%) and nausea (pooled RR 1.42, 95% CI, 1.00 to 2.03, I^2=10%, ARD 4%, 95% CI, −3% to 10%). There were no differences between DAA therapy versus placebo in risk of serious adverse events, withdrawal due to adverse events, diarrhea, fatigue, headache, or anemia.
- Two new randomized trials found ombitasvir / paritaprevir / ritonavir / dasabuvir with or without ribavirin associated with decreased risk of any adverse event (RR 0.65, 95% CI, 0.50 to 0.84, I^2=87%; ARD −34%, 95% CI, −51% to −16%), serious adverse events (RR 0.08, 95% CI, 0.02 to 0.34, I^2=0%; ARD −8%, 95% CI, −15% to −1%), withdrawal due to adverse events (RR 0.06, 95% CI, 0.01 to 0.29, I^2=0%; ARD −9%, 95% CI, −14% to −3%), fatigue (RR 0.37, 95% CI, 0.21 to 0.63, I^2=32%; ARD −18%, 95% CI, −27% to −10%), headache (RR 0.70, 95% CI, 0.52 to 0.95; ARD −0.10, 95% CI, −0.20 to −0.01), nausea (RR 0.31, 95% CI, 0.16 to 0.59, I^2=65%; ARD −28%, 95% CI, −37% to −19%), anemia (RR 0.09, 95% CI, 0.04 to 0.23, I^2=41%; ARD −37%, 95% CI, −46% to −28%), and rash (RR 0.19, 95% CI, 0.06 to 0.58, I^2=48%; ARD −17%, 95% CI, −24% to −9%) versus telaprevir / pegylated interferon / ribavirin.
- Forty-nine new trials reported the proportion of patients on DAA regimens with adverse events:
    - Any adverse event (44 trials): 73.3 percent (95% CI, 68.0% to 78.1%, I^2=95%)
    - Serious adverse events (44 trials): 1.9 percent (95% CI, 1.5% to 2.4%, I^2=33%)
    - Withdrawal due to adverse events (44 trials): 0.4 percent (95% CI, 0.3% to 0.6%, I^2=0%)
    - Anemia (13 trials): 2.4 percent (95% CI, 0.9% to 6.3%, I^2=85%)
    - Fatigue (37 trials): 18.4 percent (95% CI, 15.6% to 21.7%, I^2=90%)
    - Headache (42 trials): 18.7 percent (95% CI, 15.6% to 22.2%, I^2=90%)
    - Insomnia (18 trials): 8.1 percent (95% CI, 6.7% to 9.9%, I^2=60%)
    - Nausea (36 trials): 11.1 percent (95% CI, 9.1% to 13.5%, I^2=82%)
    - Diarrhea (19 trials): 8.7 percent (95% CI, 7.0% to 10.8%, I^2=69%)
    - Vomiting (6 trials): 5.8 percent (95% CI, 3.4% to 9.7%, I^2=43%)
    - Rash (17 trials): 5.4 percent (95% CI, 4.1% to 7.1%, I^2=70%)
- There was some variability by DAA regimens in adverse events estimates; estimates were generally higher for ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin than without ribavirin.
- Adverse event estimates were generally similar when trials were stratified according to baseline cirrhosis status (excluded or included up to 20%) and prior antiviral therapy experience.

Evidence

Adults

The prior Agency for Healthcare Research and Quality review found no difference between triple therapy with boceprevir or telaprevir plus pegylated interferon and ribavirin versus dual therapy with pegylated interferon and ribavirin in risk of serious adverse events (pooled event rates ranged from 8.5% to 16%) or withdrawal due to adverse events (pooled event rates 12% to 15%).[5,90] There were also no differences in rates of fatigue (pooled event rates 51% to 64%), influenza-like symptoms (pooled event rates 19% to 40%), depression (pooled event rates 19% to 22%), headache (pooled event rates 42% to 52%), or myalgia (pooled event rates 18% to 26%), but these adverse events occurred frequently with all regimens. Triple therapy was associated with increased risk of hematological adverse events versus dual therapy. Boceprevir was associated with increased risk of thrombocytopenia (3.8% vs. 1.4%, RR 3.2, 95% CI, 1.4 to 2.8) and neutropenia (33% vs. 18%, RR 1.8, 95% CI, 1.5 to 2.3), and telaprevir was associated with increased risk of anemia (52% vs. 39%, RR 1.3, 95% CI, 1.1 to 1.3). Triple therapy with telaprevir was also associated with increased risk of rash versus dual therapy (49% vs. 35%, RR 1.4, 95% CI, 1.1 to 1.7) and boceprevir with increased risk of dysgeusia versus dual therapy (35% vs. 13%, RR 2.5, 95% CI, 2.0 to 3.2).

Forty-nine new trials (in 44 publications) of DAA regimens without interferon reported the proportion of patients who experienced adverse events (**Table 15**; **Appendix B Tables 10** and **11**).[137,139,141-167,185-199] One DAA trial[158] included in the SVR analysis was excluded from pooled analyses of adverse events because a high proportion of patients had cirrhosis (about 40%) and adverse event rates were not reported separately for persons without cirrhosis. Eleven trials (in 9 publications) of ombitasvir / paritaprevir / ritonavir / dasabuvir included ribavirin, which is recommended for treatment of genotype 1a and 4 infections.[137,149,162,186-189,191,192] Regimens containing ribavirin were otherwise excluded from the adverse event analyses. Eight trials (in 6 publications) reporting adverse events compared a current DAA regimen versus placebo,[139,151,164,187] triple therapy with telaprevir,[137] or an older DAA regimen.[147] Reporting of methods used to assess harms was suboptimal, with few details regarding use of active versus passive assessment or definitions of harms. Trial characteristics are described in more detail in KQ 7.

Adverse Events in Comparative Trials

DAA Regimen vs. Placebo

Four randomized trials (total N=2,113) reported adverse events associated with current DAA regimens versus placebo.[139,151,164,187] Each trial evaluated a different DAA regimen: sofosbuvir / velpatasvir (n=706),[139] ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin (n=477),[187] ombitasvir / paritaprevir / dasabuvir (n=321),[151] and elbasvir / grazoprevir (n=609)[164] (**Table 15, Appendix B Tables 10** and **11**). The trials of sofosbuvir / velpatasvir and elbasvir / grazoprevir enrolled people with mixed genotype (1, 2, 4, 5, and/or 6) infections, and the other trials enrolled persons with genotype 1 infection. One trial enrolled treatment-naïve patients;[164] in the

remaining trials, approximately one-third of patients had previously received interferon therapy. In two trials,[139,164] approximately 19 percent of patients had cirrhosis at baseline, and the other two trials restricted enrollment to persons without cirrhosis. All trials used a double-blind design.

DAA therapy was associated with slightly increased risk of any adverse event versus placebo that was of borderline statistical significance (4 trials, RR 1.12, 95% CI, 1.02 to 1.24, I^2=46%; ARD 8%, 95% CI, 8% to 15%; **Figure 9**).[139,151,164,187] Among patients randomized to DAA therapy, the proportion reporting any adverse event ranged from 47 percent to 86 percent. There were no differences between DAA therapy versus placebo in risk of serious adverse events (4 trials, RR 1.90, 95% CI, 0.73 to 4.95, I^2=0%; **Figure 10**) or withdrawal due to adverse events (4 trials, RR 0.47, 95% CI, 0.14 to 1.58, I^2=14%; **Figure 11**), though there were few events and estimates were imprecise.[139,151,164,187] Among patients randomized to DAA therapy, the proportion with serious adverse events ranged from 2.0 percent to 3.3 percent, and the proportion who withdrew due to adverse events ranged from 0.2 percent to 0.9 percent. DAA therapy was associated with increased risk of nausea versus placebo (3 trials, RR 1.42, 95% CI, 1.00 to 2.03, I^2=10%; ARD 4%, 95% CI, -3% to 10%; **Figure 12**).[139,151,187] The point estimate was similar for diarrhea, but the difference was not statistically significant (2 trials, RR 1.53, 95% CI, 0.88 to 2.68, I^2=29%; **Figure 13**).[139,187] There were no differences between DAA therapy versus placebo in risk of fatigue (3 trials, RR 1.05, 95% CI, 0.78 to 1.40; I^2=32%; **Figure 14**)[139,164,187] or headache (four trials, RR 1.12, 95% CI, 0.92 to 1.37, I^2=0%; **Figure 15**).[139,151,164,187] One trial[139] found no difference between sofosbuvir / velpatasvir versus placebo in risk of anemia (0.3% vs. 0%, RR 2.21, 95% CI, 0.11 to 46); no cases of anemia were reported in the other three trials.

DAA Regimen vs. Telaprevir / Pegylated Interferon / Ribavirin

Two randomized trials (reported in one publication) compared ombitasvir / paritaprevir / ritonavir / dasabuvir with or without ribavirin for 12 weeks versus triple therapy with telaprevir (12 weeks) / pegylated interferon / ribavirin (24 or 48 weeks) in patients with genotype 1 infection.[137] One trial (n=311) enrolled treatment-naïve patients, and one trial (n=148) enrolled patients previously treated with pegylated interferon and ribavirin. The DAA regimen was associated with decreased risk of any adverse event (RR 0.65, 95% CI, 0.50 to 0.84, I^2=87%; ARD −34%, 95% CI, −51% to −16%; **Figure 16**), serious adverse events (RR 0.08, 95% CI, 0.02 to 0.34, I^2=0%; ARD −8%, 95% CI, −15% to −1%; **Figure 17**), withdrawal due to adverse events (RR 0.06, 95% CI, 0.01 to 0.29, I^2=0%; ARD −9%, 95% CI, −14% to −3%; **Figure 18**), fatigue (RR 0.37, 95% CI, 0.21 to 0.63, I^2=32%; ARD −18%, 95% CI, −27% to −10%; **Figure 19**), headache (RR 0.70, 95% CI, 0.52 to 0.95, I^2=0%; ARD −0.10, 95% CI, −0.20 to −0.01; **Figure 20**), nausea (RR 0.31, 95% CI, 0.16 to 0.59, I^2=65%; ARD −28%, 95% CI, −37% to −19%; **Figure 21**), anemia (RR 0.09, 95% CI, 0.04 to 0.23, I^2=41%; ARD −37%, 95% CI, −46% to −28%; **Figure 22**), and rash (RR 0.19, 95% CI, 0.06 to 0.58, I^2=48%; ARD −17%, 95% CI, −24% to −9%; **Figure 23**) versus the telaprevir regimen. The association between DAA therapy versus telaprevir and risk of any adverse event was less pronounced when ribavirin was included with DAA therapy (2 trials, RR 0.74, 95% CI, 0.65 to 0.84, I^2=43%; **Figure 16**) than without ribavirin (1 trial, RR 0.50, 95% CI, 0.40 to 0.62; p for interaction=0.003). There was no interaction between prior antiviral treatment experience and risk estimates for any adverse event.

Pooled Adverse Event Rates for DAA Regimens

Any Adverse Event

Forty-four trials (in 41 publications, total N=8,045) reported the proportion of patients reporting any adverse event with eight different DAA regimens.[137,139,141-156,159-167,185-190,192-199] Across regimens, the pooled rate for any adverse event was 73.3% (95% CI, 68.0% to 78.1%, I^2=95%; **Figure 24**). Stratified by antiviral regimen, the rate of any adverse event ranged from 62.3% (95% CI, 56.1% to 68.1%) for glecaprevir / pibrentasvir (7 trials) to 82.7% (95% CI, 58.5% to 94.2%) for sofosbuvir / daclatasvir (2 trials). The rate of any adverse event was higher in trials of ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin (10 trials [in 8 publications] pooled event rate 81.1%, 95% CI, 74.2% to 86.5%; I^2=87%) than without ribavirin (6 trials, pooled event rate 75.1%, 95% CI, 62.3% to 84.6%; I^2=92%) (**Table 16**). The proportion of patients with any adverse event was similar when trials were stratified according to whether they excluded patients with cirrhosis (24 trials, pooled event rate 75.5%, 95% CI, 69.0% to 81.1%) or included some patients with cirrhosis (19 trials, pooled event rate 72.4%, 95% CI, 64.6% to 79.0%; p for interaction=0.52), and there was no interaction between prior treatment experience status and rates of any adverse event (p for interaction=0.76).

Serious Adverse Events

Forty-four trials (in 40 publications, total N=8,070) reported the proportion of patients reporting serious adverse events with eight different DAA regimens.[137,139,141-144,146-157,160-167,185-194,196-199] Across regimens, the pooled rate for serious adverse events was 1.9 percent (95% CI, 1.5% to 2.4%, I^2=33%; **Figure 25**). Stratified by antiviral regimen, the rate of any adverse event ranged from 0.6 percent (95% CI, 0.1% to 4.1%, I^2=0%) for simeprevir / sofosbuvir (2 trials) to 2.1 percent for elbasvir / grazoprevir (6 trials, 95% CI, 1.1% to 3.9%, I^2=42%) and ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin (11 trials, 95% CI, 1.5% to 3.0%, I^2=26%) (**Table 16**). The rate of serious adverse events for ombitasvir / paritaprevir / ritonavir / dasabuvir without ribavirin (7 trials, pooled event rate 1.9%, 95% CI, 1.2% to 3.2%, I^2=31%) was similar to the rate with ribavirin. Estimates were similar when trials were stratified according to whether they excluded patients with cirrhosis (23 trials, pooled event rate 1.8%, 95% CI, 1.3% to 2.5%) or included some patients with cirrhosis (21 trials, pooled event rate 2.0%, 95% CI, 1.4% to 2.7%; p for interaction=0.69), and there was no interaction between prior treatment experience status and rates of serious adverse events (p for interaction=0.96).

Withdrawal Due to Adverse Events

Forty-four trials (in 40 publications, total N=8,060) reported the proportion of patients who withdrew due to adverse events with eight different DAA regimens.[137,139,141-156,160-167,185-194,196-199] Across regimens, there were a total of 35 withdrawals due to adverse events, with a pooled rate of 0.4 percent (95% CI, 0.3% to 0.6%, I^2=0%; **Figure 26**). The proportion of patients who withdrew due to adverse events was less than or equal to 1 percent for all regimens (**Table 16**).

Anemia

Thirteen trials (in 9 publications, total N=1,555) reported the proportion of patients with anemia with five different DAA regimens.[137,149,154,185,186,190-192,199] Across regimens, the pooled rate for anemia was 2.4 percent (95% CI, 0.9% to 6.3%, I^2=85%; **Figure 27**). The rate of anemia was much higher in trials of ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin (6 trials, pooled event rate 8.3%, 95% CI, 5.8% to 11.8%, I^2=49%) than the same regimen without ribavirin (3 trials, pooled event rate 0.8%, 95% CI, 0.2% to 3.1%, I^2=0%) or with other regimens (pooled event rates <0.5%) (**Table 17**).

Fatigue

Thirty-seven trials (in 33 publications, total N=7,571) reported the proportion of patients with fatigue with eight different DAA regimens.[137,139,141-150,153,155-157,159-162,164,167,185-192,194-196] Across regimens, the pooled rate for fatigue was 18.4 percent (95% CI, 15.6% to 21.7%, I^2=90%; **Figure 28**). Stratified by antiviral regimen, rates of fatigue ranged from 10.9 percent (95% CI, 4.3% to 25.1%, I^2=88%) for elbasvir / grazoprevir (3 trials) to 26.9 percent (95% CI, 20.5% to 34.4%, I^2=88%) for ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin (11 trials) (**Table 17**). The rate of fatigue was higher for ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin than the same regimen without ribavirin (6 trials, pooled event rate 15.8%, 95% CI, 9.1% to 26.1%, I^2=91%). Estimates were similar when trials were stratified according to whether they excluded patients with cirrhosis (18 trials, pooled event rate 20.2%, 95% CI, 16.0% to 25.3%, I^2=92%) or included some patients with cirrhosis (18 trials, pooled event rate 16.7%, 95% CI, 13.1% to 21.2%; p for interaction=0.27) and there was no interaction between prior treatment status and rates of fatigue (p for interaction=0.54).

Headache

Forty-two trials (in 38 publications, total N=7,790) reported the proportion of patients with headache with 8 different DAA regimens.[137,139,141-151,153,155-157,159-162,164,165,167,185-197,199] Across regimens, the pooled rate for headache was 18.7 percent (95% CI, 15.6% to 22.2%, I^2=90%; **Figure 29**). Stratified by antiviral regimen, rates of headache ranged from 13.7 percent (95% CI, 8.4% to 21.5%, I^2=85%) for ledipasvir / sofosbuvir (9 trials) to 27.7 percent (95% CI, 24.0% to 31.6%, I^2=62%) for ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin (11 trials) (**Table 17**). The rate of headache was higher for ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin than the same regimen without ribavirin (7 trials, pooled event rate 20.7%, 95% CI, 15.6% to 26.9%, I^2=83%). Estimates were similar when trials were stratified according to whether they excluded patients with cirrhosis (22 trials, pooled event rate 19.6%, 95% CI, 15.6% to 24.4%) or included some patients with cirrhosis (19 trials, pooled event rate 19.1%, 95% CI, 14.9% to 24.1%; p for interaction=0.88), and there was no interaction between prior treatment experience status and rates of headache (p for interaction=0.11)

Insomnia

Eighteen trials (in 17 publications, total N=3,517) reported the proportion of patients with insomnia with eight different DAA regimens.[139,146,147,149,150,157,159-162,185,187,189,190,192,194,195] Across

regimens, the pooled rate for insomnia was 8.1 percent (95% CI, 6.7% to 9.9%, I^2=60%; **Figure 30**). Stratified by antiviral regimen, rates of insomnia ranged from 6.0% (95% CI, 4.5% to 8.0%; I^2=58%) for ledipasvir / sofosbuvir (3 trials) to 12.2% (95% CI, 9.4% to 15.7%; I^2=37%) for ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin (6 trials) (**Table 17**). The only trial of glecaprevir / pibrentasvir reported no cases of insomnia.[160] Estimates were similar when trials were stratified according to whether they excluded patients with cirrhosis (10 trials, pooled event rate 8.9%, 95% CI, 7.0% to 11.4%) or included some patients with cirrhosis (8 trials, pooled event rate 8.2%, 95% CI, 6.3% to 10.5%; p for interaction=0.63), and there was no interaction between prior treatment experience status and rates of insomnia (p for interaction=0.99)

Gastrointestinal Adverse Events

Thirty-six trials (in 34 publications, total N=6,145) reported the proportion of patients with nausea on eight different DAA regimens.[137,139,142,144-151,153,157,159-162,167,185,186,188-196,199] Across regimens, the pooled rate for nausea was 11.1 percent (95% CI, 9.1% to 13.5%, I^2=82%; **Figure 31**). Stratified by antiviral regimen, rates of nausea ranged from 6.5 percent (95% CI, 4.3% to 9.7%, I^2=70%) for ombitasvir / paritaprevir / ritonavir / dasabuvir without ribavirin (7 trials) to 15.2 percent (95% CI, 9.6% to 23.2%, I^2=90%) for ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin (11 trials) (**Table 18**). Estimates were similar when trials were stratified according to whether they excluded patients with cirrhosis (21 trials, pooled event rate 10.6%, 95% CI, 8.2% to 13.5%) or included some patients with cirrhosis (14 trials, pooled event rate 12.9%, 95% CI, 9.6% to 17.1%; p for interaction=0.31), and there was no interaction between prior treatment experience status and rates of nausea (p for interaction=0.63).

Nineteen trials (in 18 publications, total N=2,960) of six different DAA regimens reported the proportion of patients with diarrhea.[141,142,146,148,150,155,157,160,161,185-191,195] Across regimens, the pooled rate of diarrhea was 8.7 percent (95% CI, 7.0% to 10.8%, I^2=69%; **Figure 32**). Stratified by antiviral regimen, rates of diarrhea ranged from 6.8 percent (95% CI, 4.2% to 10.9%, I^2=72%) for ledipasvir / sofosbuvir (6 trials) to 11.6 percent (95% CI, 4.9% to 25.0%) for elbasvir / grazoprevir (1 trial) (**Table 18**). The rate of diarrhea was similar for ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin (6 trials, pooled event rate 10.9%, 95% CI, 7.8% to 14.9%, I^2=73%) and the same regimen without ribavirin (5 trials, pooled event rate 11.1%, 95% CI, 7.7% to 15.9%, I^2=72%). Estimates were similar when trials were stratified according to whether they excluded patients with cirrhosis (10 trials, pooled event rate 10.1%, 95% CI, 7.9% to 12.8%) or included some patients with cirrhosis (8 trials, pooled event rate 8.0%, 95% CI, 5.8% to 10.9%; p for interaction=0.25), and there was no interaction between prior treatment experience status and rates of diarrhea (p for interaction=0.92).

Six trials (total N=444) of five different DAA regimens reported the proportion of patients with vomiting.[148-150,159,161,192] Across regimens, the pooled rate of vomiting was 5.8 percent (95% CI, 3.4% to 9.7%, I^2=43%; **Figure 33**). Stratified by antiviral regimen, rates of vomiting ranged from 1.9 percent (95% CI, 0.5% to 7.2%, I^2=0%) for sofosbuvir / daclatasvir (2 trials) to 12.0 percent (2 trials, 95% CI, 7.4% to 18.9%; I^2=0%) with ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin.

Rash

Seventeen trials (in 15 publications, total N=2,256) reported the proportion of patients with rash on eight different DAA regimens.[137,146,153,154,158-160,185-188,190,192,193,197] Across regimens, the pooled rate for rash was 5.4 percent (95% CI, 4.1% to 7.1%, I^2=70%; **Figure 34**). Stratified by antiviral regimen, rates of rash ranged from 1.5 percent (95% CI, 0.2% to 10.1%) for sofosbuvir / daclatasvir (1 trial) to 8.3 percent (95% CI, 4.9% to 13.7%, I^2=45%) for sofosbuvir / velpatasvir (2 trials) (**Table 18**). The rate of rash was higher for ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin (7 trials, pooled event rate 7.6%, 95% CI, 5.5% to 10.3%, I^2=57%) than the same regimen without ribavirin (4 trials, event rate 2.6%, 95% CI, 1.0% to 6.7%, I^2=66%). Estimates were similar when trials were stratified according to whether they excluded patients with cirrhosis (13 trials, pooled event rate 5.2%, 95% CI, 3.8% to 7.0%) or included some patients with cirrhosis (4 trials, pooled event rate 6.2%, 95% CI, 3.7% to 10.1%; p for interaction=0.56), and there was no interaction between prior treatment experience status and rates of rash (p for interaction=0.49).

HBV Infection Reactivation

All trials but one[195] excluded persons coinfected with HBV infection, and no cases of HBV reactivation were reported.

Adolescents

Seven trials of DAA regimens in adolescents reported harms (**Table 19; Appendix B Tables 7-9**).[171,173,175,176,201-203] Study characteristics were described in detail in KQ 7; four trials evaluated regimens FDA-approved for use in adolescents (ledipasvir and sofosbuvir,[175,202] sofosbuvir and ribavirin,[173] or glecaprevir / pibrentasvir[171]), and three trials evaluated DAA regimens recommended in adults but not approved in children (sofosbuvir and daclatasvir[176,201] or ombitasvir / paritaprevir / ritonavir / dasabuvir[203]). Methods for reporting and assessing harms were generally not well described.

Five trials reported no withdrawals due to adverse events,[171,173,175,176,203], and one of five trials reported a single serious adverse event (a grade 3 joint injury) in adolescents treated with sofosbuvir plus ribavirin.[173] The rate of any adverse event was 27 percent in one study of sofosbuvir and daclatasvir (not FDA-approved for use in adolescents)[176] and 71 to 87 percent in four trials of other regimens.[171,173,175,203] Rates of specific adverse events ranged from 3 to 48 percent for headache (7 trials),[171,173,175,176,201-203] 5 to 53 percent for fatigue (7 trials),[171,173,175,176,201-203] and 3 to 28 percent for gastrointestinal (nausea, vomiting, or diarrhea) adverse events (5 trials).[173,175,176,201,202] One trial of ledipasvir and sofosbuvir reported insomnia in 23 percent (9/40) of participants.[202] Stratification by DAA regimen did not appear to explain the observed variability in adverse event estimates, though assessments were limited by the small number of trials and methodological limitations.

Key Question 9. What Is the Association Between Experiencing SVR Following Antiviral Treatment and Reduction in Risk of HCV-Related Adverse Health Outcomes?

Summary

- The prior review included 10 studies of patients in which less than 25 percent had cirrhosis at baseline that found SVR after interferon-based antiviral therapy associated with decreased risk of all-cause mortality (7 studies, adjusted HR 0.12 to 0.71), liver-related mortality (5 studies, adjusted HR 0.04 to 0.22), and HCC (4 studies, adjusted HR 0.12 to 0.36) versus no SVR.
- Including studies published since the prior review, SVR after antiviral therapy was associated with decreased risk of all-cause mortality, liver mortality, cirrhosis, and HCC versus no SVR in studies in which less than 25 percent of the population had cirrhosis at baseline.
    - All-cause mortality (13 studies): Pooled adjusted HR 0.40 (95% CI, 0.28 to 0.56, I^2=52%).[69,168,204-214]
    - Liver mortality (4 studies): Pooled adjusted HR 0.11 (95% CI, 0.04 to 0.27, I^2=0%).[204,208,210,213]
    - Cirrhosis (4 cohorts reported in 3 studies): Pooled HR 0.36 (95% CI, 0.33 to 0.40; I^2=0%).[206,215,216]
    - HCC (20 studies): Pooled adjusted HR 0.29 (95% CI, 0.23 to 0.38; I^2=19%).[168,204,207,211,214,215,217-230]
- Estimates favored SVR in all studies and results were consistent when studies with potentially overlapping populations were excluded from analyses, when the analysis was restricted to studies that adjusted at a minimum for age, sex, genotype, and baseline fibrosis, and in stratified analyses based on duration of followup and geographic setting. For all-cause mortality, the effect of SVR was stronger in studies with followup longer than 5 years.
- All studies except for three evaluated SVR after interferon-based therapy; results were similar from two studies of SVR after DAA therapy, and estimates from a third study of SVR after DAA therapy were very imprecise.

Evidence

The prior review included 19 cohort studies that consistently found an SVR after interferon-based antiviral therapy associated with decreased risk of all-cause mortality (10 studies, adjusted HR ranged from 0.07 to 0.39), liver-related mortality (9 studies, adjusted HR 0.04 to 0.27), and HCC (11 studies, adjusted hazards ratios 0.12 to 0.71) versus no SVR after 3 to 9 years of followup. Six studies in the prior review evaluated populations of patients with cirrhosis at baseline, and in three other studies the proportion of patients with cirrhosis at baseline ranged from 30 to 70 percent. When results were restricted to 10 studies in which less than 25 percent of

persons had cirrhosis at baseline, results also indicated an association between SVR after antiviral therapy and decreased risk of all-cause mortality (7 studies, adjusted HR 0.12 to 0.71), liver-related mortality (5 studies, adjusted HR 0.04 to 0.22), and HCC (4 studies, adjusted HR 0.12 to 0.36). The largest study (n=16,864), which also had the fewest methodological shortcomings, found SVR after antiviral therapy in a predominantly male, VA population associated with lower risk of all-cause mortality versus no SVR after a median of 3.8 years (adjusted HR 0.70, 95% CI, 0.59 to 0.83, 0.64, 95% CI, 0.46 to 0.88, and 0.51, 95% CI, 0.35 to 0.73, for genotypes 1, 2, and 3, respectively).[69]

Thirty cohort studies (30 publications) reported associations between achieving SVR following antiviral treatment versus no SVR and clinical outcomes (**Appendix B Tables 14** and **15**).[69,168,204-231] Nine of the studies were included in the prior report;[69,204,208-211,213,214,222] nine other studies[70,232-238] from the prior review were excluded because more than 25 percent of the populations had cirrhosis at baseline, and one study[239] from the prior review was excluded because it did not report usable data.

Sample sizes ranged from 131 to 50,886 (total N=116,659), mean age ranged from 42 to 69 years, and the proportion of female participants ranged from 1 to 56 percent with five studies including samples that were less than 10 percent female.[69,205,207,215,221] The proportion of patients with cirrhosis at baseline ranged from 0 percent to 21 percent. Seventeen studies were conducted in Japan,[204,208,210,211,213,217-220,222-224,226-230] seven in the United States,[69,205-207,212,215,221] two in South Korea,[225,231] two in Taiwan,[214,216] one in France,[168] and one in the United Kingdom.[209] All of the U.S.-based studies except for one[212] were conducted in VA populations. Several Japanese studies also appeared to evaluate overlapping or partially overlapping populations (**Table 20; Appendix B Tables 14** and **15**). None of the studies conducted in Asian countries reported race; among studies in the United States and the United Kingdom, white patients comprised 38 to 92 percent of the study population, black patients comprised 8 to 43 percent of the population, and Hispanic patients comprised 0.4 to 14 percent of the population. When genotype was reported, genotype 1 was generally the most common (36% to 89%), with genotype 2 the second most common (6% to 52%). One study reported that 52 percent of patients were genotype 2,[231] and two studies reported large proportions (54% and 55%) of 'non-genotype 1' patients, but did not otherwise specify genotype.[209,214]

Three studies were prospective,[168,218,224] and the others were either retrospective cohort studies or analyzed a prospectively collected dataset retrospectively. Twenty-six studies, including all of the studies carried forward from the prior USPSTF review, evaluated the association between SVR and clinical outcomes following treatment exclusively with interferon-based treatments.[69,204,206-214,216-220,222-231] Three studies focused on DAAs,[168,205,221] one study evaluated interferon-based treatments and DAAs,[221] and one study did not report what type of treatment was administered (likely primarily interferon-based therapies, given study date).[215] Average followup ranged from 1.5 to 10 years in all studies except for one study that described followup of at least a year.[231]

Twenty studies evaluated the outcome HCC,[168,204,207,211,214,215,217-230] thirteen studies all-cause mortality,[69,168,204-214] seven liver-related mortality,[204,207-210,213,214] four cohorts (in three publications) cirrhosis,[206,215,216] and one study liver transplantation.[207] Two studies evaluated

composite outcomes related to mortality and liver outcomes,[206,231] and one study assessed liver-related hospital episodes.[209]

All studies were rated fair quality (**Appendix B Table 16**). Although studies had to perform statistical analyses on potential confounders, 13 studies did not address all four pre-specified factors (age, sex, fibrosis stage, and genotype).[206,208,210,213,216,218,220,222,224,226,227,230,231] No study matched patients who achieved SVR with patients who did not achieve SVR on potential confounders. Studies did not report baseline characteristics according to SVR status or reported large baseline differences between groups. Other methodological shortcomings included failure to report missing data or attrition and unclear masking of outcome assessors.

All-Cause Mortality

SVR after antiviral therapy was associated with decreased risk of all-cause mortality versus no SVR (13 studies, pooled HR 0.40, 95% CI, 0.28 to 0.56, I^2=52%) (**Figure 35**).[69,168,204-214] Results favored SVR in all studies except for one[168] which reported an imprecise estimate (HR 1.36, 95% CI 0.15 to 12.35). In the other studies, the HRs ranged from 0.11 to 0.66. Findings were similar when three studies[206-208] with potentially overlapping populations were excluded from the analysis (pooled HR 0.37, 95% CI, 0.25 to 0.56). The estimate was slightly weaker in ten "fully adjusted" studies (defined as study methods controlled for age, sex, fibrosis stage, and genotype at a minimum; pooled HR 0.42, 95% CI, 0.29 to 0.62) than studies with partial adjustment (pooled HR 0.29, 95% CI, 0.15 to 0.55), but the difference was not statistically significant (p for interaction=0.34) (**Table 21**). Trials with longer duration of followup (more than 5 years) reported a stronger association between SVR after antiviral therapy and reduced risk of all-cause mortality (pooled HR 0.33, 95% CI, 0.24 to 0.46) than those with shorter followup (pooled HR 0.64, 95% CI, 0.56 to 0.74; p for interaction=0.003). In stratified analyses, there was no association between geographic setting (United States or Europe vs. Asia, p for interaction=0.10) or the proportion of patients with cirrhosis at baseline (more than 10% vs. 0 to 10%, p for interaction=0.58) and risk of all-cause mortality following SVR (**Table 21**). Patients received interferon therapy without a DAA in all studies, with the exception of one[205] U.S. study conducted in a VA population and one French study[168] in which patients received DAA therapy. The VA study found an SVR after DAA therapy associated with decreased risk or mortality compared with no SVR (adjusted HR 0.57, 95% CI, 0.33 to 0.99), though duration of followup was relatively short (1.5 years);[205] the estimate from the French study was very imprecise (adjusted HR 1.36, 95% CI, 0.15 to 12.35).[168]

Liver Mortality

SVR after antiviral therapy was associated with decreased risk of liver mortality versus no SVR (4 studies, pooled HR 0.11, 95% CI, 0.04 to 0.27, I^2=0%) (**Figure 36**).[204,208,210,213] Estimates favored SVR in all studies, and HRs ranged from 0.05 to 0.13. All of the studies were conducted in Asia in patients who received interferon therapy without a DAA with duration of followup longer than 5 years. Estimates were very similar when studies were stratified according to whether they were fully or partially adjusted or whether the proportion of patients with cirrhosis at baseline was 0 to 10 percent or over 10 percent, with HR estimates ranging from 0.10 to 0.13 (**Table 21**).

Cirrhosis

SVR after antiviral therapy was associated with decreased risk of cirrhosis versus no SVR (4 cohorts reported in 3 studies, pooled HR 0.36, 95% CI, 0.33 to 0.40; I^2=0%) (**Figure 37**).[206,215,216] Estimates favored SVR in all studies, with HRs ranging from 0.29 to 0.43. Three cohorts were from the United States and one[216] from Asia. All patients received treatment with interferon therapy without a DAA, or the antiviral regimen was not reported[215] but likely to be interferon therapy based on the study date. Estimates were very similar when studies were stratified according to whether they were fully or partially adjusted or the proportion of patients with cirrhosis at baseline (**Table 21**).

Hepatocellular Carcinoma

SVR after antiviral therapy was associated with decreased risk of HCC versus no SVR (20 studies, pooled HR 0.29, 95% CI, 0.23 to 0.38; I^2=19%) (**Figure 38**).[168,204,207,211,214,215,217-230] Estimates favored SVR in all studies, and HRs ranged from 0.06 to 0.41. Findings were similar when four studies with potentially overlapping populations[207,215,219,222] were excluded from the analysis (pooled HR 0.25, 95% CI, 0.18 to 0.34). Pooled estimates were similar for four studies conducted in the United States and Europe (pooled HR 0.32, 95% CI, 0.28 to 0.36)[168,207,215,221] and 16 studies conducted in Asia (pooled HR 0.24, 95% CI, 0.18 to 0.33; p for interaction=0.37). Pooled estimates were also very similar when studies were stratified according to whether they were fully or partially adjusted, the duration of followup (longer or shorter than 5 years), or the proportion of patients with cirrhosis at baseline (greater or less than 10%) (**Table 21**). Patients received or were likely to have received interferon therapy without a DAA in all studies except for one VA study[221] of DAA-only therapy, DAA plus interferon, or interferon-only therapy and one French study[168] of DAA-only therapy. Like the other studies, the VA study found SVR after antiviral therapy associated with decreased risk of HCC versus no SVR (adjusted HR 0.39, 95% CI, 0.35 to 0.43). Estimates were similar when the analysis was stratified according to receipt of a DAA-only regimen (adjusted HR 0.29, 95% CI, 0.23 to 0.37), a DAA plus interferon (adjusted HR 0.48, 95% CI, 0.32 to 0.73), or interferon-only (adjusted HR 0.32, 95% CI, 0.28 to 0.37). The French study was also consistent with an association between SVR after DAA therapy and decreased risk of HCC, though the estimate was imprecise and not statistically significant (adjusted HR 0.22, 95% CI, 0.03 to 1.76).[168]

Contextual Question 1. Based on Population Level Estimates, What Are Recent Trends in the Epidemiology, Prevalence, and Incidence of HCV Infection in the United States, Including in Primary Care Settings, Over the Past 5 to 10 Years?

The incidence of HCV infection increased 3.5-fold from 2010 to 2016, rising each year during that period.[20] The annual increase was 20 percent from 2012 to 2013, 2.6 percent in 2014, 11 percent in 2015, and 22 percent in 2016. An estimated 41,200 new HCV infections occurred in 2016.

The increase in HCV incidence in the United States has primarily been concentrated among young persons and PWID.[20] From 2004 to 2010, the proportion of cases of acute HCV infection reporting injection drug use in each year ranged from 59 percent to 72 percent; since 2011, the proportion has been at least 75 percent in each year (84% in 2014).[240] Acute HCV incidence in persons 18 to 29 years of age increased from 0.4 cases per 100,000 in 2004 to 2.0 cases per 100,000 in 2014 and in persons 30 to 39 years of age from 0.4 cases per 100,000 to 1.7 cases per 100,000 over the same time period.[240] Among persons 40 to 49 years of age, the incidence of acute HCV infection increased slightly from 0.5 to 0.7 cases per 100,000, and in persons 50 to 59 years of age incidence was unchanged at 0.2 cases per 100,000. The increase in acute HCV incidence in young persons was greater in nonurban counties (13% annually) than in urban counties (5% annually).[241] Similar trends in acute HCV incidence have been reported in specific regions in the United States. One study found a 364 percent increase between 2006 and 2012 in HCV infection among persons 12 to 29 years of age living in the Appalachian region of the United States.[21,22] Another study found that new cases of HCV infection among persons 15 to 24 years of age in Massachusetts nearly doubled from 2002 to 2009.[23]

Recent trends towards increased HCV prevalence among reproductive aged (15 to 44 years) females have also been observed.[24,25] Analyses of national laboratory databases (reasons for testing not available) estimate that the number of reproductive aged females with acute and past or present HCV infection doubled from 2006 to 2014,[25] with an increase of 22 percent from 2011 to 2014.[24] Among pregnant females who underwent testing from 2011 to 2014, 0.73 percent had HCV infection.[25] Over the same time period there was a 68 percent increase (from 0.19% to 0.32%) in the proportion of infants born to HCV-infected females.[24] Similar trends have been observed in several states. For example, in Kentucky, the rate of HCV detection among females of childbearing age increased 21 percent from 2011 to 2014 (from 139 to 169 per 100,000), and the proportion of infants born to HCV-infected females increased from 0.71 percent to 1.59 percent.[24] In Wisconsin Medicaid recipients, the prevalence of HCV infection increased from 0.27 percent in 2011 to 0.52 percent in 2015.[242] Nationally, 29,000 females with HCV infection are estimated to give birth each year, resulting in 1,700 infected infants.[25]

Within the United States., there are geographic variations in trends regarding incidence and prevalence of HCV infection. From 2004 to 2014, six states (Kansas, Maine, New Jersey, Wisconsin, Ohio, and Massachusetts) reported increases in HCV incidence of 1,000 percent or higher.[240] A positive correlation was observed between increases in acute HCV infection incidence at the state level and increases in the proportion of treatment admissions reporting opioid injection drug use. Nine states (California, Texas, Florida, New York, Pennsylvania, Ohio, Michigan, Tennessee, and North Carolina) account for over half (51.9%) of persons living with HCV infection; five of these states are in the Appalachian region.[243]

Population level estimates of HCV prevalence based on the 2013 to 2016 NHANES data of noninstitutionalized civilians in the United States and incorporating estimates from four additional populations not included in NHANES (incarcerated persons, unsheltered homeless persons, active duty military personnel, and nursing home residents) indicate approximately 4.1 (range 3.4 to 4.9) million persons positive for HCV antibody and 2.4 (range 2.0 to 2.8) million persons chronically infected.[16] This is lower than an earlier estimate of total HCV prevalence that used 2003 to 2010 NHANES data (4.6 million positive for HCV antibody and 3.5 with

chronic infection),[13] but there were differences in estimation methods, making it difficult to assess time trends. Based on NHANES data alone, the prevalence of chronic HCV infection decreased slightly in 2013 to 2016 to 0.84 percent (95% CI, 0.75% to 0.96%) from 1.0 percent (95% CI, 0.8 to 1.2%) in 2003 to 2010.[18] Factors influencing the observed trends include declines in prevalence due to mortality primarily in the 1945 to 1965 birth cohort and use of more effective antiviral therapies, offset by the higher incidence of acute HCV infection in younger persons primarily related to injection drug use. Data to determine how recent trends in the epidemiology of acute HCV infection among young white persons have impacted the epidemiology of chronic HCV infection are not yet available.

Contextual Question 2. What Are the Effects of Different Risk- or Prevalence-Based Methods for Screening for HCV Infection in Modeling Studies?

The USPSTF previously reviewed two modeling studies that found birth-cohort screening of all persons in the United States born between 1945 and 1965 to be cost-effective compared with risk-based screening.[8,9] Although one analysis assumed rates of progression to cirrhosis and mortality substantially higher than observed in longitudinal cohorts,[8] the other study utilized more conservative estimates consistent with natural history data.[9] Several other cost-effectiveness analyses also found birth cohort screening in the general U.S. population to be cost-effective compared with risk based screening alone.[244-246] All of these analyses were based on treatment with outdated antiviral regimens (i.e., no all DAA regimens), reducing relevance to current practice, and did not compare expanded screening strategies versus currently recommended screening (risk-based plus birth cohort screening).

Five studies published since the prior USPSTF modeled the cost-effectiveness of HCV screening in U.S. settings based on use of DAA regimens (**Table 22**). Two studies evaluated cost-effectiveness of screening in the general adult population,[247,248] one focused on screening persons 15 to 30 years of age,[249] and two evaluated cost-effectiveness of prenatal HCV screening.[250,251] The analyses generally found expanded HCV screening strategies associated with incremental cost-effectiveness ratios of less than $50,000/quality adjusted life year (QALY), though there was variability in the screening strategies compared and cost-effectiveness estimates, due in part to differences in the assumptions used in each model.

One analysis by Barocas et al. of HCV screening in the general adult population utilized the Hepatitis C Cost-Effectiveness (HEP-CE) model, an individual-based, stochastic Monte Carlo simulation model with an embedded Markov state transition matrix.[247] It compared one time "standard of care" birth cohort screening of all U.S. persons born between 1945 and 1965 versus one time screening of all persons at least 18, at least 30, or at least 40 years of age. All screening strategies included targeted screening of high-risk persons. The model assumed that all cases of incident HCV infection were related to injection drug use (12 cases per 100 person-years), with background (not related to screening) testing rates of 33 percent in PWID and 2.6 percent to 27 percent in other persons. Treatment was based on sofosbuvir / velpatasvir at a cost of $23,026 per month ($0 to $38,000 in sensitivity analyses), with an SVR rate in persons without cirrhosis

of 99 percent (50 to 99% in sensitivity analyses) and in persons with cirrhosis of 93 percent (93 to 96% in sensitivity analyses).

The model estimated that compared with birth cohort screening, the 18 and over strategy would identify 256,000 additional cases of HCV infection and lead to 280,000 additional cures and 4,400 fewer cases of HCC over the cohort lifetime, with an incremental cost-effectiveness ratio of $28,193/QALY. More cures than additional cases of HCV infection occurred in the model because of reinfections. Among persons with HCV infection, the 18 and over strategy was associated with an average increase in life expectancy of 0.68 years (0.63 QALY) compared with standard of care screening. The 18 and over strategy dominated (less costly and more effective or lower incremental cost-effectiveness ratio) the 30 and over or 40 and over strategies in the base analysis and remained associated with incremental cost-effectiveness ratios of less than $40,000/QALY in one-way sensitivity analyses that assumed reduced linkage to care, absence of mortality benefit from SVR, higher HCV treatment costs ($130,000), lower HCV prevalence, or greater restrictions on HCV treatment (i.e., restricting treatment to persons with more advanced fibrosis), compared with the base case assumptions. The 18 and over strategy was less cost-effective in scenarios in which antiviral treatment was assumed to be half as effective ($53,500/QALY), when fibrosis progression was assumed to be half as rapid ($65,500/QALY), and when testing was assumed to be twice as inefficient (i.e., need to screen twice as many patients to identify the same number of HCV-infected persons, $44,100/QALY). In some sensitivity analyses (e.g., high treatment costs, less rapid fibrosis progression, lower HCV prevalence, lower rates of linkage to care, greater treatment restrictions), the 30 and over strategy was more cost-effective than the 18 and over strategy. The 30 and over strategy performed best relative to the 18 and over strategy in the decreased fibrosis ($42,800/QALY vs. $65,500/QALY) and inefficient testing ($33,900/QALY vs. $44,100/QALY) scenarios. The 40 and over strategy was dominated in all sensitivity analyses. An analysis of screening in the general adult population by Eckman et al. compared one-time screening of all persons 18 years or older with screening of persons born between 1945 to 1965 (birth cohort screening) or no screening in a 2-stage Markov simulation model.[248] Unlike the cost-effectiveness analysis by Barocas et al.,[247] screening strategies did not include risk-based screening. The Eckman et al. analysis also assumed lower utilities for chronic HCV infection without cirrhosis (0.79, compared with 0.94 in the other analysis), lower costs of DAA therapy ($24,270 vs. $69,078 for a full 12 week course), and higher rates of linkage to care (100% vs. 18% to 29%). It did not model HCV incidence (including reinfection) following successful treatment with antiviral therapy. Despite these differences, the Eckman et al. analysis also found expanded HCV screening to be cost-effective compared with birth cohort screening.

In the Eckman et al. analysis, screening all persons 18 years of age and older was associated with an average gain of 0.0022 QALYs compared with birth cohort screening, and 0.0101 QALYs compared with no screening. The incremental cost-effectiveness of the 18 and older strategy versus birth cohort screening was $11,378/QALY, and the 18 and older strategy dominated no screening. In sensitivity analysis, the incremental cost-effectiveness ratio of the 18 and older strategy versus birth cohort screening exceeded $50,000/QALY when the HCV prevalence in the non-birth cohort was less than 0.07 percent (base case 0.29%) or when the monthly cost of antiviral therapy exceeded $28,000. Cost-effectiveness estimates were also sensitive to the age at time of HCV infection (older age at acquisition associated with lower cost-effectiveness).

An analysis based on the HEP-CE model (used in the study by Barocas et al.) estimated effects of nine one-time screening strategies in U.S. persons, focusing on the population 15 to 30 years of age.[249] The screening strategies differed on three factors: 1) routine (screen all persons) versus expanded targeted testing (validated HCV screening checklist used to identify high-risk persons) versus current practice (risk-based testing in persons perceived to be at high risk, without the checklist), 2) rapid finger stick versus venipuncture, and 3) screening ordered by physician versus by counselor or tester using standing orders. Testing rates were assumed to be lower with physician ordering and receipt of results higher with rapid testing. Current practice screening rates were assumed to be 5 percent in PWID and 3 percent otherwise. The model was based on treatment with sofosbuvir / ledipasvir or sofosbuvir / velpatasvir with the cost of a course of treatment ranging from $71,950 to $137,820 and SVR rates of 93 percent to 99 percent, depending on cirrhosis status and genotype.

The model found that strategies involving rapid testing dominated strategies involving venipuncture testing. Compared with current practice, counselor-initiated, routine rapid testing identified more cases (20% vs. 5%), resulted in a greater number of patients achieving SVR (18% vs. 2%), and resulted in fewer HCV-related deaths (34% to 31%), with an incremental cost-effectiveness ratio of $71,000/QALY. In probabilistic sensitivity analyses, the incremental cost-effectiveness ratio with this strategy remained below $100,000/QALY unless the prevalence of injection drug use was less than 0.59 percent, the HCV prevalence in PWID was less than 16 percent, the reinfection rate was more than 26 cases per 100 person-years, or reflex confirmatory testing was performed following all reactive venipuncture tests. Although physician-ordered, counselor-performed, expanded targeted rapid testing ($40,000/QALY) and counselor-initiated, expanded targeted testing ($44,000/QALY) were more cost-effective than counselor-initiated, routine rapid testing, average gains in QALYs were lower with these strategies than with the counselor-initiated, routine rapid testing strategy (incremental differences 0.0008 to 0.0011 QALYs).

Two studies focused on prenatal HCV screening.[250,251] An analysis by Tasillo et al. evaluated prenatal screening using the HEP-CE model.[251] The analysis compared universal one-time screening during pregnancy versus current practice (14% screened during pregnancy); both strategies lifetime testing that occurred following pregnancy. The model assumed that therapy with a DAA regimen would be offered 6 months postpartum, with a base cost of $39,600 for glecaprevir / pibrentasvir (for persons without cirrhosis) and $68,773 for sofosbuvir / velpatasvir (for persons with cirrhosis). The analysis did not include neonatal outcomes in cost-effectiveness estimates or model the lifetime of neonates born with HCV infection, but estimated the proportion of neonates identified as exposed to HCV infection. HCV prevalence in pregnancy was assumed to be 0.38 percent; assumptions regarding HCV incidence, utilities associated with HCV infection, and rates of linkage to care were similar to the study by Barocas et al. on HCV screening in the general adult population.

The Tasillo et al. analysis found prenatal screening associated with earlier diagnosis and time to cure of HCV infection, with 27 percent of cases achieving SVR within 5 years and 36 percent within 10 years (compared with 16% and 37%, respectively, with current practice). Prenatal screening was associated with a 16 percent reduction in HCV-attributable mortality over the lifetime of the cohort, and average gains of 0.002 QALYs in the entire cohort and 0.0.5 QALYs

in HCV-infected persons compared with current practice, with an incremental cost-effectiveness ratio of $41,000/QALY. The incremental cost-effectiveness ratio was $83,000/QALY when prevalence was half (0.18%) of the base case assumption (0.18%) and less than or equal to $50,000/QALY when HCV testing rates were higher (50%) in PWID, when treatment initiation rates were lower (64.5%), and when neonatal testing costs were considered. The incremental cost-effectiveness ratio was $168,000/QALY when the rate of fibrosis progression was reduced by half (average time to cirrhosis, 70 years) and $137,000/QALY when HCV infection before cirrhosis had no associated cost or decrease in quality of life. Prenatal screening increased the identification of neonates exposed to HCV at birth from 44 percent to 92 percent.

An analysis by Chaillon et al. also evaluated prenatal screening versus risk-based screening, using a closed cohort Markov model.[250] The analysis assumed antiviral treatment after pregnancy with a DAA regimen (base cost $25,000 for a full treatment course) and a background testing and linkage rate of 5 percent per year; it did not model costs or effects on the neonate. Compared with the analysis by Tasillo et al., base case assumptions in Chaillon et al. included higher HCV prevalence (0.73% vs. 0.38%), lower antiviral treatment costs ($25,000 vs. $39,600 in persons with cirrhosis and $68,773 in persons without cirrhosis), and lower utilities for F1 to F3 fibrosis in HCV-infected persons (0.83-0.86 vs. 0.94). In addition, the model appeared to assume that all persons diagnosed with HCV infection would be linked to care and receive treatment.

In the Chaillon et al. analysis, prenatal screening was estimated to result in the detection and treatment of 7,000 additional females, with an average gain of 0.019 QALY and an incremental cost-effectiveness ratio of $2,826/QALY, compared with risk-based screening. Incremental cost-effectiveness ratios remained below $5,000/QALY in sensitivity analyses based on alternative treatment eligibility scenarios, lower HCV prevalence rates (0.03% to 0.04%), lower fibrosis progression rates (21% cirrhosis at 35 years), lower SVR (85%), higher baseline rates of diagnosis and linkage to care (40%), higher loss to followup (50% per year), and higher background testing (20% per year). Screening was estimated to result in detection and treatment of an estimated 300 children born to mothers infected by HCV.

Identification and treatment of HCV infection prior to pregnancy could result in the additional benefit of reducing the risk of mother-to-child transmission following successful treatment.[252] However, we identified no study on the cost-effectiveness of screening strategies aimed at women prior to pregnancy.

Contextual Question 3. What Is the Effect of Antiviral Treatments on Behavioral Outcomes?

No trial of DAA therapy included in this report reported behavioral outcomes. Two open-label studies of HCV-infected PWID found receipt of interferon-based therapy associated with reductions in some self-reported drug and substance use behaviors.[253,254] A non-randomized study (n=124) found interferon-based therapy associated with reduced likelihood of injection drug use equipment sharing (adjusted OR 0.85, 95% CI, 0.74 to 0.99) compared with no treatment at median followup of 1.8 years after adjusting for age, sex, housing status, education level, employment status, and social functioning level, but no effect on injection drug use in the

last 30 days (adjusted OR 1.06, 95% CI, 0.93 to 1.21).[254] A before-after analysis of persons with current or past injection drug use (n=93) found decreased likelihood of injection drug use (unadjusted OR 0.89, 95% CI, 0.83 to 0.95) and alcohol use (unadjusted OR 0.56, 95% CI, 0.40 to 0.77) 24 weeks after completing interferon-based therapy compared with prior to therapy, but no difference in likelihood of injection drug use equipment sharing (unadjusted OR 0.87, 95% CI, 0.70 to 1.07).[253]

Chapter 4. Discussion

Summary of Review Findings

This report updates prior reviews on HCV screening and treatments in adults, and interventions to prevent mother-to-child transmission.[2,3,90] It expands upon the prior reviews by adding evidence on adolescents and addressing the benefits and harms of currently recommended all-oral, DAA regimens. As in the prior USPSTF review,[2] we found no direct evidence on the clinical benefits of screening for HCV versus not screening or on the yield of repeat screening. We also found no new evidence to better evaluate harms of screening; the prior review included studies suggesting potential negative psychological and social effects of screening, but the quality of the evidence was poor. Other evidence reviewed for this update is summarized in **Table 23**.

Since the prior USPSTF recommendation, there has been a major shift in antiviral therapy to use of all-oral DAA regimens without interferon.[74] At the time of the prior review, standard antiviral therapy for HCV infection for genotype 1 infection was transitioning to boceprevir or telaprevir with pegylated interferon and ribavirin (SVR rates 68% to 72%); for genotypes 2 and 3 standard therapy was pegylated interferon plus ribavirin (SVR rates 68% to 78%).[90] New evidence indicates that SVR rates with currently recommended all-oral DAA regimens are substantially higher than with prior therapies. Pooled SVR rates ranged from 95.5 percent to 98.9 percent across genotypes; for the three most common genotypes in the United States (1, 2, and 3), pooled SVR rates ranged from 95.5 percent to 98.9 percent. Evidence was most robust for genotype 1 infection (32 trials), the most frequent genotype in the United States (approximately 75%), followed by genotype 4 infection (10 trials); data were limited for other genotypes (4 to 6 trials each). SVR estimates generally exceeded 95 percent when analyses were stratified according to DAA regimen, study quality, inclusion of patients with cirrhosis at baseline (with the exception of genotype 3 infection, which was associated with a lower SVR rate in one trial that included patients with cirrhosis),[165] geographic setting, prior experience with older antiviral regimens, and use of ribavirin. Few trials directly compared a current DAA regimen versus placebo or an older antiviral regimen, but those available supported high DAA regimen effectiveness. In one trial of patients with mixed genotype infection, the SVR rate was 99 percent with sofosbuvir / velpatasvir and 0 percent with placebo,[139] and in two trials of patients with mixed genotype infection the SVR rate was 98 percent to 99 percent with ombitasvir / paritaprevir / ritonavir / dasabuvir (with or without ribavirin) and 66 percent to 80 percent with telaprevir / pegylated interferon / ribavirin.[137] Evidence on DAA regimens in adolescents is limited but indicates SVR rates similar to those observed in adults (97% to 100%).[171,173,175,176,201-203] Some trials of DAA regimens in adolescents evaluated regimens that are not FDA-approved for use in adolescents but that are recommended in adults.

Evidence also indicates that current DAA regimens are associated with fewer harms than older interferon-containing therapies; the duration of treatment is also shorter at 12 weeks (8 weeks for glecaprevir / pibrentasvir or ledipasvir / sofosbuvir in persons with genotype 1 infection who are non-black, HIV-uninfected, and whose HCV RNA level is under 6 million IU/mL)[74] compared with prior interferon-containing regimens (24 to 48 weeks). The prior review found therapies

with interferon associated with rates of serious adverse events of 8.5 percent to 16 percent and withdrawal due to adverse events of 12 percent to 15 percent.[90] Interferon-based therapies were also associated with high rates of fatigue (51% to 64%), depression (19% to 22%), influenza-like symptoms (19% to 40%), and other adverse events. Boceprevir and telaprevir containing regimens were associated with increased risk of hematological adverse events compared with pegylated interferon plus ribavirin. Four new randomized trials found DAA regimens associated with slightly increased risk of any adverse event (ARD 8%, for a number needed to harm [NNH] of approximately 13) and nausea (ARD 4%, for a NNH of approximately 25) versus placebo, with no difference in risk of serious adverse events, withdrawal due to adverse events, or specific adverse events (e.g., diarrhea, fatigue, headache, or anemia).[139,151,164,187] Two trials found DAA regimens associated with decreased risk of any adverse event versus triple therapy with telaprevir (ARD −34%, for a number needed to avoid harm [NNAH] of approximately 3), serious adverse events (ARD −8%, NNAH approximately 12), withdrawal due to adverse events (ARD −9%, NNAH approximately 11), and specific adverse events (NNAH for fatigue, nausea, anemia, and rash ranged from approximately 3 to 6).[137] Across DAA trials, the pooled rate of any adverse event was relatively high at 73.3 percent, but rates of serious adverse events and withdrawal due to adverse events were low (1.9% and 0.4%, respectively) relative to older interferon-containing regimens. Pooled rates of specific adverse events ranged from 2.4 percent for anemia to 18.4 percent for headache, also lower than observed with interferon-containing therapies. Ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin was generally associated with increased rates of adverse events compared with the same regimen without ribavirin, with a marked increase in risk of anemia (pooled rates 8.3% vs. 0.8%). All DAA trials in this report excluded patients with HBV coinfection, and no cases of HBV reactivation were reported. One cohort study of VA patients with HCV infection treated with a DAA regimen (n=34,632) that did not meet inclusion criteria reported an HBV reactivation rate of 30.0 per 1,000 person-years.[255] Eleven percent of patients in this cohort were surface antigen of HBV-positive at baseline. The HBV reactivation rate with DAA therapy was similar to the reactivation rate with pegylated interferon plus ribavirin (25.4 per 1,000 person-years, p=0.8).

Direct evidence on the effects of antiviral therapy on clinical outcomes is limited. Although several randomized trials found interferon therapy associated with decreased risk of HCC compared with no antiviral therapy, they did not meet inclusion criteria for this report because they focused on patients with cirrhosis at baseline or used a non-standard (i.e. indefinite duration of treatment) regimen.[127-134] Trials of DAA therapies were not designed to assess effects on mortality or other long-term clinical outcomes. Ten DAA trials reported improvements in some quality of life and functional outcomes following treatment compared with prior to treatment, but differences were small, studies were open-label, and there was no non-DAA comparison group, making it difficult to interpret more subjective outcomes like these.[135-137] Large cohort studies conducted on a large national VA database in which approximately 20 percent of patients had cirrhosis at baseline found DAA therapy associated with reduced risk of cardiovascular events, HCC, and mortality versus no therapy after adjusting for potential confounders, with effects similar to or stronger than interferon-based therapy.[169,170] A French study found no association between DAA therapy versus no antiviral therapy in risk of all-cause mortality or HCC in the subgroup of patients without cirrhosis at baseline, but there were few events, and estimates were imprecise.[168] In this study, when patients with cirrhosis (approximately 33% of the population) were included in the analysis, DAA therapy was associated with decreased risk of all-cause

mortality (adjusted HR 0.48, 95% CI, 0.33 to 0.70), liver-related mortality (adjusted HR 0.39, 95% CI, 0.21 to 0.71), and HCC (adjusted HR 0.66, 95% CI, 0.46 to 0.93).

No study evaluated effects of DAA therapies on behaviors associated with HCV acquisition. There was limited evidence that interferon-based therapies are not associated with increased injection drug use behaviors, and may be associated with reductions in some behaviors.[253,254] No study evaluated effects of DAA therapy on HCV transmission.[256] Such studies would be difficult to design and carry out, but assessments of potential transmission effects could be informed by modeling studies.[257,258] One study that modeled effects on transmission risk estimated that among PWID, decreasing HCV prevalence in half within 15 years would require increasing the proportion of patients treated 2- to 15-fold, depending on the baseline HCV prevalence.[259]

In lieu of limited direct evidence on the effects of antiviral therapy on clinical outcomes, cohort studies of SVR after antiviral therapy versus no SVR may help to understand potential clinical effects. Our findings of a consistent association between SVR after antiviral therapy and improved clinical outcomes were consistent with the prior review.[90] Moreover, our findings may be more applicable to screening because we excluded previously utilized studies in which a high proportion of patients had cirrhosis at baseline. SVR after antiviral therapy (primarily interferon-based therapy) was associated with decreased risk of all-cause mortality (pooled adjusted HR 0.40, 95% CI, 0.28 to 0.56), liver mortality (pooled adjusted HR 0.11, 95% CI, 0.04 to 0.27), cirrhosis (pooled adjusted HR 0.36, 95% CI, 0.33 to 0.40), and HCC (pooled adjusted HR 0.29, 95% CI, 0.23 to 0.38). Evidence was most robust for all-cause-mortality and HCC (reported in 13 and 20 studies, respectively), and less robust for liver mortality and cirrhosis (reported in 4 studies each). Findings were consistent when studies were stratified according to how well they adjusted for potential confounders, duration of followup, and geographic setting (United States or Europe vs. Asia), though effects on mortality were stronger in studies with longer followup. Although most studies on the association between SVR after antiviral therapy and clinical outcomes evaluated interferon-based therapy, results were similar in two studies of SVR after DAA therapy,[205,221] with one study showing similar effects of DAA and interferon regimens on HCC risk. Estimates from a third study of SVR after DAA therapy were very imprecise. This is consistent with a recent systematic review that found no evidence for differential hepatocellular occurrence or recurrence risk following SVR from DAA or interferon-based therapy, though most studies in that review evaluated patients with cirrhosis or a history of HCC.[260]

Our findings regarding the benefits and harms of current DAA regimens were consistent with a recent systematic review that also reported high SVR rates (greater than 95%) in patients with HCV genotype 1 infection without cirrhosis, high SVR rates but limited evidence for other HCV genotypes, low rates of serious adverse events and treatment discontinuation rates, and higher adverse event rates with ribavirin.[73] Our results are also consistent with a systematic review that found insufficient evidence from clinical trials to determine effects of DAA regimens on HCV-related mortality and morbidity;[261] unlike that review, we also evaluated the indirect chain of evidence linking DAA therapy with clinical outcomes. Our review is consistent with prior reviews that found a consistent association between an SVR after antiviral therapy and reduced risk of mortality and HCC.[72,260,262-264] Our review differs from prior reviews in focusing on populations more likely to be identified by screening, by excluding studies in which a high proportion of patients had cirrhosis, and by restricting inclusion to currently recommended DAA

regimens. One review on effects of antiviral therapy on extrahepatic manifestations of HCV infection found SVR after antiviral therapy associated with increased likelihood of cryoglobulinemia vasculitis remission and malignant B-cell lymphoproliferative disease response, outcomes not considered in our review because they relate to symptomatic and uncommon conditions.[262] It also found attaining SVR associated with reduced risk of insulin resistance and a protective effect on diabetes incidence; we restricted analysis of the association between SVR versus no SVR to mortality and long-term hepatic outcomes and did not identify any studies on the effects of DAA therapy versus no therapy on diabetes.

New evidence on interventions to reduce the risk of mother-to-infant transmission of HCV was limited and did not change the conclusion from the prior review that no intervention has been clearly demonstrated to reduce risk.[3] All studies were observational; in addition, we excluded most of the studies in the prior review because they were poor quality and did not conduct multivariate analyses. Studies on the effects of cesarean versus vaginal delivery (5 studies, 1 new)[107] and breastfeeding versus no breastfeeding (3 studies, 1 new)[107] continued to show inconsistent effects on risk of mother-to-child transmission. Although use of internal fetal monitoring and prolonged rupture of membranes were both associated with markedly increased risk of mother-to-child transmission, each was evaluated in only 1 study.[104]

Evidence to determine the yield of alternative screening strategies remains limited. Although one new study found that risk-based screening would identify slightly more HCV cases and require testing of fewer patients than birth cohort screening, this was based on a retrospective analysis and the assumption of perfect implementation of risk-based testing, which has not been attained in clinical practice.[99] Modeling studies suggest that expanded screening strategies may be cost-effective in the general population as well as in pregnant females. Two studies found expanded screening of all persons 18 years and older associated with incremental cost-effectiveness ratios under $30,000/QALY compared with birth cohort screening, despite different assumptions regarding utilities associated with chronic HCV virus infection states, costs of DAA therapy, and rates of linkage to care. In most sensitivity analyses, incremental cost-effectiveness ratios remained less than $50,000/QALY.[247,248] Another study found routine HCV screening of persons 15 to 30 years of age associated with incremental cost-effectiveness ratios less than $50,000/QALY under certain scenarios.[249] Two modeling studies found routine prenatal screening associated with incremental cost-effectiveness ratios of $50,000/QALY versus current practice, though there was more variability in estimates ($2,826/QALY and $41,000/QALY).[250,251] Both studies assumed that antiviral treatment was withheld until after childbirth and did not attempt to model effects on neonatal costs or outcomes. A factor complicating interpretation of the cost-effectiveness analyses are marked differences in base-case assumptions regarding costs of DAA therapy (range approximately $25,000 [similar to the current cost of a full course of therapy with a generic DAA regimen][265] to over $100,000), though expanded HCV screening appeared cost-effective even in analyses that assumed high DAA therapy costs. Costs of DAA therapy are expected to decline further,[266-268] which would further enhance the cost-effectiveness of expanded screening strategies.

Limitations

Our report has potential limitations. Because there were few trials of current DAA regimens versus placebo or older antiviral therapies, we utilized non-randomized trials of DAA therapies, including trials without a non-DAA therapy comparison group. Pooled SVR rates derived from such trials were considered highly informative because SVR rates are very objective, and SVR rates without treatment are close to zero. However, more subjective outcomes such as quality of life, function, and adverse events are more difficult to interpret in the absence of randomization or a comparison group. SVR is a well-established marker for sustained viral clearance (HCV infection cure) but is an intermediate (non-clinical) outcome. There was little evidence directly evaluating effects of antiviral therapies versus no antiviral therapy on clinical outcomes, due in part to the long duration required to evaluate effects on mortality and other long-term sequelae of HCV infection and ethical considerations related to withholding recommended treatment in randomized trials. Therefore, we included cohort studies on the association between SVR versus antiviral therapy versus no SVR and effects on clinical outcomes. Because such studies are susceptible to residual confounding if other factors associated with achieving an SVR also predict better outcomes, we restricted inclusion to studies that reported multivariate risk estimates and performed stratified analyses based on the degree to which studies adjusted for potential confounders.[269] No trial of DAA therapy was conducted in screen-detected patients, and few trials reported presence or severity of baseline symptoms. In order to evaluate effectiveness of DAA therapies in populations likely to be identified by screening, we focused on studies in which patients with cirrhosis, who are more likely to be symptomatic, were excluded, or in which the proportion with cirrhosis was small. Although we included trials of patients previously treated with interferon-based therapies or boceprevir or telaprevir with pegylated interferon and ribavirin, who would not be identified by screening, such patients may be asymptomatic or mildly asymptomatic, and SVR rates were similar in treatment-naïve and -experienced patients. Trials of DAA therapy could overestimate SVR rates compared with typical clinical practice. However, observational studies, including a study of difficult to treat persons in a safety net health system, report SVR rates of 90 percent, or only modestly lower than observed in the trials.[270,271] We did not assess effects of counseling or immunizations on clinical outcomes in persons diagnosed with HCV infection, though prior reviews found no evidence to estimate effects,[91] and no study evaluated effects of DAA treatments on HCV transmission. We excluded studies of patients coinfected with HBV or HIV and with advanced renal disease since management of these conditions was determined to be outside the scope of screening. We excluded non-English language articles, which could result in language bias, though we identified no non-English language studies that would have met inclusion criteria. We did not search for studies published only as abstracts. We did not formally assess for publication bias using graphical or statistical methods to detect small sample effects due to the small number of randomized trials meeting inclusion criteria; the usefulness of such methods when assessing event rates (rather than risk estimates) is uncertain.

Emerging Issues/Next Steps

All DAA regimens currently recommended were approved by the FDA since the prior review. DAA regimens continue to evolve and treatment guidelines are regularly updated.[74] Several

newer DAA regimens are pangenotypic, meaning that they are effective across all genotypes,[75] and most currently recommended DAA regimens do not require use of ribavirin. Although three pangenotypic regimens (glecaprevir / pibrentasvir, sofosbuvir / velpatasvir, and sofosbuvir / velpatasvir / voxilaprevir) have been approved by the FDA, one regimen (sofosbuvir / velpatasvir / voxilaprevir) was developed for use in previously treated persons with resistant virus.[272] Advantages of pangenotypic regimens include elimination of the need for genotyping and simplified selection of therapy. Costs of current DAA regimens has been a barrier to treatment but competition and negotiated pricing have reduced prices.[266,267] Another issue is the shift towards management of HCV infection in primary care settings rather than in specialty settings, potentially facilitating access to treatment. Initial studies indicate that treatment in primary care settings is associated with similar outcomes as treatment in specialty settings, though more data are needed.[78,79]

Relevance for Priority Populations, Particularly Racial/Ethnic Minorities and Older Adults

In the 2003 to 2010 NHANES survey, persons 40 to 49 years of age (OR 6.0, 95% CI, 3.2 to 11.1) and those 50 to 59 years of age (OR 9.5, 95% CI, 5.3 to 16.8) were more likely to have HCV infection than persons 20 to 39 years of age.[18] Subgroup analyses from trials of currently recommended DAA therapies indicate similar effectiveness in older (over 55 or over 65 years of age) versus younger adults (**Table 13**). Older patients who acquired HCV infection as a young adult are more likely to have more advanced disease due to longer duration of infection, and the HCV-related mortality rate is highest in persons 55 to 74 years of age. Therefore, antiviral therapy may have greater impact on clinical outcomes in older patients.[273]

Subgroup analyses from trials of current DAA therapies also indicate similar effectiveness among different racial and ethnic groups. An analysis of the national VA ERCHIVES database (n=21,095) that did not meet inclusion criteria found that SVR rates with DAA regimens were similar in black patients (90%), Hispanic patients (86%), white patients (90%), and Asian/Pacific Islander/American Indian/Alaska Native patients (91%).[271] However, black patients and Hispanic patients were less likely to achieve SVR than white patients after adjusting for baseline characteristics (OR 0.77, $p<0.001$ and OR 0.76, $p<0.007$, respectively).

Most trials of DAA therapies have excluded persons with current drug use or those receiving treatment for opioid use disorder. However, five trials included in this report of persons with current or recent use of methadone or buprenorphine for opioid use disorder reported SVR rates that ranged from 90 to 100 percent.[149,150,167,192] This is consistent with a systematic review that included observational studies, which found a pooled SVR rate of DAA treatment of almost 90 percent among patients with current or recent injection drug use.[274] A systematic review of 57 studies found a 5-year HCV reinfection rate of 10.67 percent in PWID following SVR, compared with 0.95 percent in non-PWID, indicating the need for followup after treatment in this population.[275] Current guidelines do not consider ongoing injection drug use a contraindication to DAA therapy.[74]

Although DAA therapy appears similarly effective in adolescents and adults, only three antiviral therapies (ledipasvir / sofosbuvir, sofosbuvir / ribavirin, and glecaprevir / pibrentasvir) are FDA-approved for use in adolescents. Though DAA treatment options in this population are currently limited, a number of trials of DAA regimens in adolescents are ongoing.[276]

Antiviral therapy is currently not recommended in pregnancy. However, prenatal screening could identify HCV-infected women who could benefit from treatment following pregnancy, facilitate testing of infants, and potentially prevent HCV transmission during subsequent pregnancies. Identification of HCV-infected women prior to pregnancy in order to initiate antiviral therapy could be a strategy to reduce risk of mother-to-child transmission, but has not yet been studied.

Future Research

Research is needed to better understand the association between use of current DAA therapy and clinical outcomes. Long-term randomized trials of treatment versus no treatment would be ethically challenging and difficult to carry out. Rather, large cohort studies that measure important confounders could be highly informative for addressing this question. Trials and cohort studies that measure effects on quality of life, function, and extrahepatic effects of HCV infection (e.g., renal function, cardiovascular effects, or diabetes) would also be helpful for understanding effects of DAA regimens on shorter-term clinical outcomes. Studies on the association between SVR after DAA therapy and clinical outcomes would help to verify the link between SVR and clinical outcomes with current therapies. Additional studies would be helpful for confirming the effectiveness of DAA regimens in adolescents and to identify additional regimens that could be used in this population.[276] Studies are also needed to understand risks of HCV reinfection following DAA therapy and optimal treatment strategies. Research is also needed to identify labor management practices (e.g., prolonged rupture of membranes or use of internal fetal monitoring) and other strategies (e.g., identification and treatment of HCV infection prior to pregnancy) on risk of mother-to-child transmission. Well-designed prospective studies are needed to understand the effects of different HCV screening strategies, including repeat screening, on diagnostic yield.

Conclusions

The USPSTF previously determined that HCV screening is highly accurate. Currently recommended all-oral DAA regimens are associated with very high SVR rates (95.5% to 98.9% across genotypes) and few harms relative to older antiviral therapies. An SVR after antiviral therapy is associated with improved clinical outcomes compared with no SVR after adjusting for potential confounders. Direct evidence on the benefits of HCV screening remains unavailable; direct evidence on the effects of antiviral therapy on clinical outcomes remains limited but indicates improved long-term outcomes.

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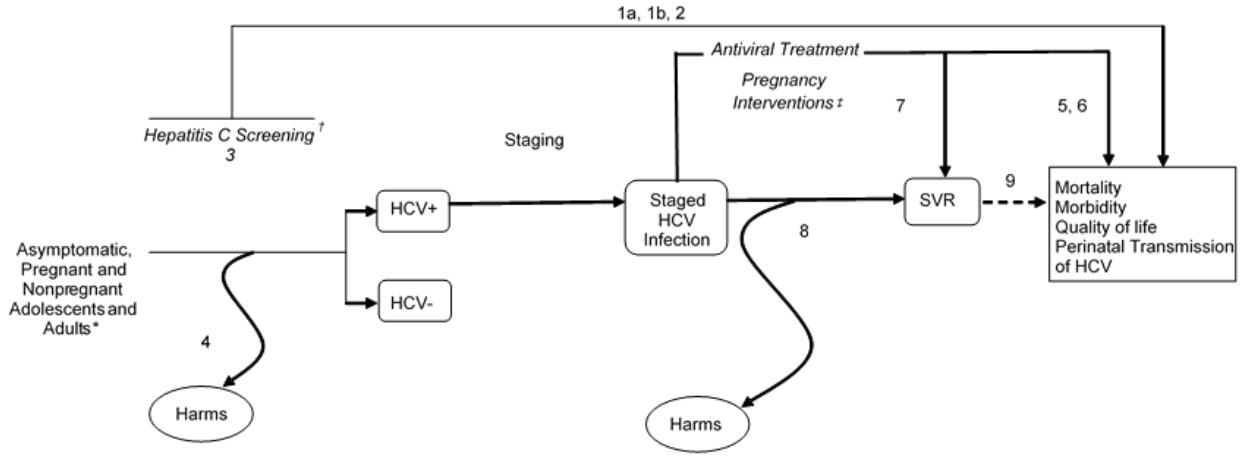
Figure 1. Analytic Framework and Key Questions



1a. Does screening for hepatitis C virus (HCV) infection in pregnant and nonpregnant adolescents and adults without known abnormal liver enzyme levels reduce HCV-related mortality and morbidity or affect quality of life?

1b. Does prenatal screening for HCV infection reduce risk of vertical transmission of HCV infection?

2. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?

3. What is the yield (number of new diagnoses per tests performed) of one-time versus repeat screening or alternative screening strategies for HCV infection, and how does the screening yield vary in different risk groups?

4. What are the harms of screening for HCV infection (e.g., anxiety and labeling)?

5. What are the effects of interventions during labor and delivery or the perinatal period on risk of vertical transmission of HCV infection?

6. What is the effectiveness of currently recommended antiviral treatments in improving health outcomes in patients with HCV infection?

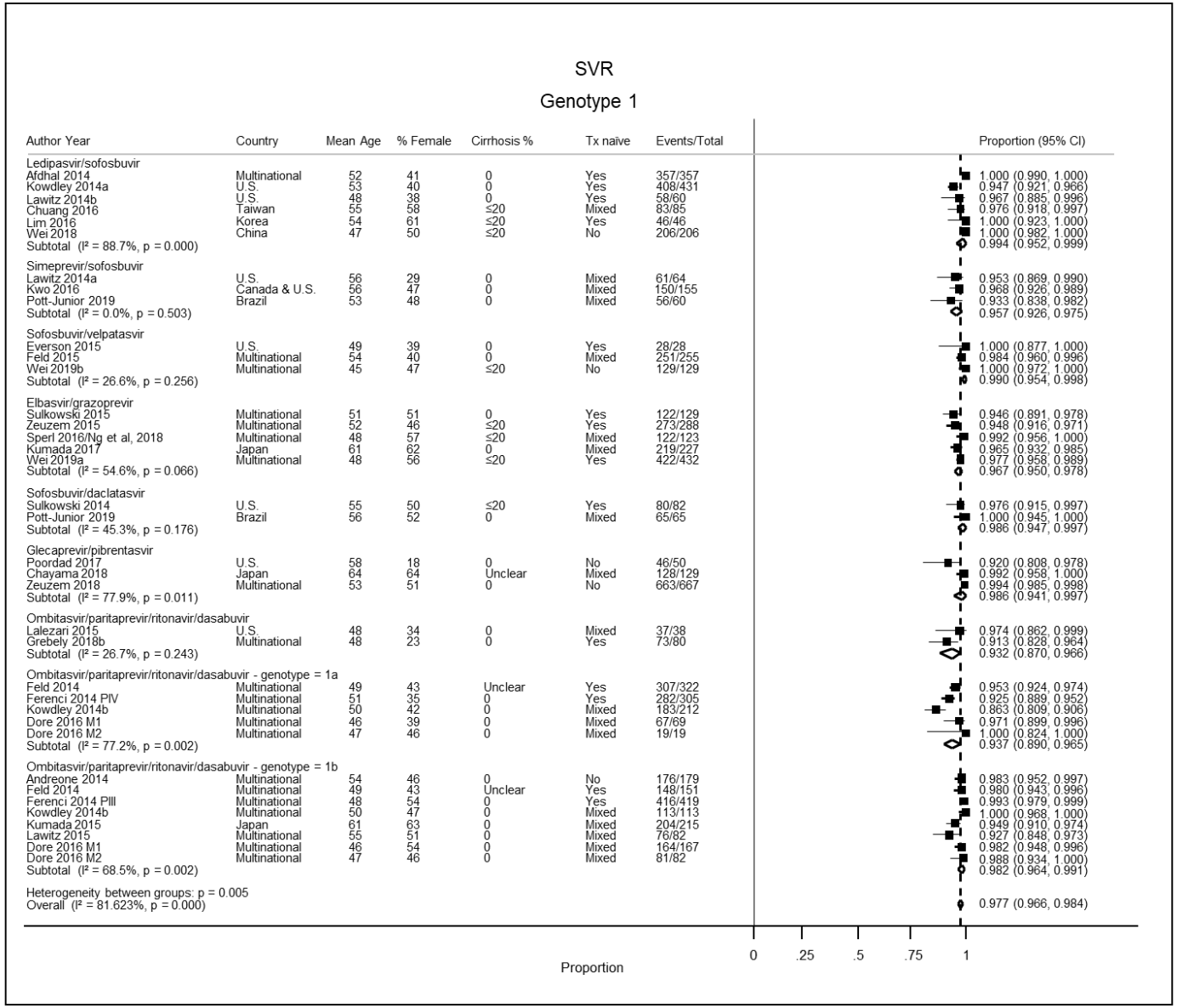
7. What is the effectiveness of currently recommended antiviral treatments in achieving a sustained virologic response in patients with HCV infection?

8. What are the harms of currently recommended antiviral treatments?

9. What is the association between experiencing sustained virologic response following antiviral treatment and reduction in risk of HCV-related adverse health outcomes?

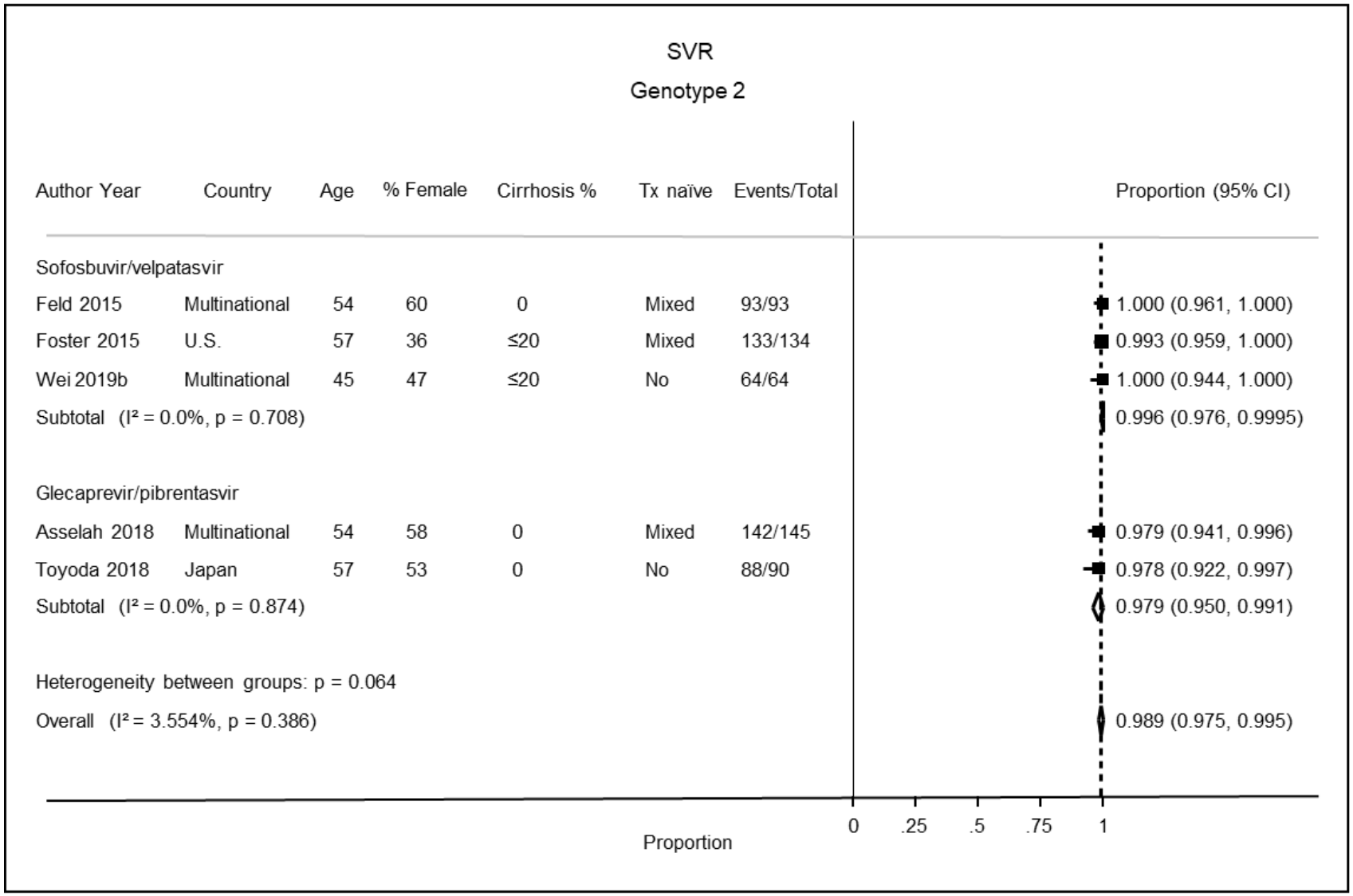
Note: The numbers in the figure correspond to the numbers of the Key Questions.
* Includes persons without abnormal laboratory values. Adolescents are defined as those ages 12 to 17 years. Excludes persons living with HIV, transplant recipients, and patients with renal failure.
† Defined as HCV antibody testing with confirmatory HCV RNA testing as indicated.
‡ Includes interventions that may affect vertical transmission of HCV, such as cesarean delivery, amniocentesis, fetal monitoring, management of ruptured membranes, breastfeeding, and antiviral treatment.
Abbreviations: HCV = hepatitis C virus; SVR = sustained virologic response.

Figure 2. Key Question 7: Direct Acting Antiviral Regimens and Pooled Sustained Virologic Response Rates, Genotype 1



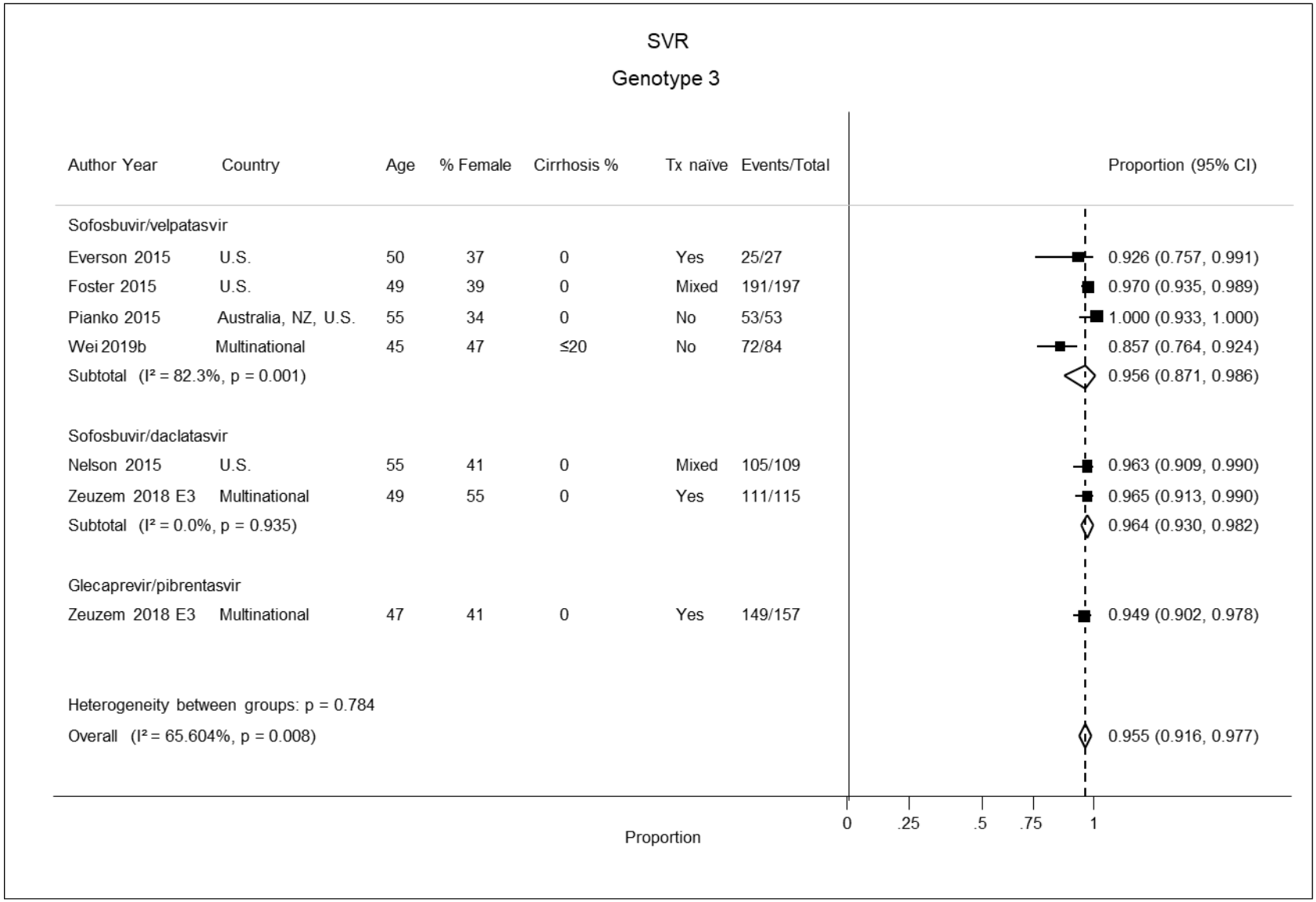
Abbreviations: CI = confidence interval; NR = not reported; SVR = sustained virologic response; Tx = treatment; U.S. = United States.

Figure 3. Key Question 7: Direct Acting Antiviral Regimens and Pooled Sustained Virologic Response Rates, Genotype 2



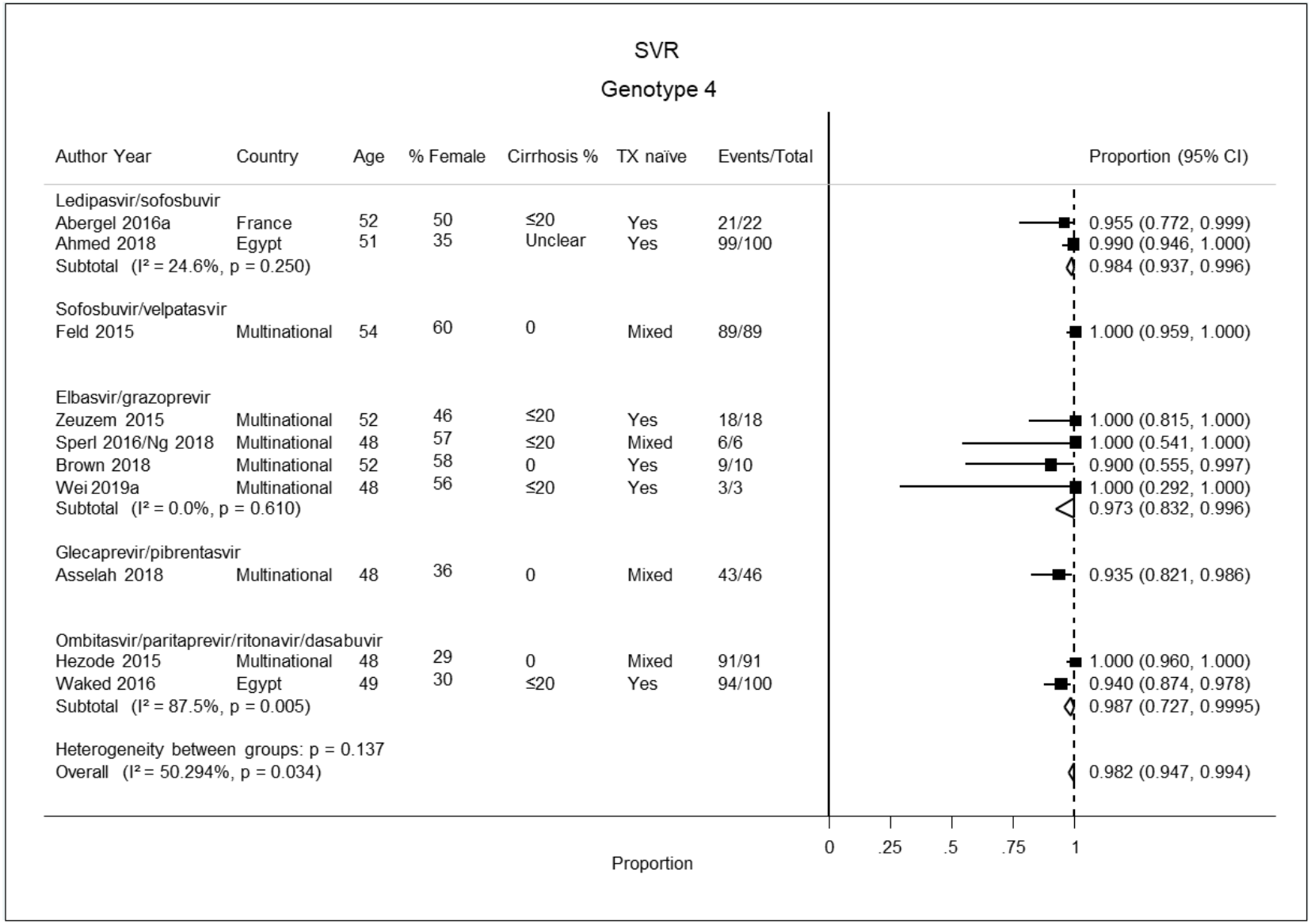
Abbreviations: CI = confidence interval; SVR = sustained virologic response; Tx = treatment; U.S. = United States.

Figure 4. Key Question 7: Direct Acting Antiviral Regimens and Pooled Sustained Virologic Response Rates, Genotype 3



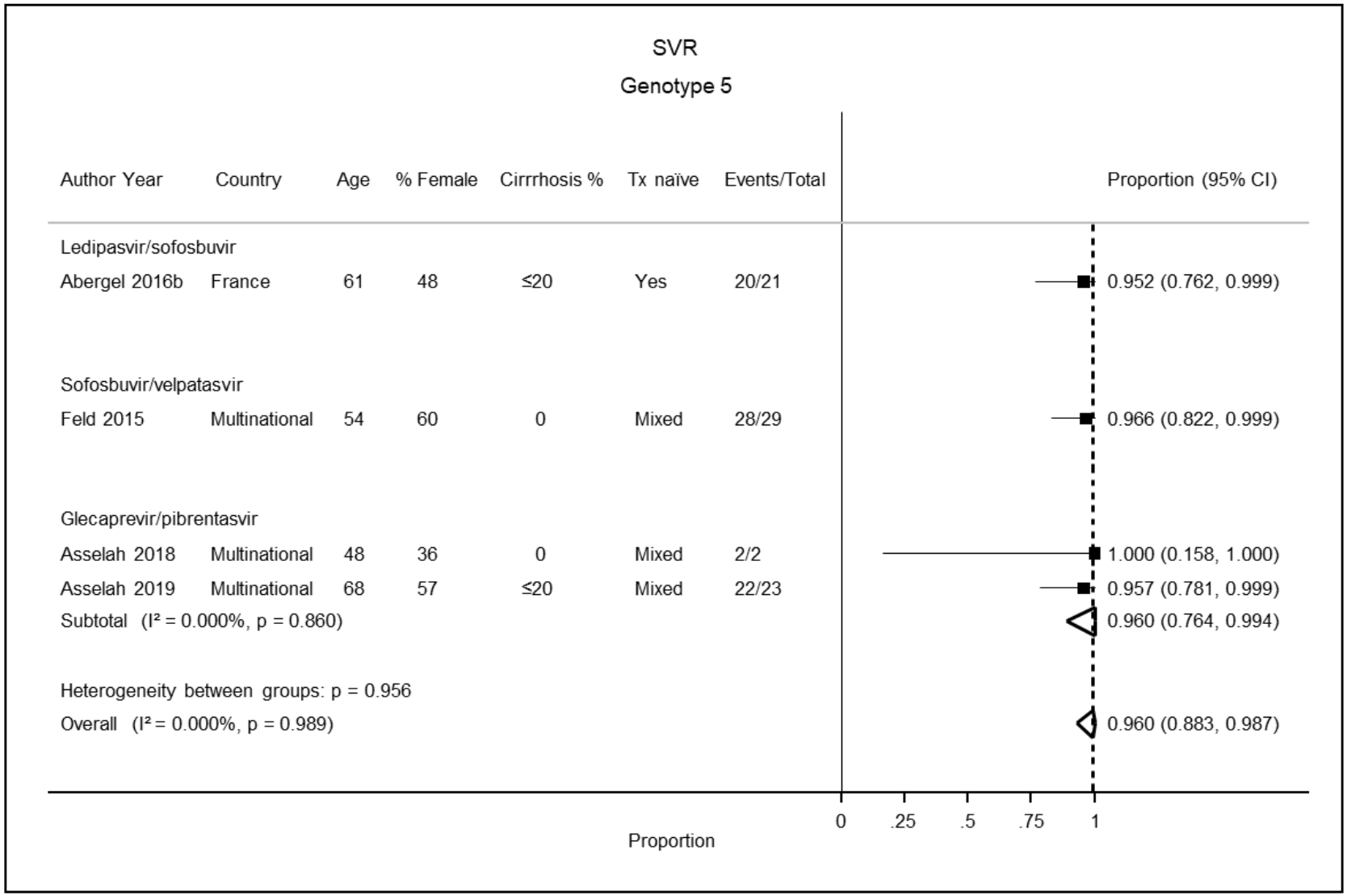
Abbreviations: CI = confidence interval; NZ = New Zealand; SVR = sustained virologic response; Tx = treatment; U.S. = United States.

Figure 5. Key Question 7: Direct Acting Antiviral Regimens and Sustained Virologic Response Rates, Genotype 4



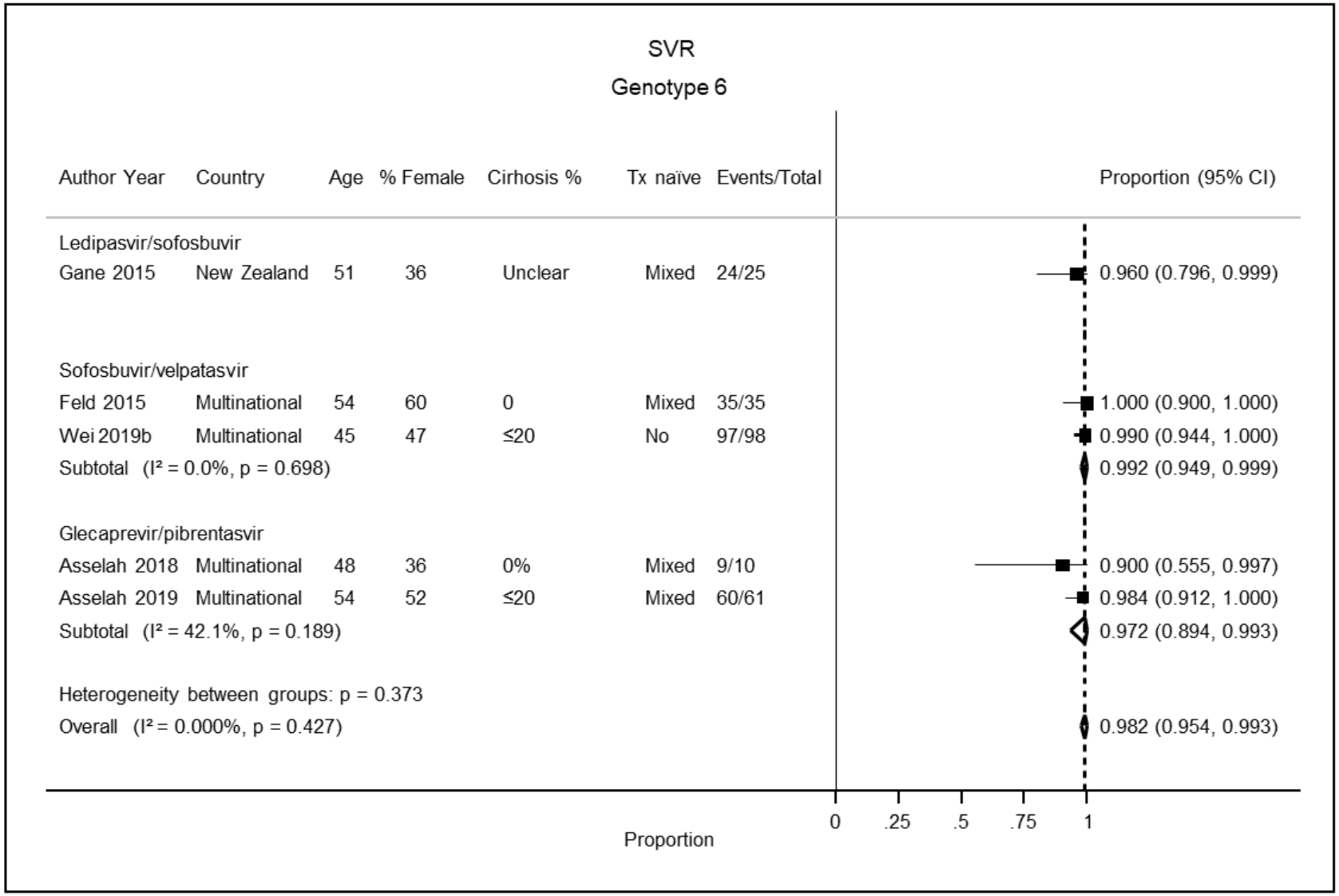
Abbreviations: CI = confidence interval; SVR = sustained virologic response; Tx = treatment.

Figure 6. Key Question 7: Direct Acting Antiviral Regimens and Sustained Virologic Response Rates, Genotype 5



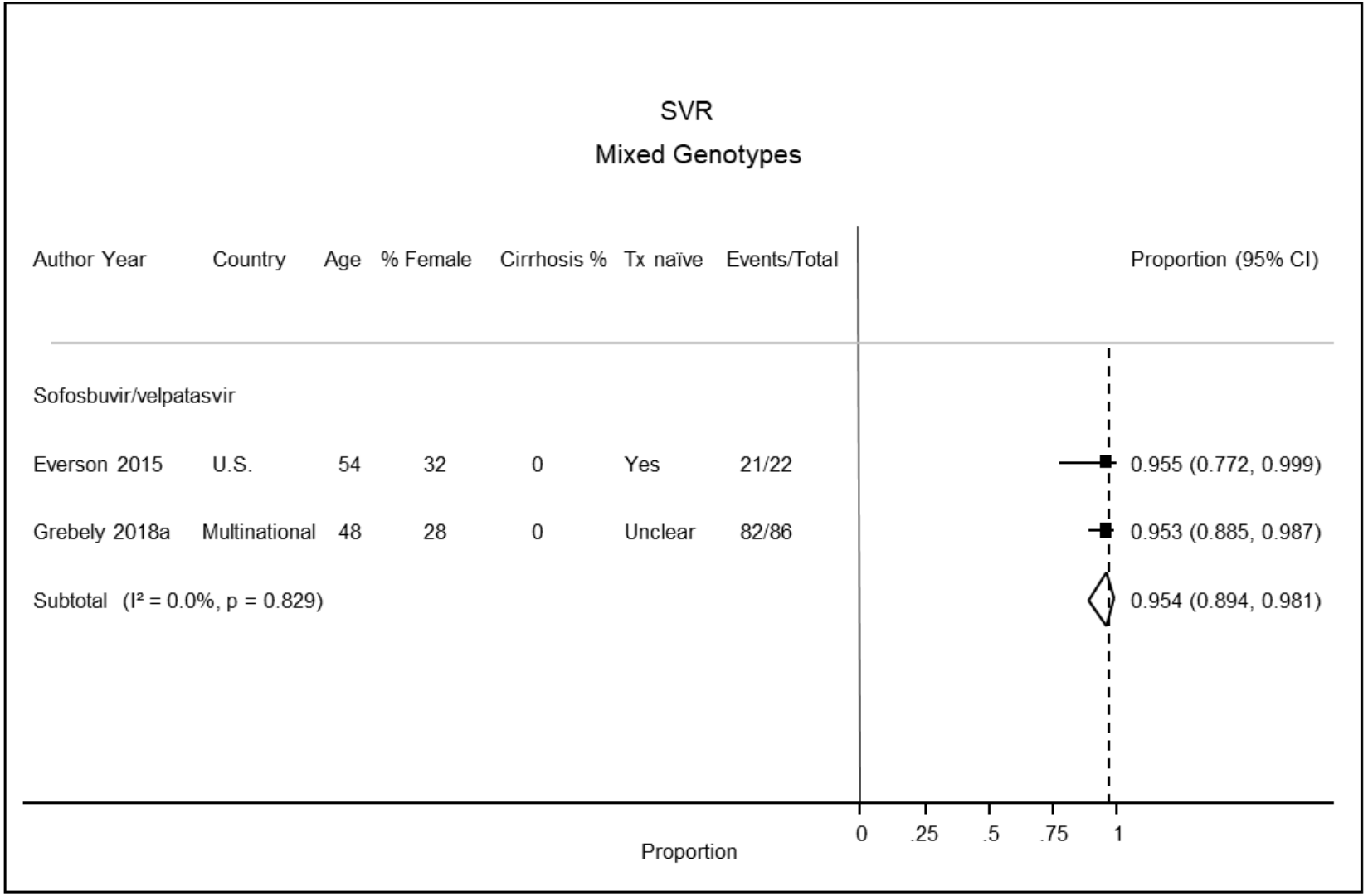
Abbreviations: CI = confidence interval; SVR = sustained virologic response; Tx = treatment.

Figure 7. Key Question 7: Direct Acting Antiviral Regimens and Sustained Virologic Response Rates, Genotype 6



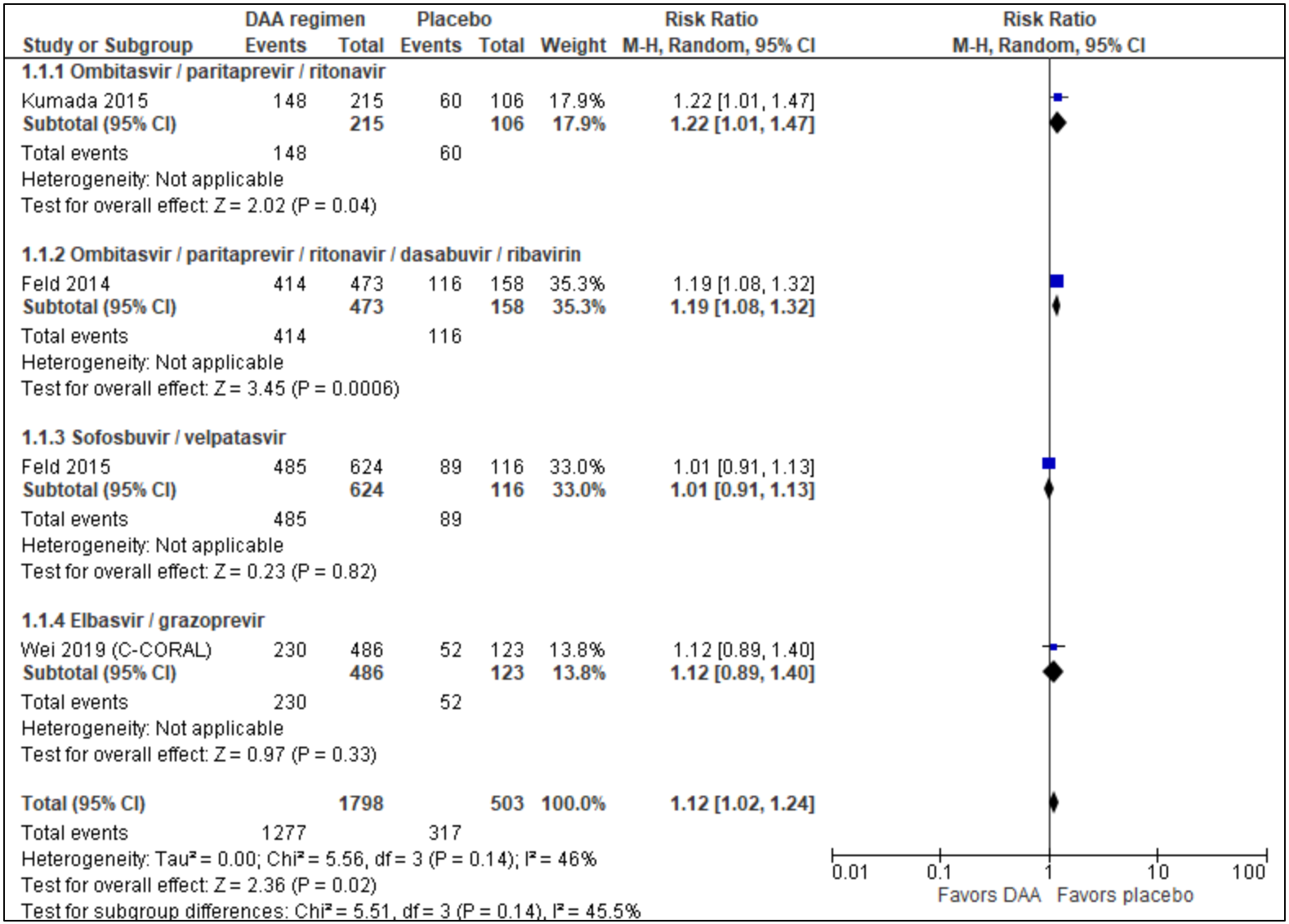
Abbreviations: CI = confidence interval; SVR = sustained virologic response; Tx = treatment.

Figure 8. Key Question 7: Direct Acting Antiviral Regimens and Sustained Virologic Response Rates, Mixed Genotypes



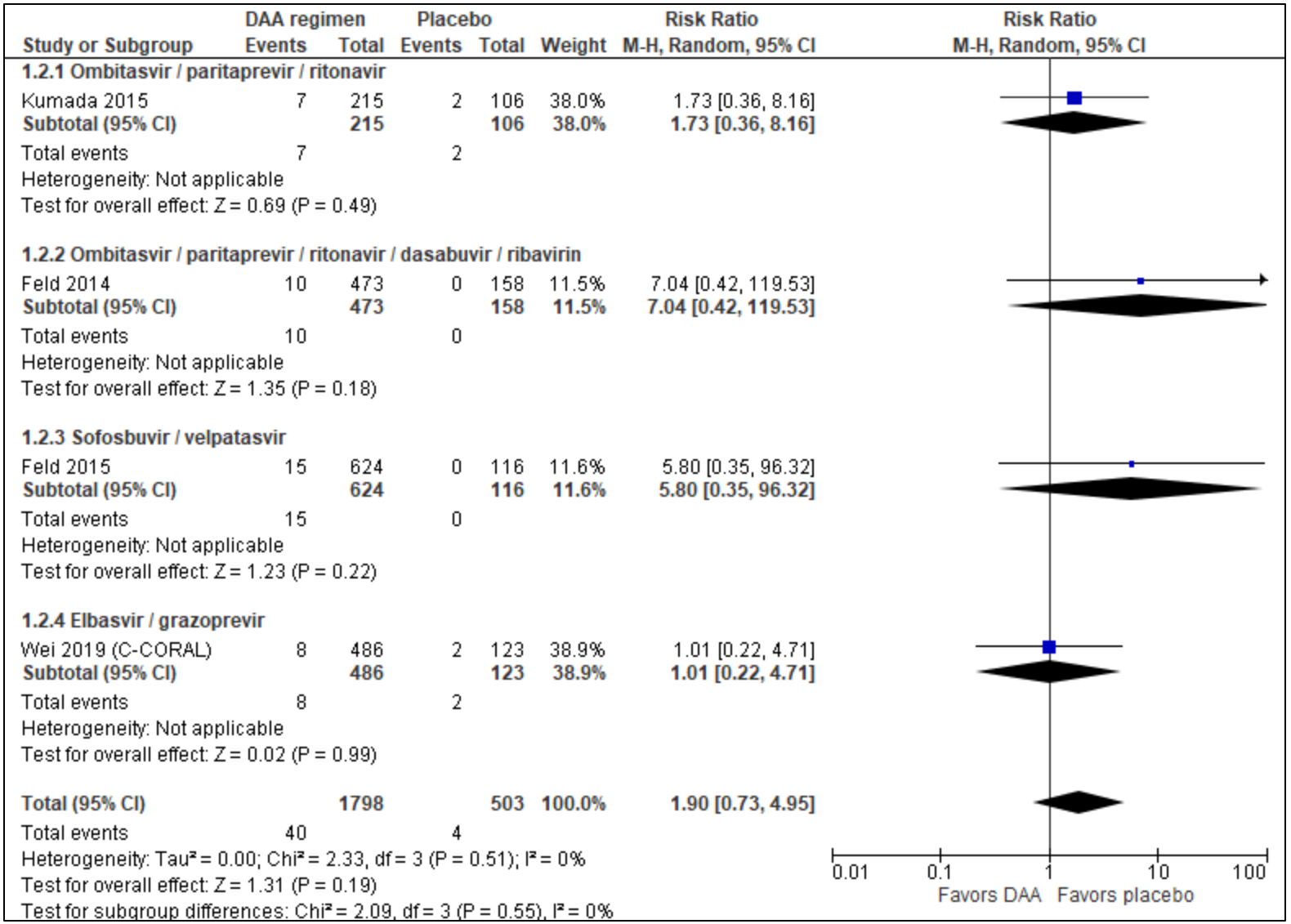
Abbreviations: CI = confidence interval; SVR = sustained virologic response; Tx = treatment; U.S. = United States.

Figure 9. Key Question 8: Direct Acting Antiviral Regimens vs. Placebo, Any Adverse Events



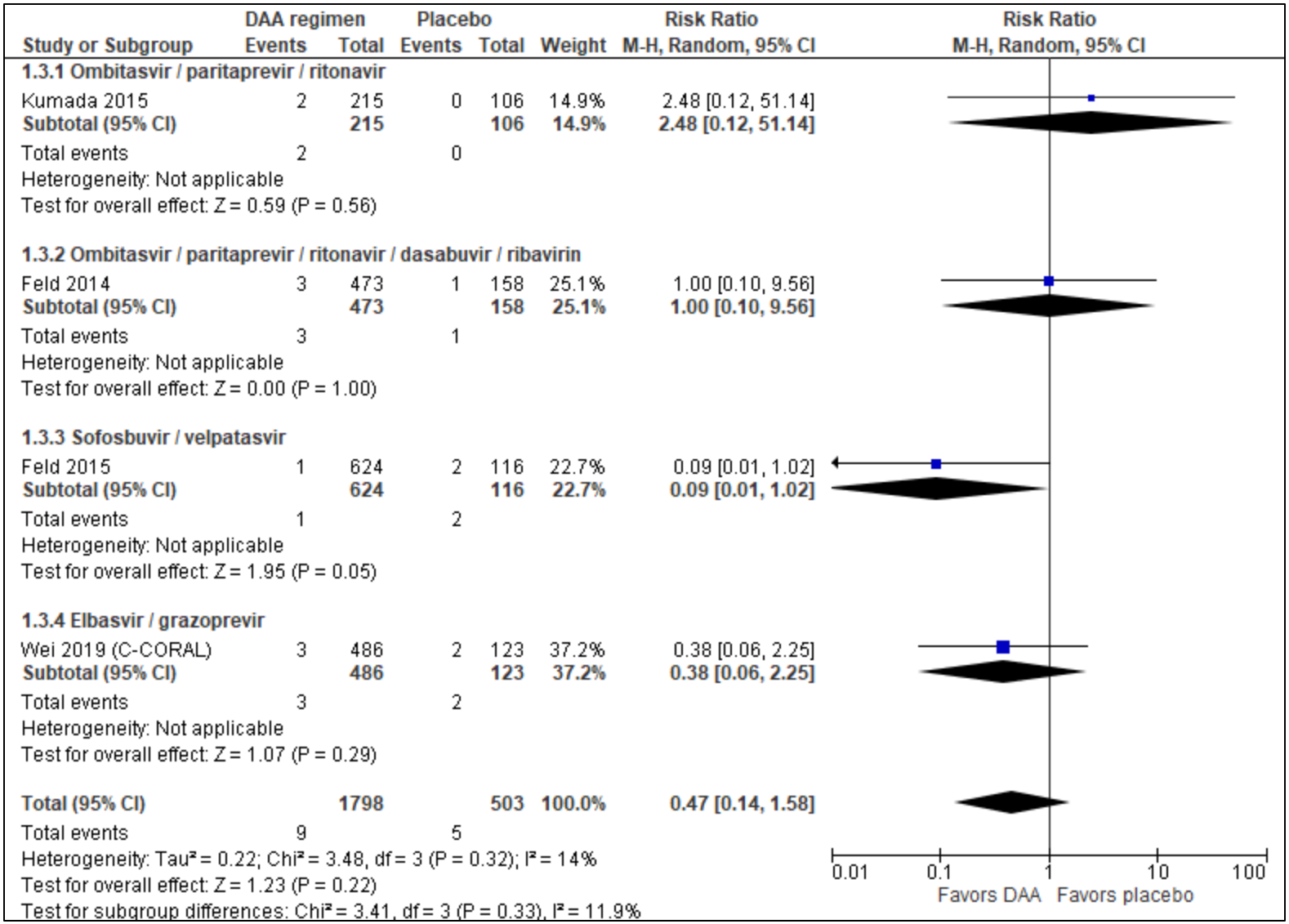
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

Figure 10. Key Question 8: Direct Acting Antiviral Regimens vs. Placebo, Serious Adverse Events



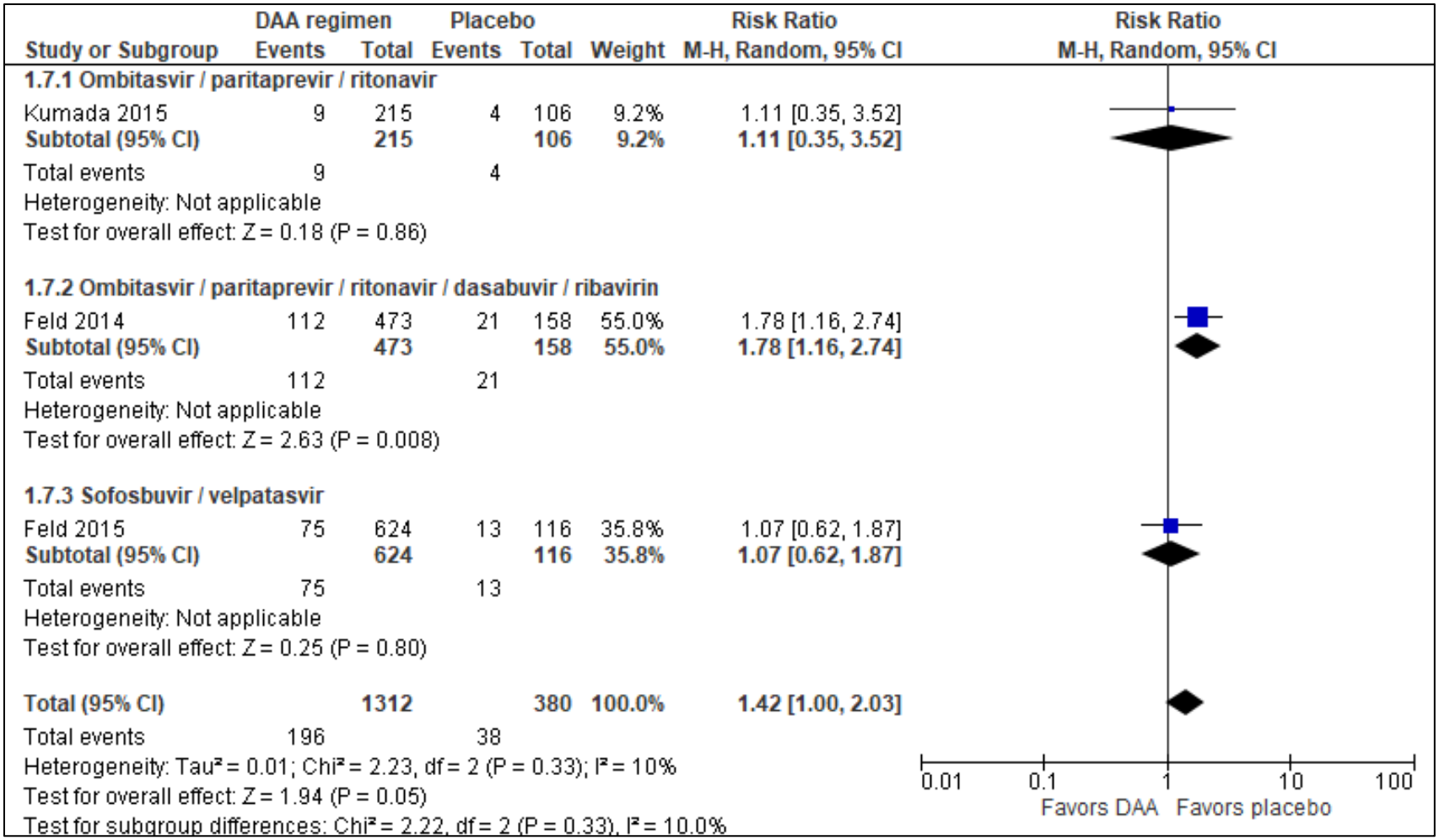
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

Figure 11. Key Question 8: Direct Acting Antivirals Regimens vs. Placebo, Withdrawals Due to Adverse Events



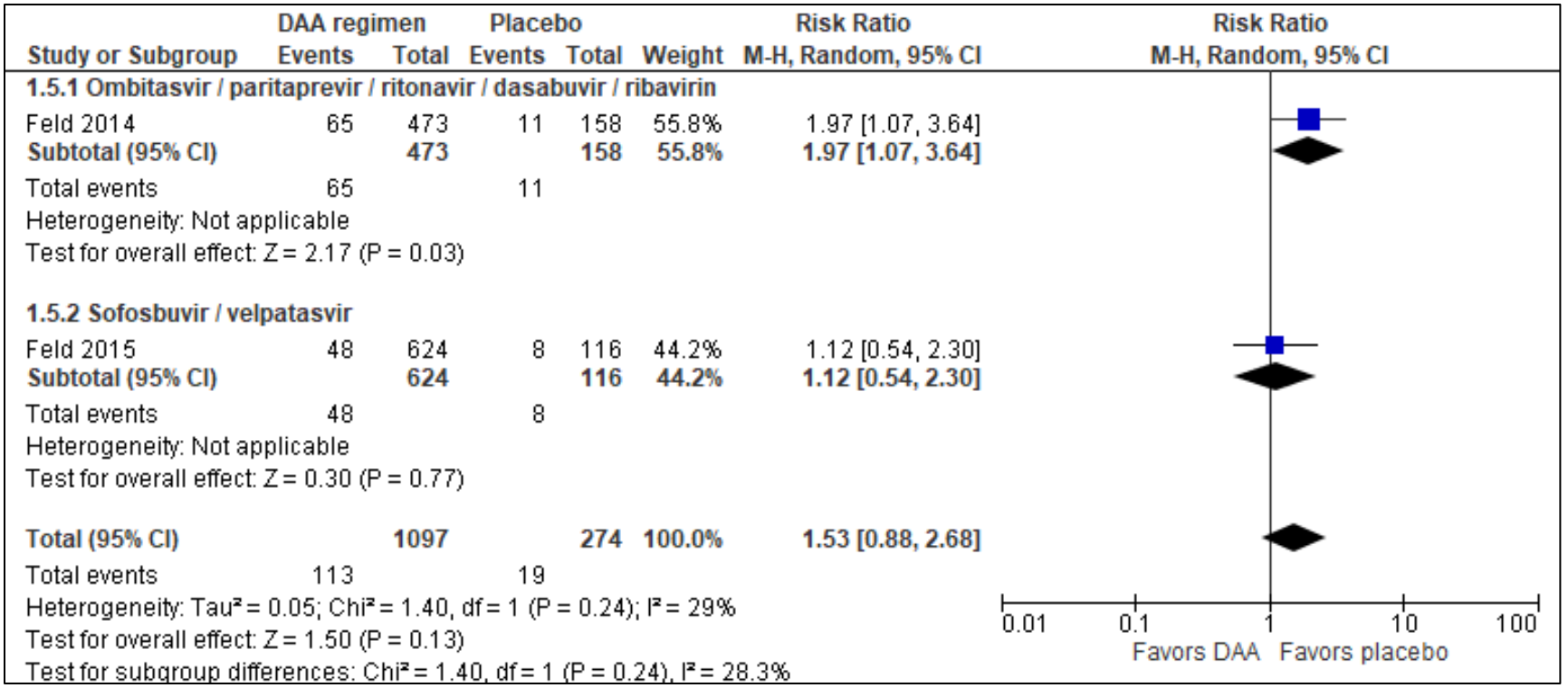
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

Figure 12. Key Question 8: Direct Acting Antivirals Regimens vs. Placebo, Nausea



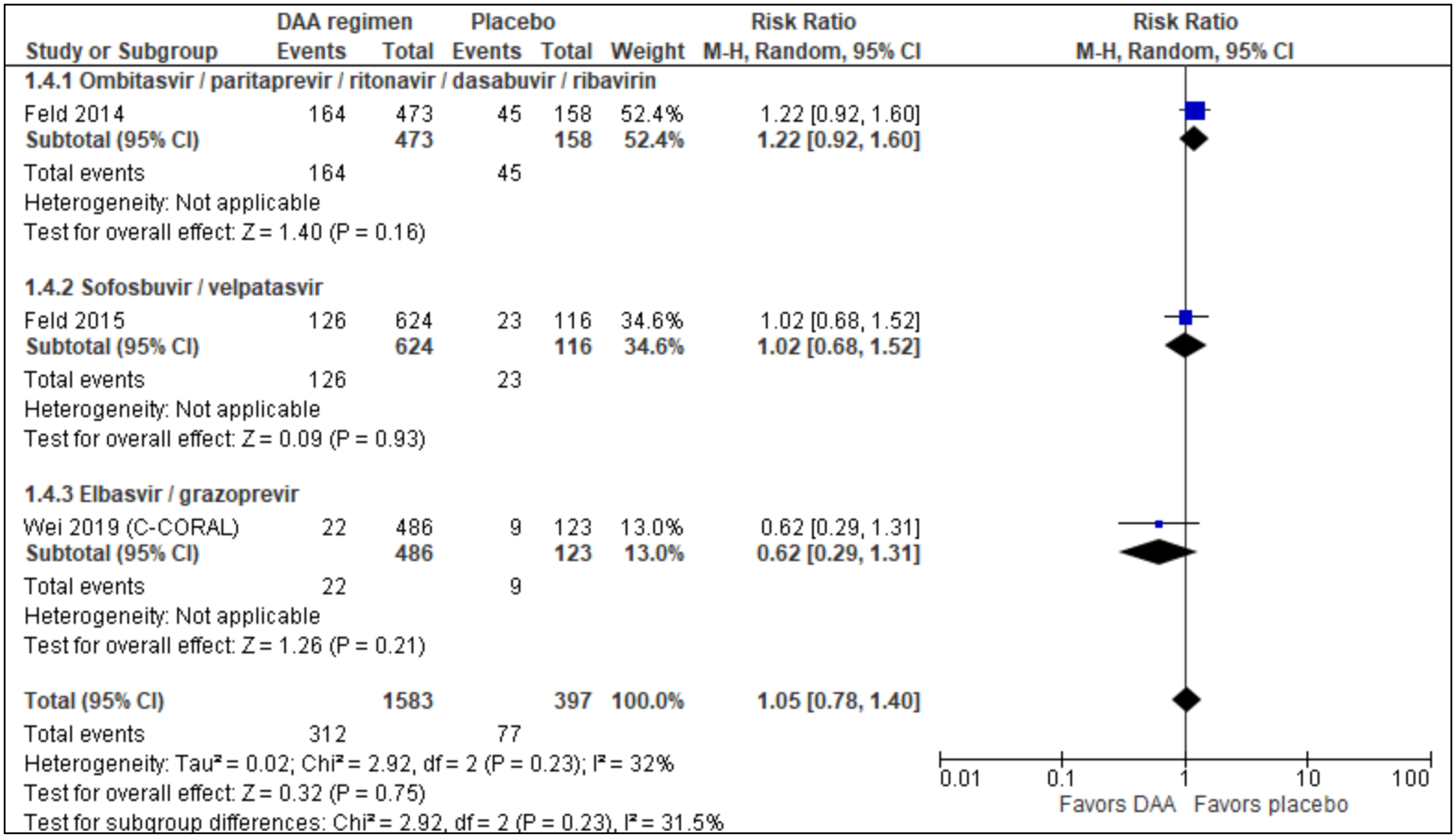
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test.

Figure 13. Key Question 8: Direct Acting Antiviral Regimens vs. Placebo, Diarrhea



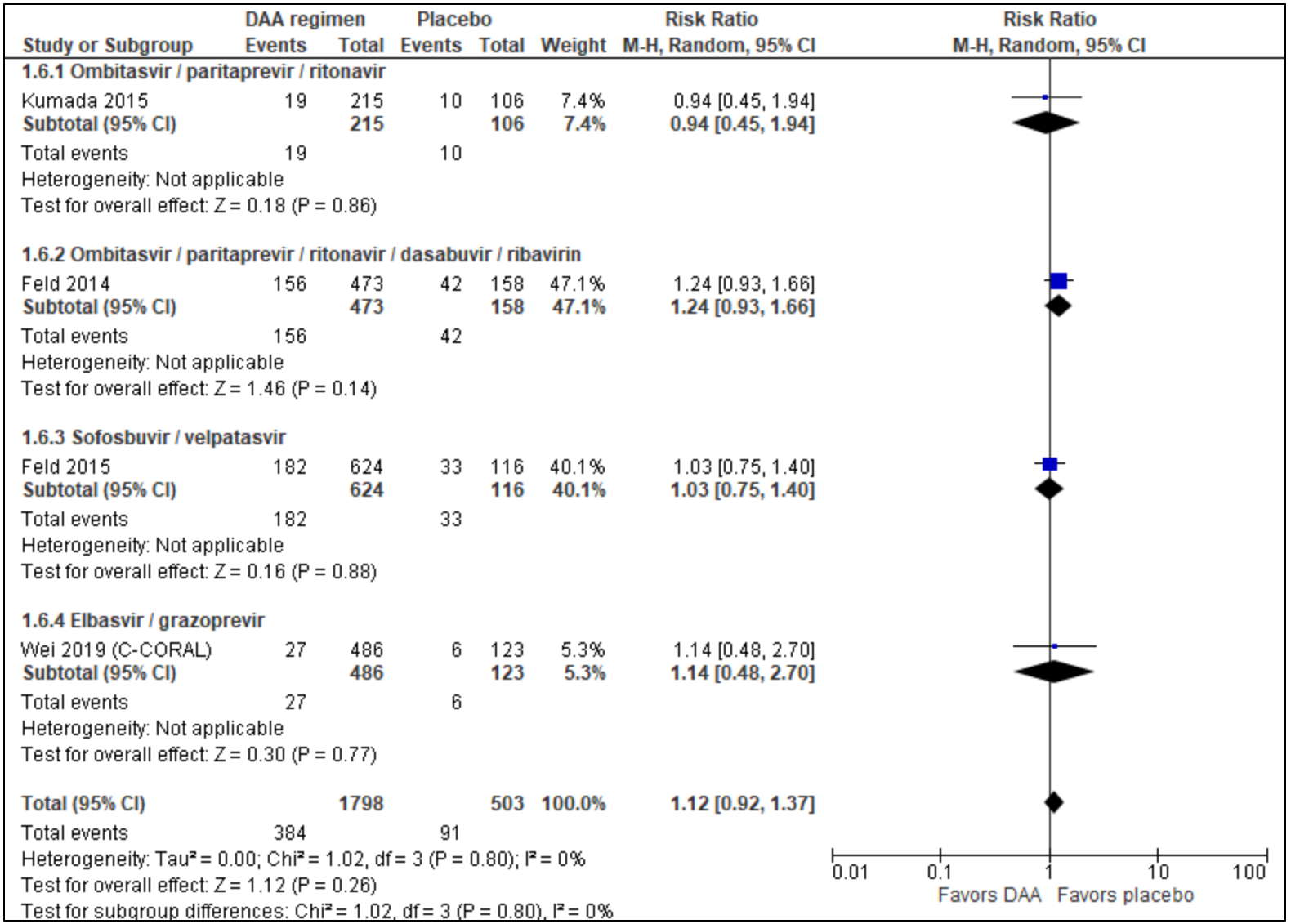
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test.

Figure 14. Key Question 8: Direct Acting Antiviral Regimens vs. Placebo, Fatigue



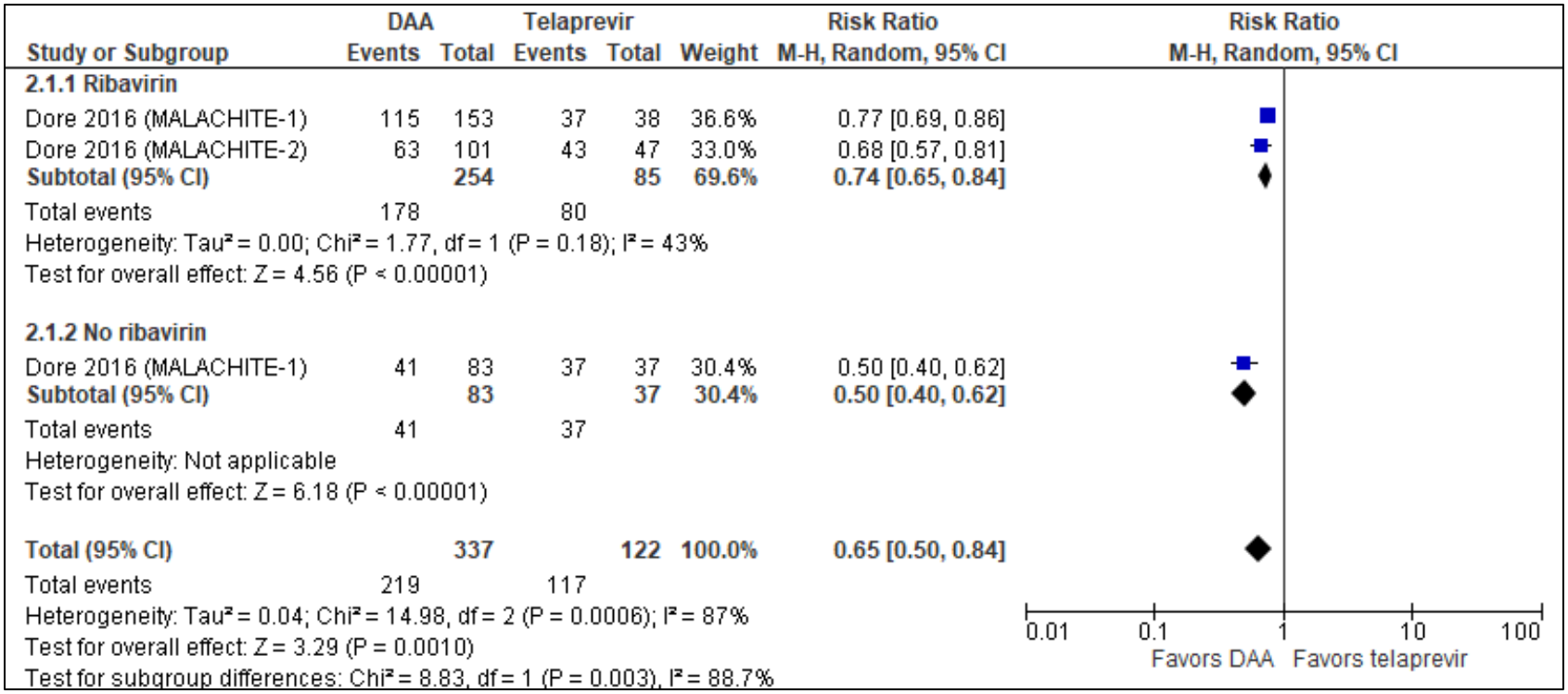
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

Figure 15. Key Question 8: Direct Acting Antiviral Regimens vs. Placebo, Headache



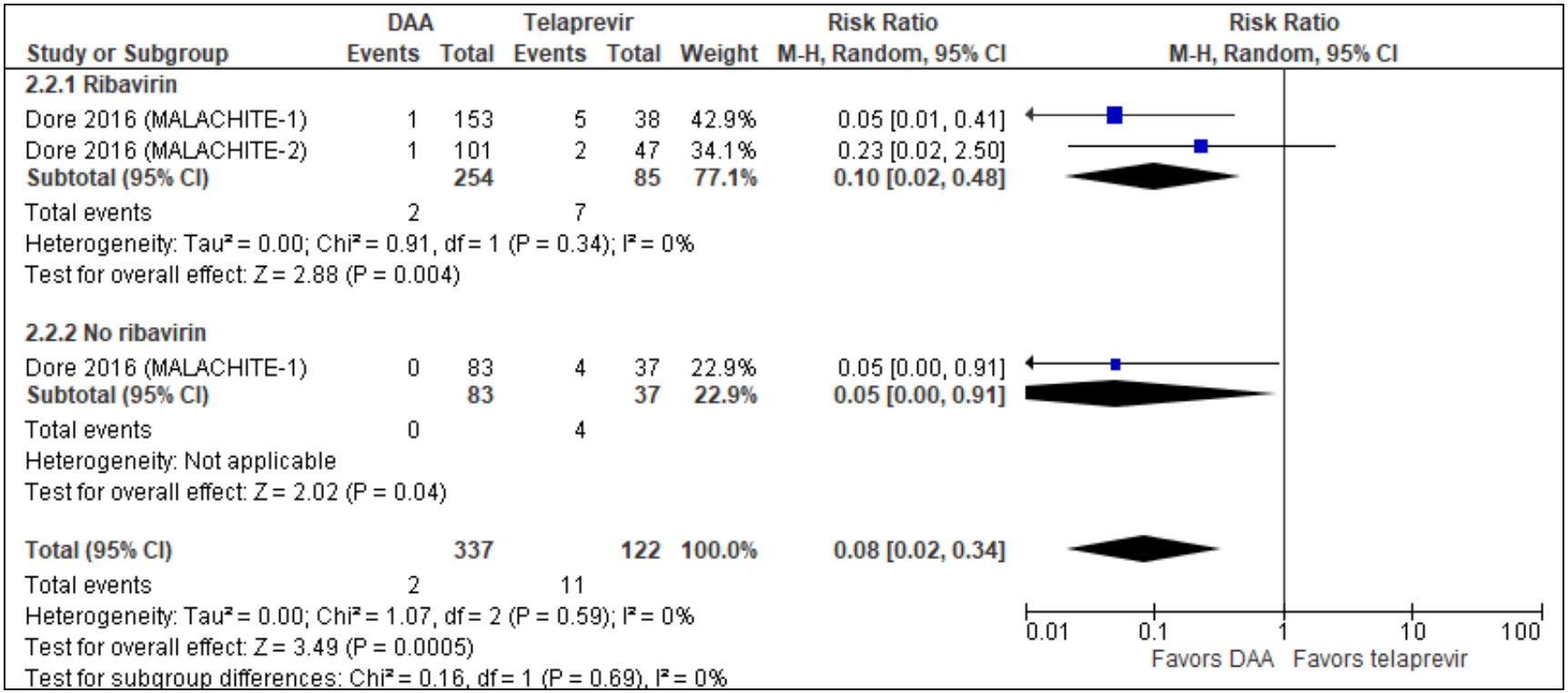
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

Figure 16. Key Question 8: Direct Acting Antiviral Regimens vs. Telaprevir, Any Adverse Events



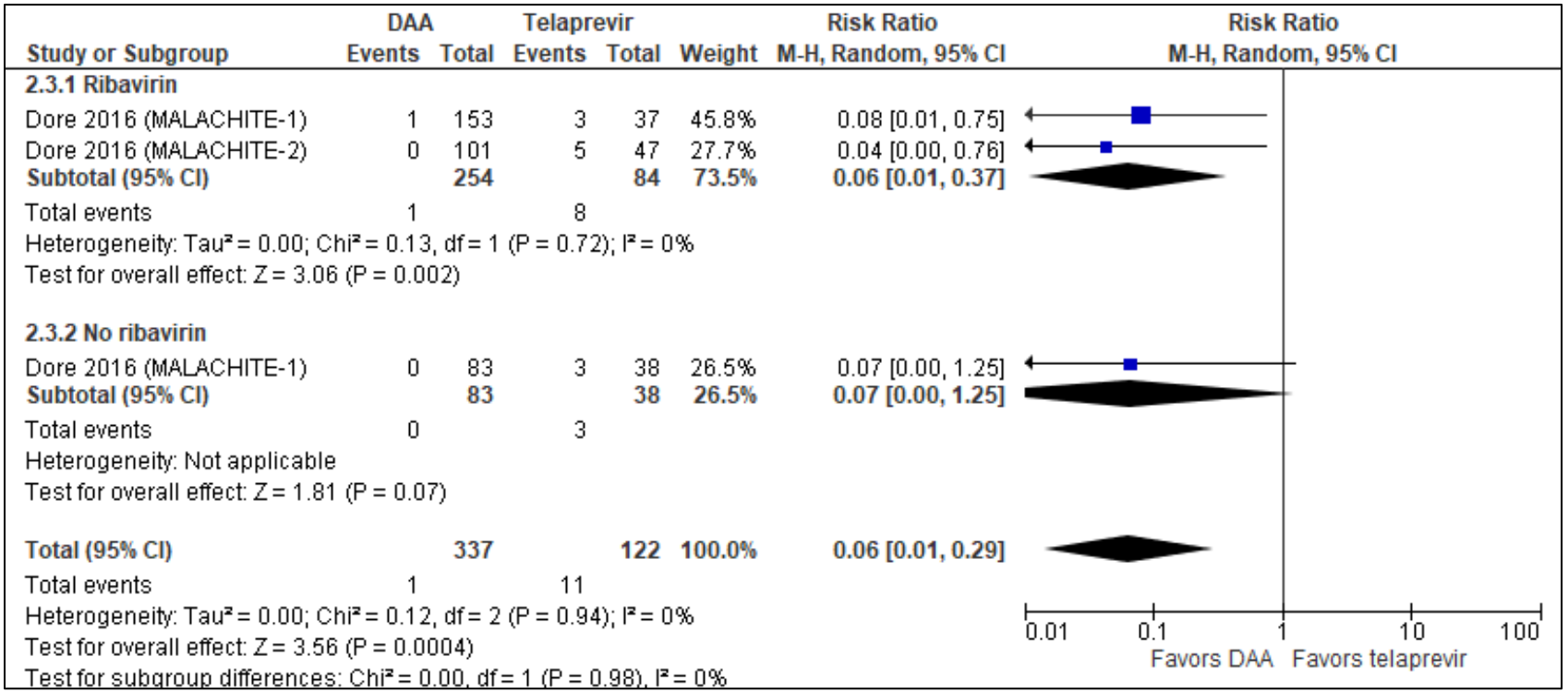
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

Figure 17. Key Question 8: Direct Acting Antiviral Regimens vs. Telaprevir, Serious Adverse Events



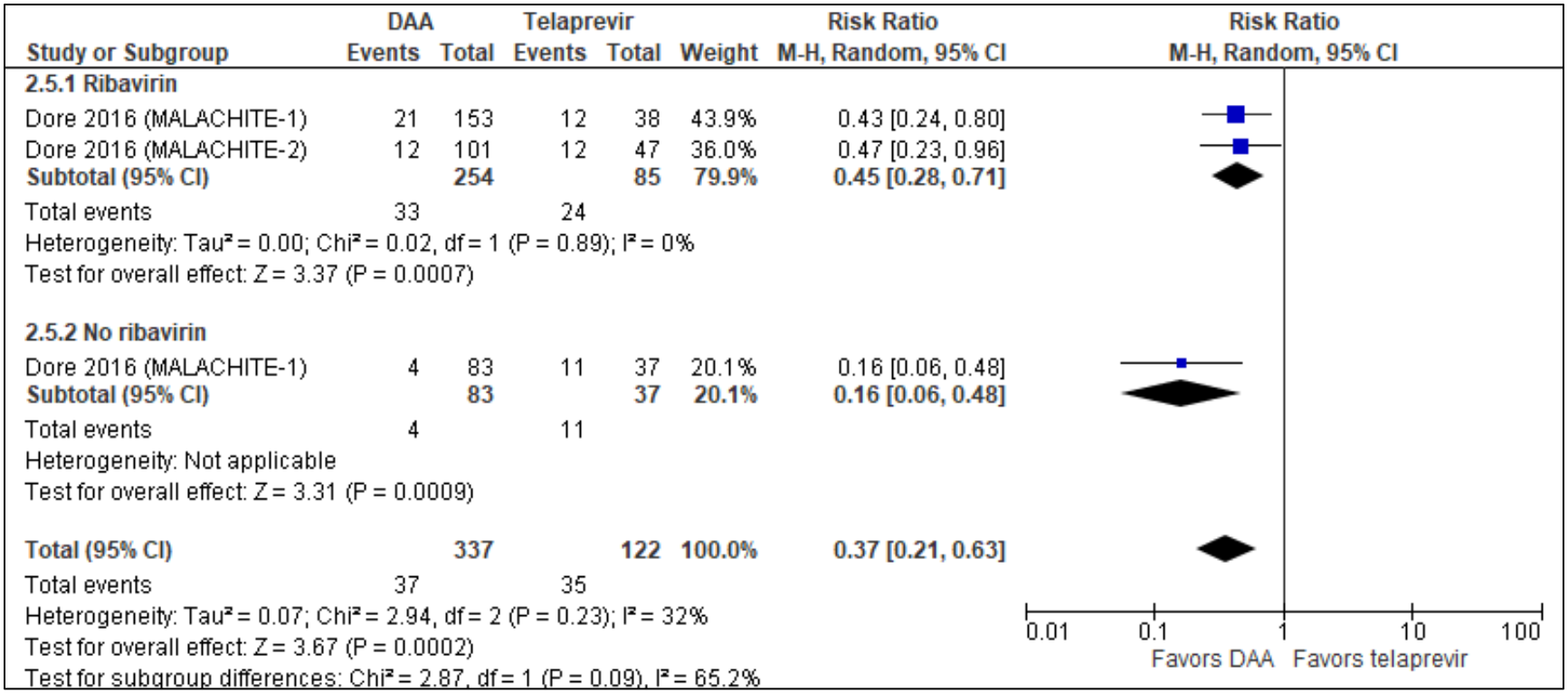
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

Figure 18. Key Question 8: Direct Acting Antiviral Regimens vs. Telaprevir, Withdrawal Due to Adverse Events



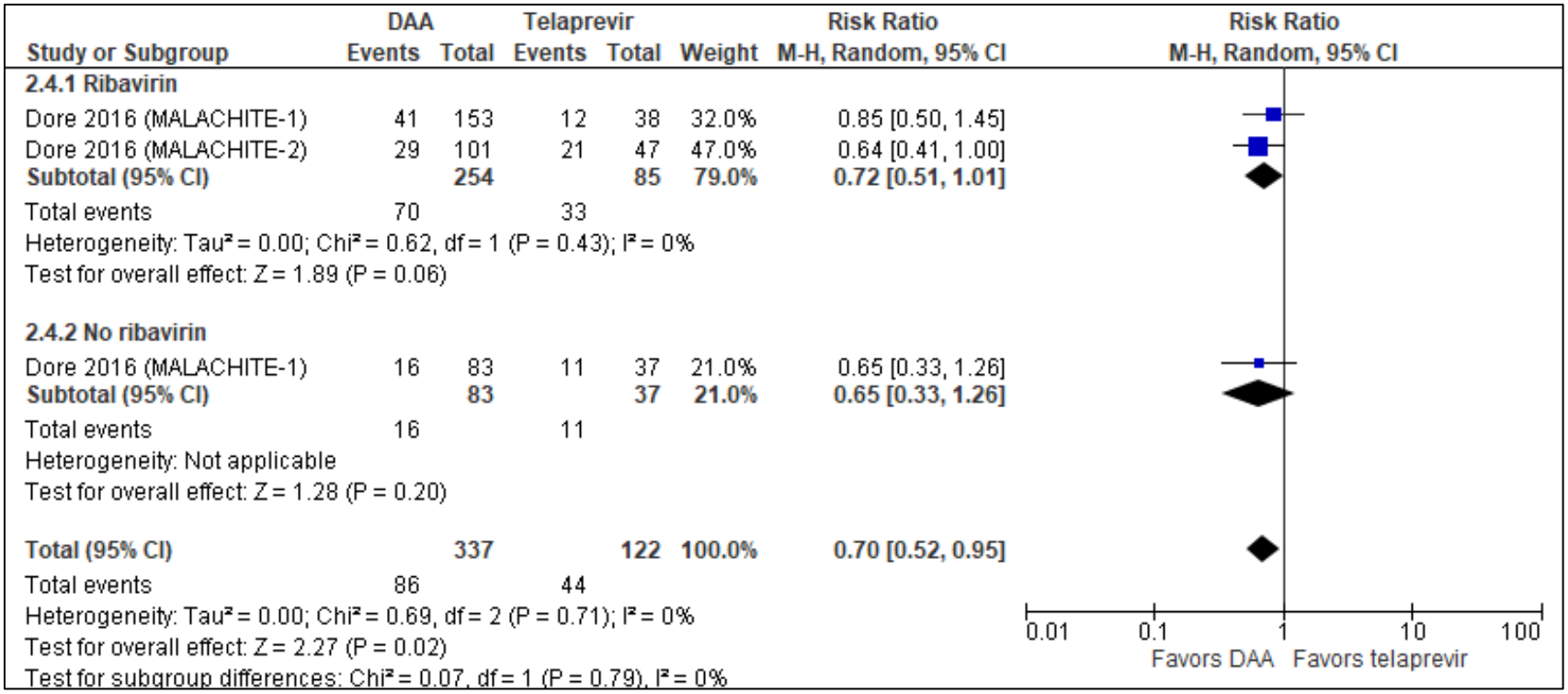
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

Figure 19. Key Question 8: Direct Acting Antiviral Regimens vs. Telaprevir, Fatigue



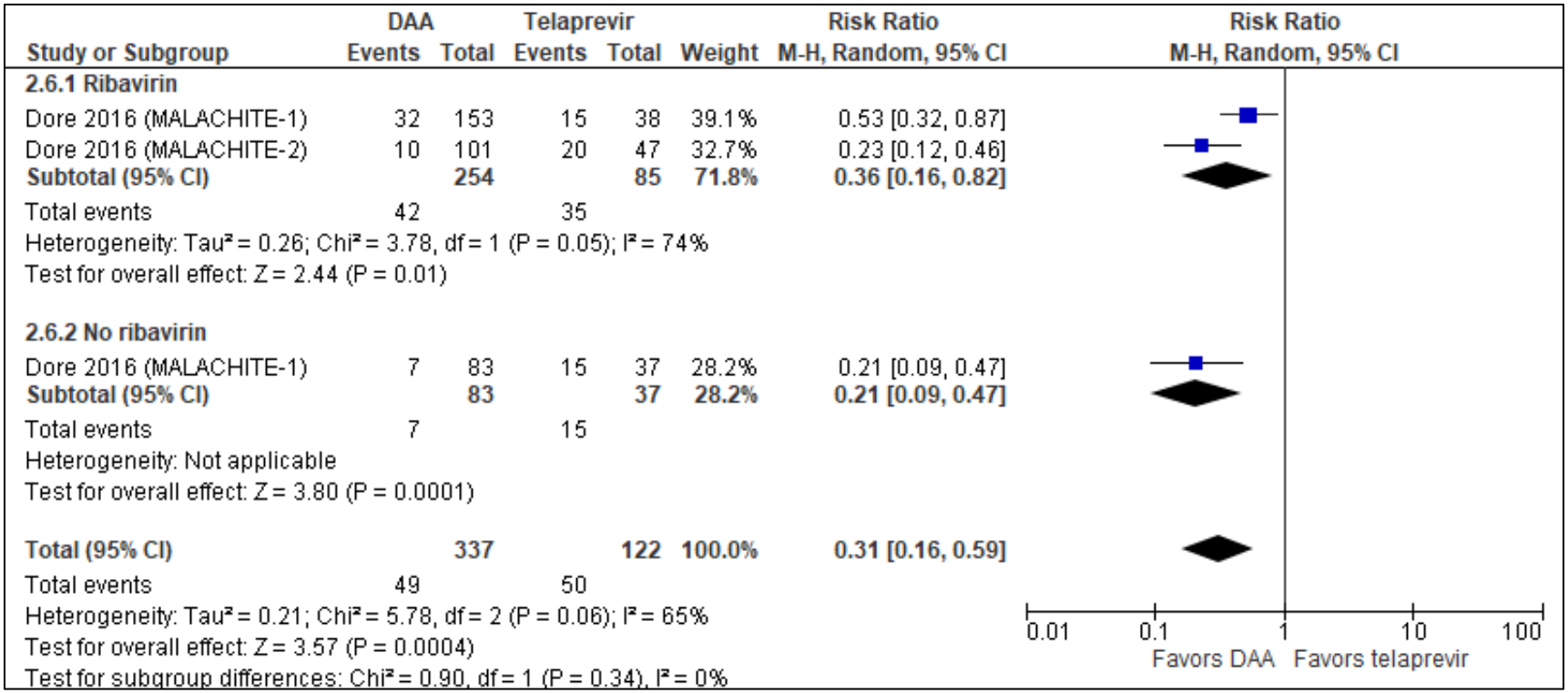
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

Figure 20. Key Question 8: Direct Acting Antiviral Regimens vs. Telaprevir, Headache



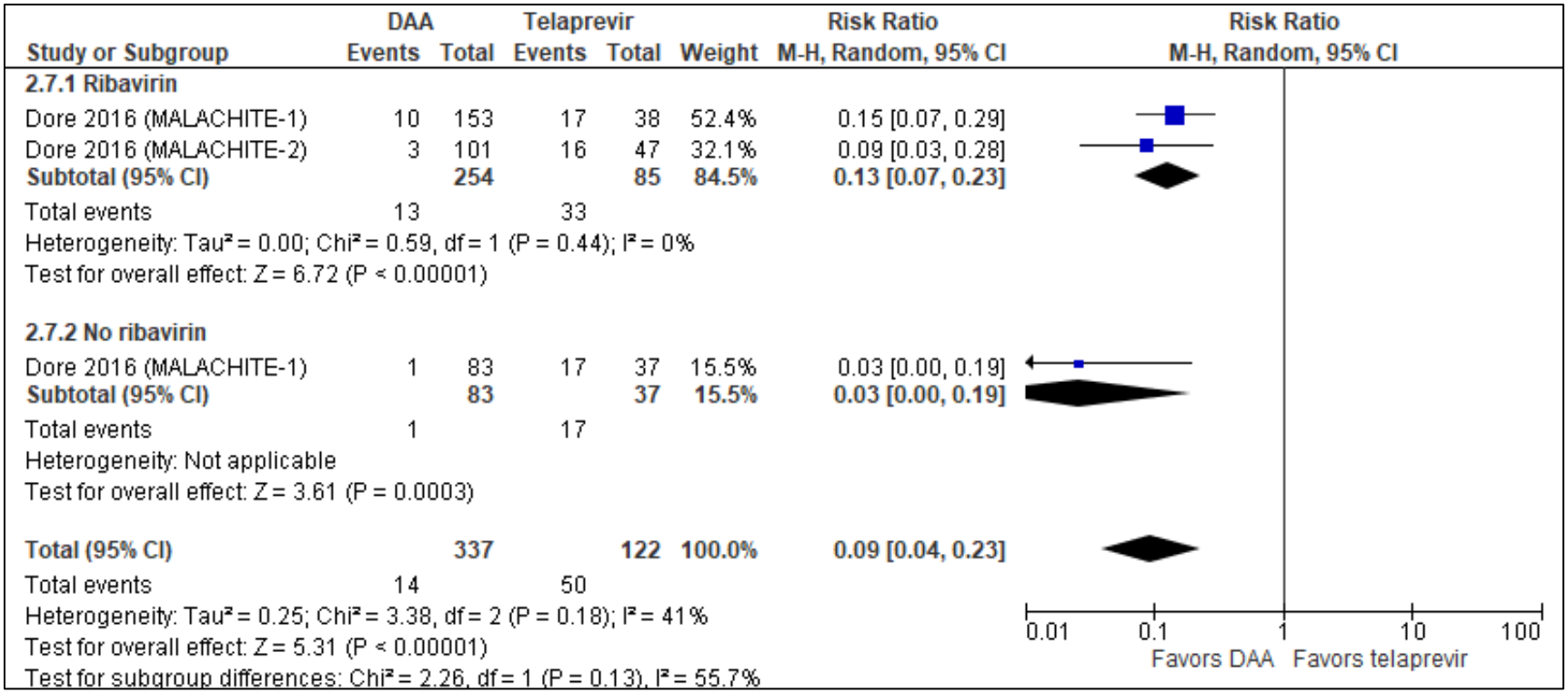
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

Figure 21. Key Question 8: Direct Acting Antiviral Regimens vs. Telaprevir, Nausea



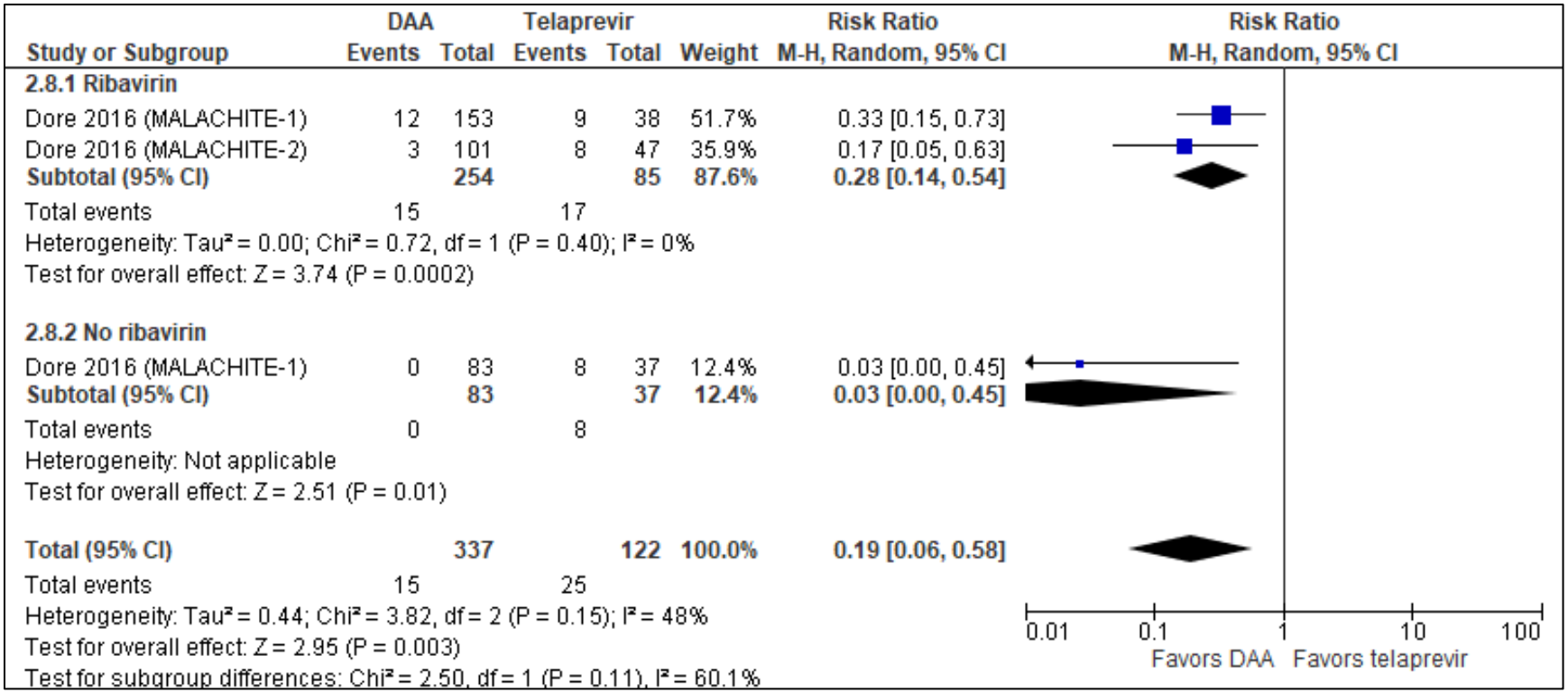
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

Figure 22. Key Question 8: Direct Acting Antiviral Regimens vs. Telaprevir, Anemia



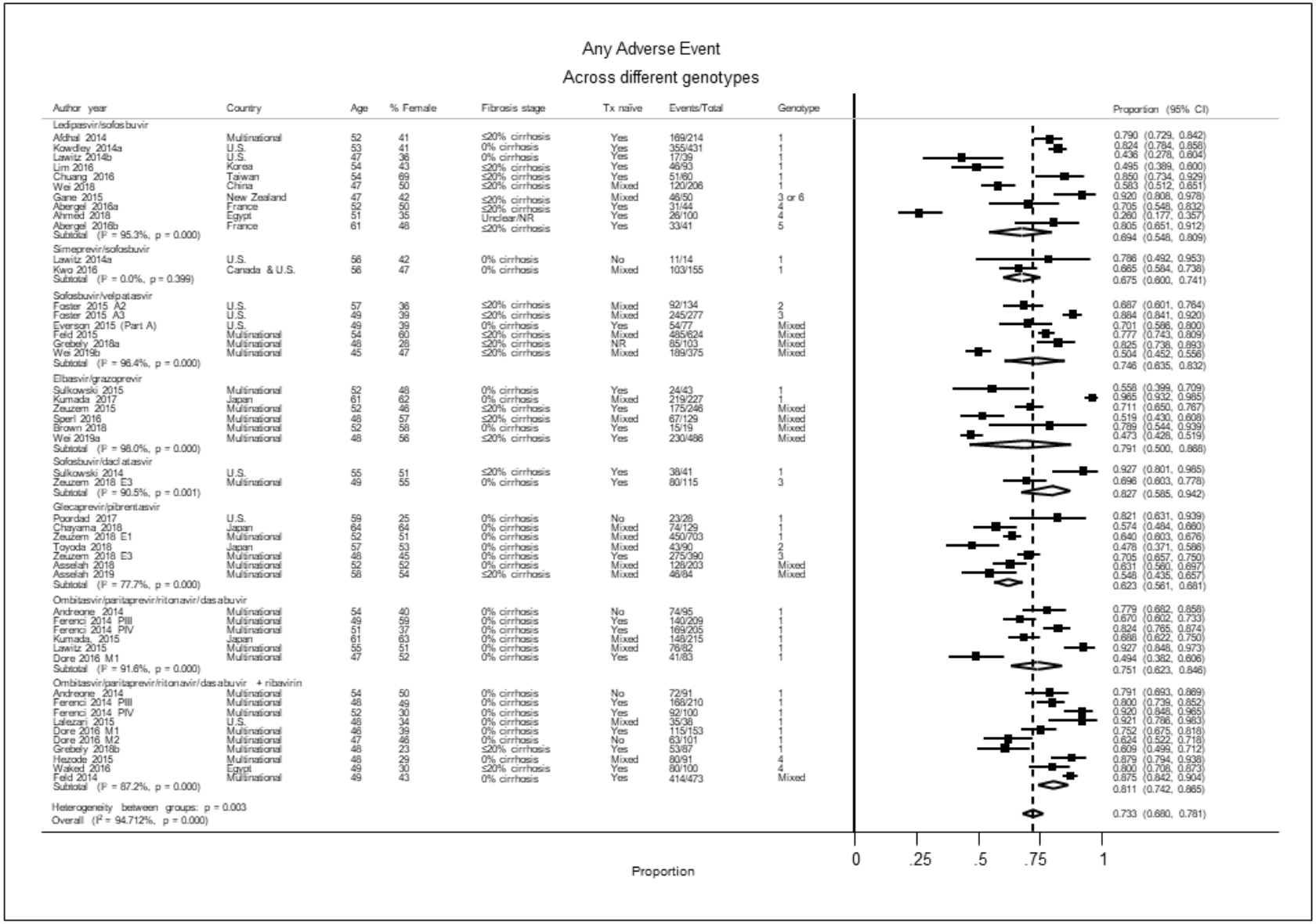
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

Figure 23. Key Question 8: Direct Acting Antiviral Regimens vs. Telaprevir, Rash



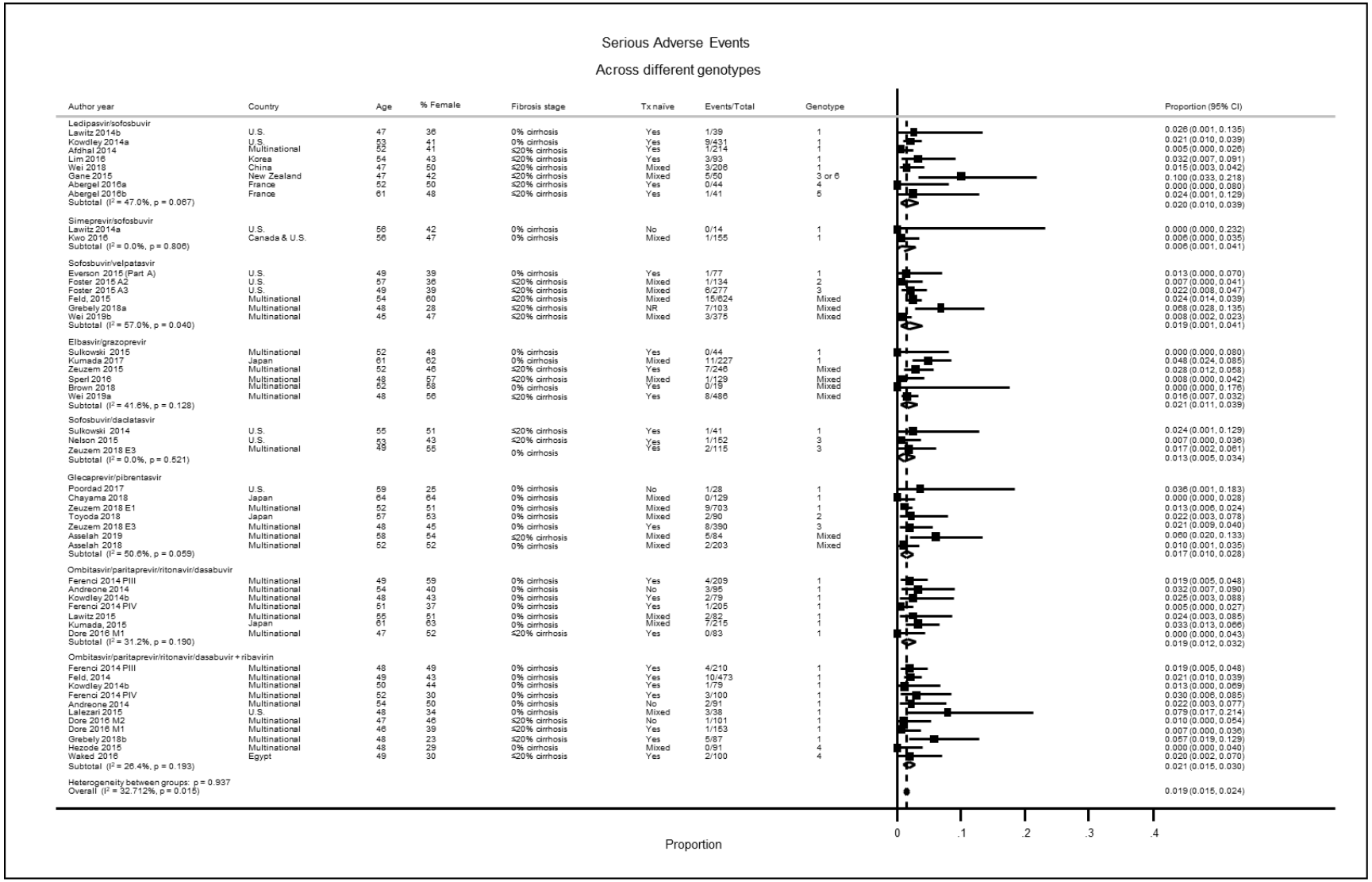
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

Figure 24. Key Question 8: Direct Acting Antiviral Regimens and Pooled Rates for Any Adverse Event



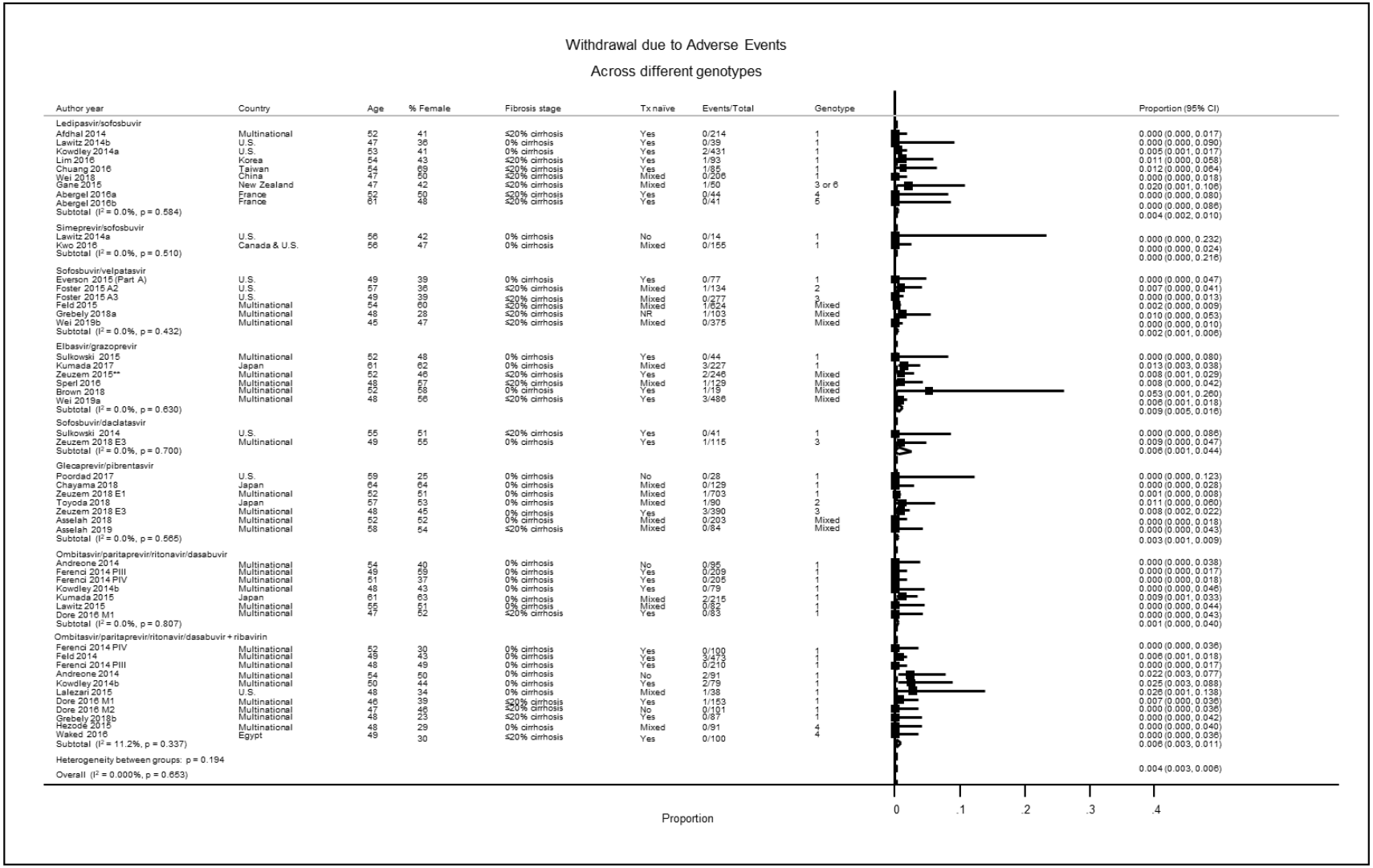
Abbreviations: CI = confidence interval; Tx = treatment; U.S. = United States.

Figure 25. Key Question 8: Direct Acting Antiviral Regimens and Pooled Rates for Serious Adverse Events



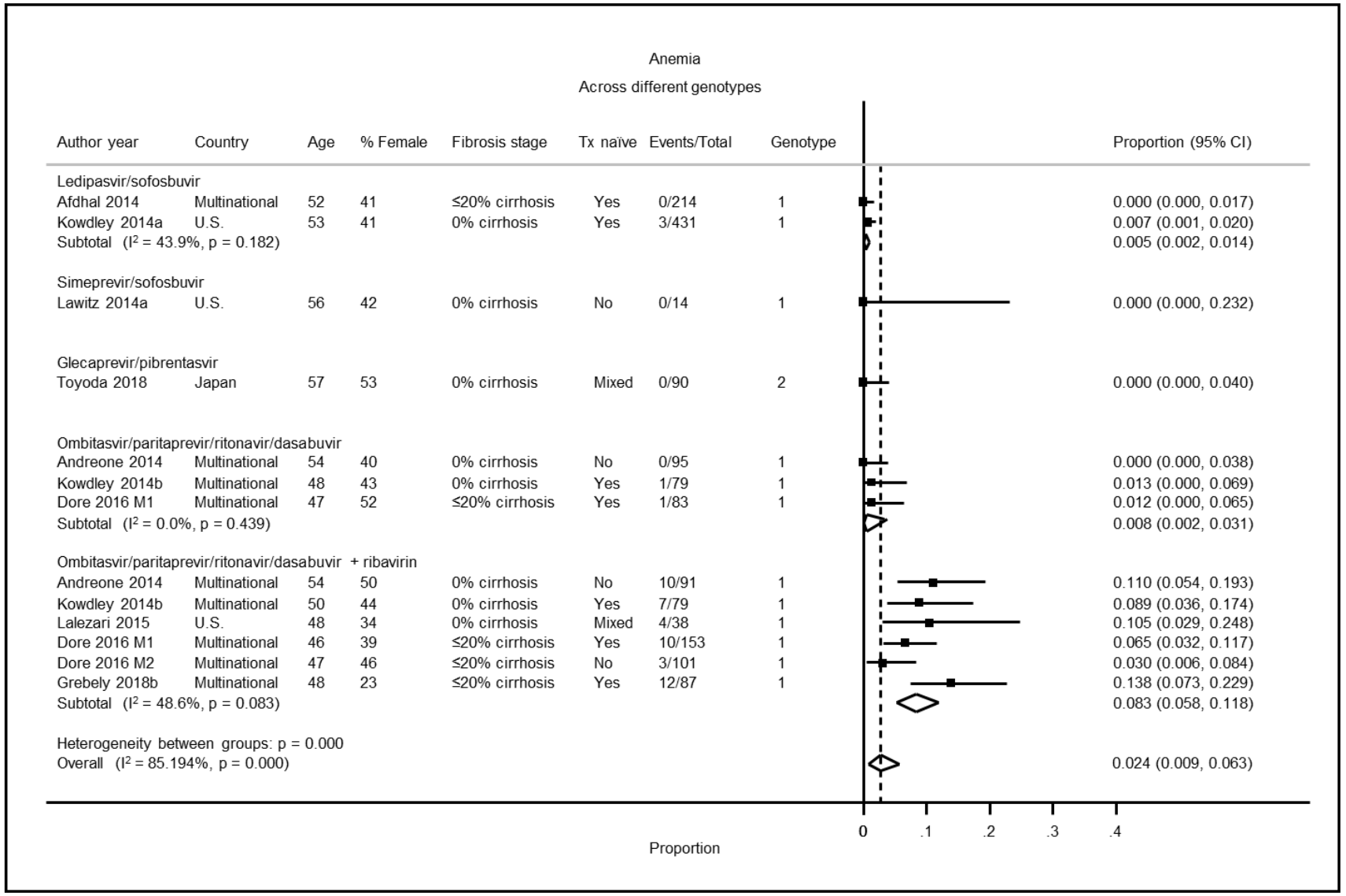
Abbreviations: CI = confidence interval; Tx = treatment; U.S. = United States

Figure 26. Key Question 8: Direct Acting Antiviral Regimens and Pooled Rates for Withdrawal Due to Adverse Events



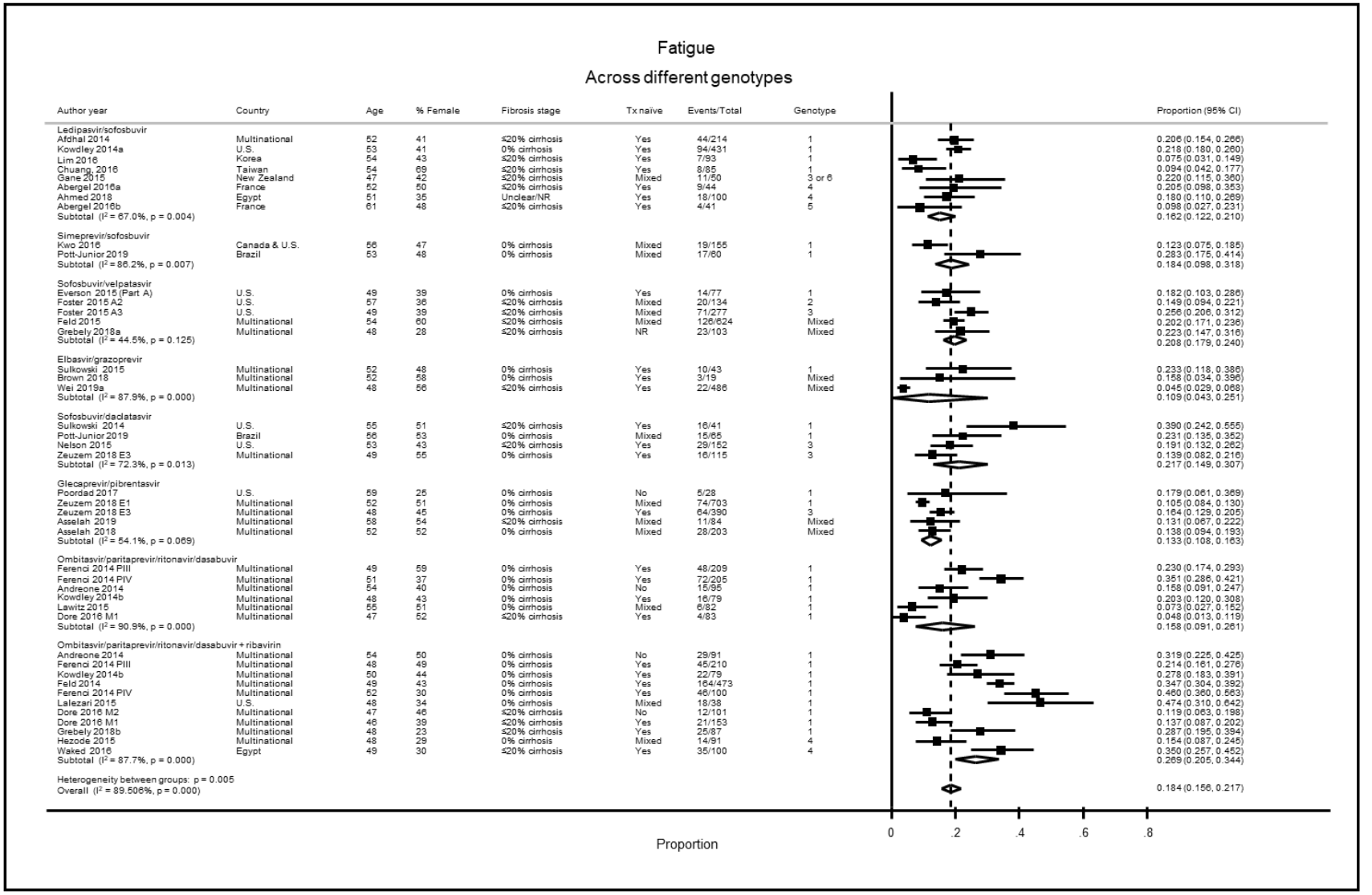
Abbreviations: CI = confidence interval; NR = not reported; Tx = treatment; U.S. = United States.

Figure 27. Key Question 8: Direct Acting Antiviral Regimens and Pooled Rates for Anemia



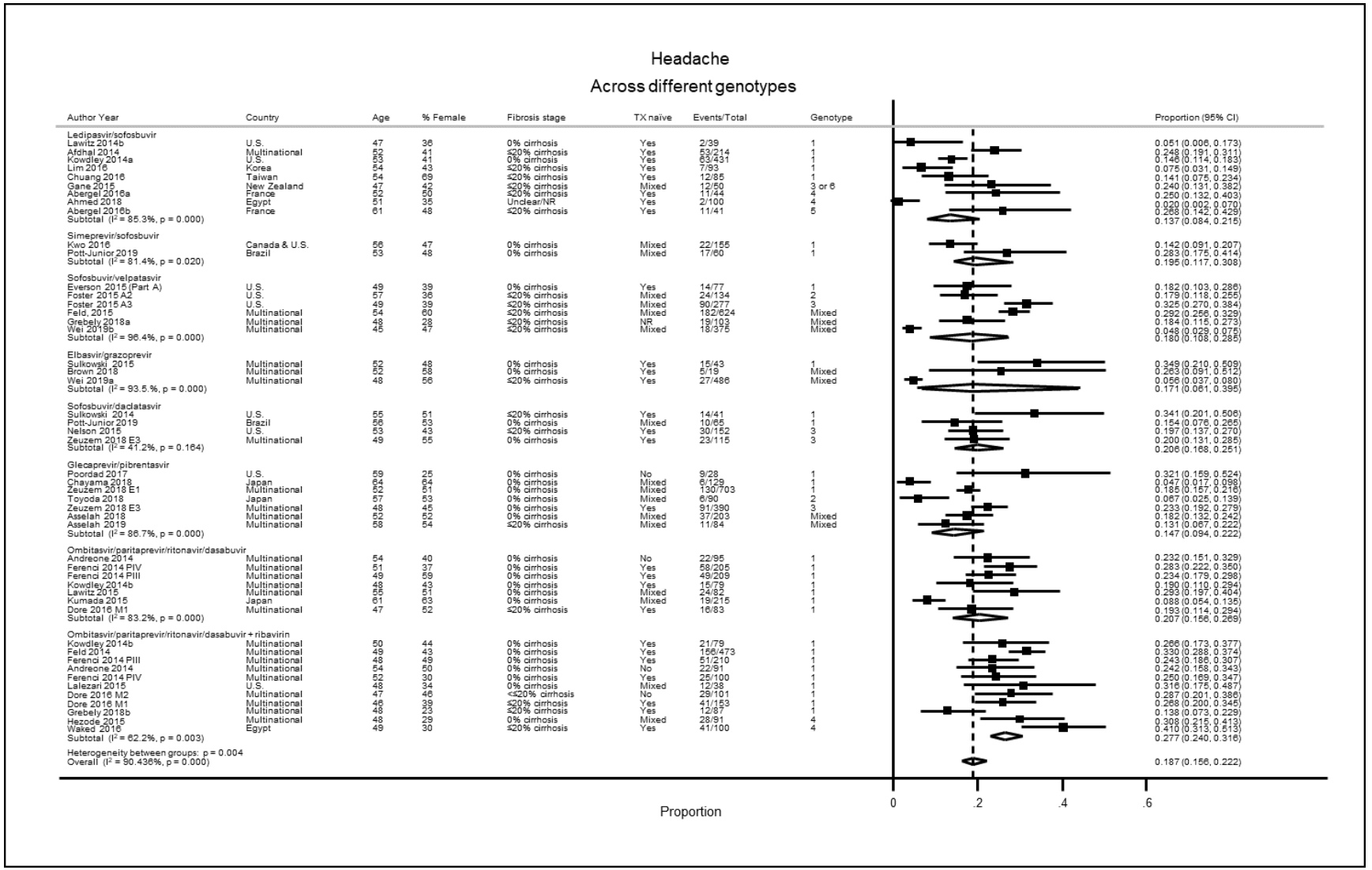
Abbreviations: CI = confidence interval; Tx = treatment; U.S. = United States.

Figure 28. Key Question 8: Direct Acting Antiviral Regimens and Pooled Rates for Fatigue



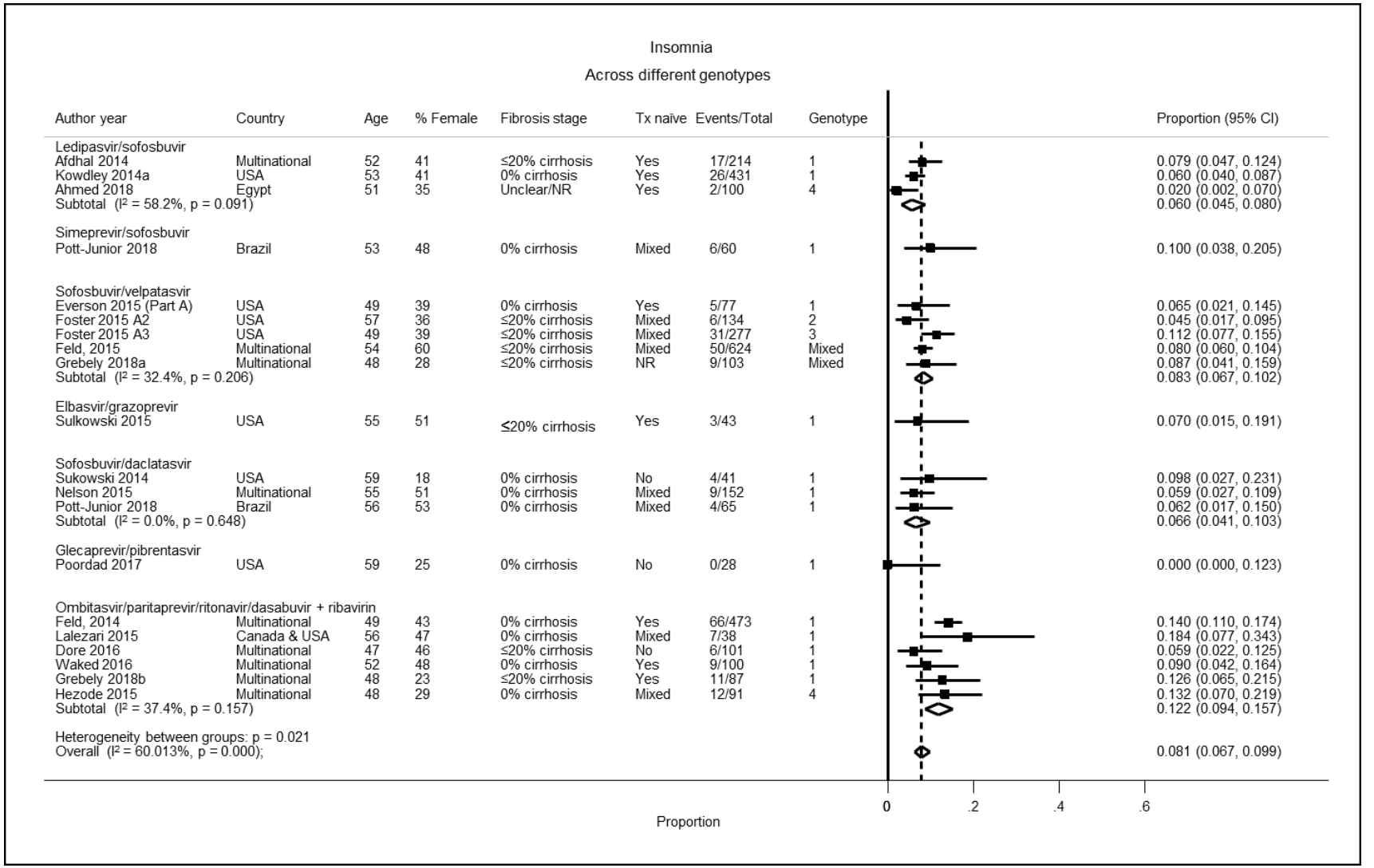
Abbreviations: CI = confidence interval; NR = not reported; Tx = treatment; U.S. = United States.

Figure 29. Key Question 8: Direct Acting Antiviral Regimens and Pooled Rates for Headache



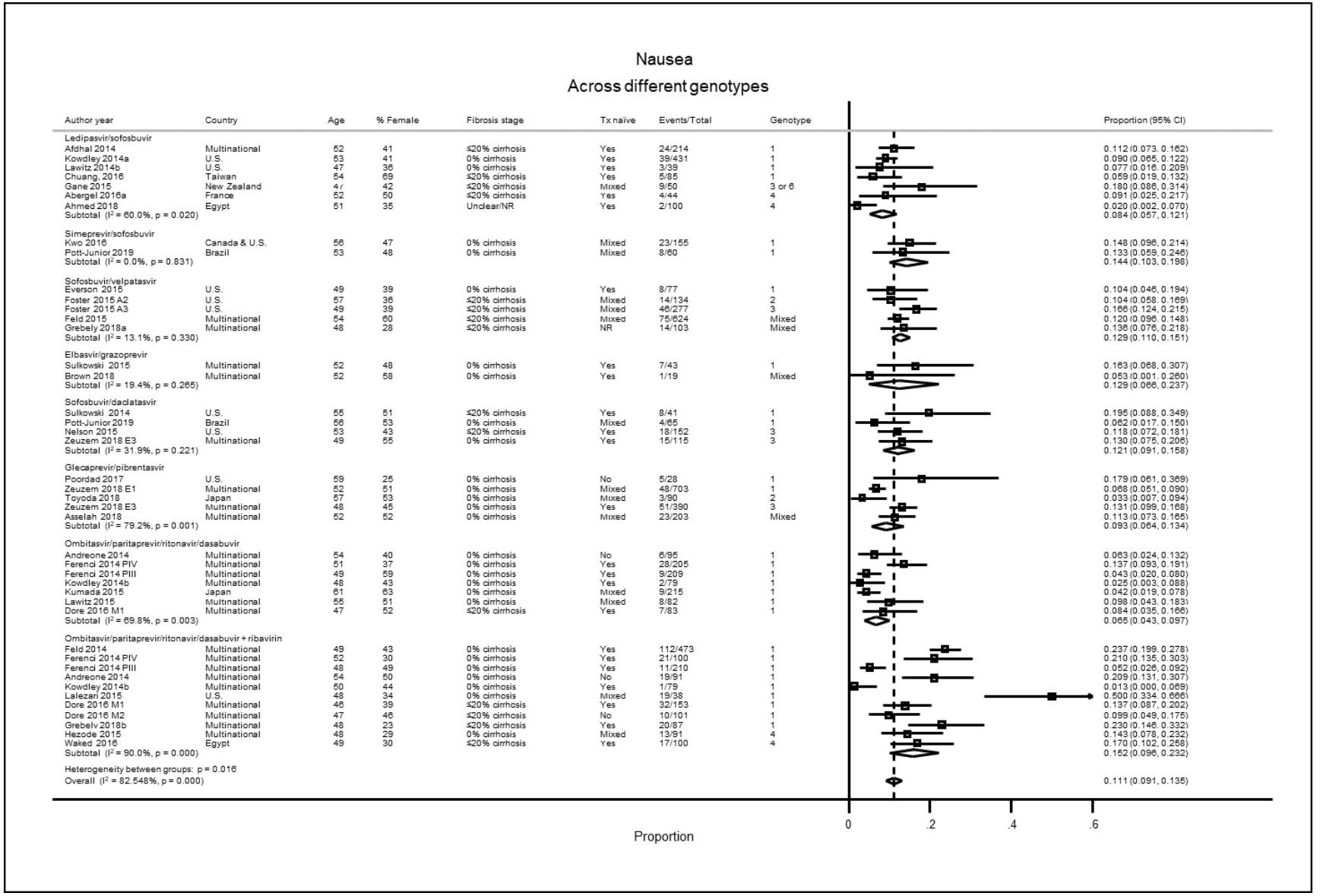
Abbreviations: CI = confidence interval; NR = not reported; Tx = Treatment; U.S. = United States.

Figure 30. Key Question 8: Direct Acting Antiviral Regimens and Pooled Rates for Insomnia



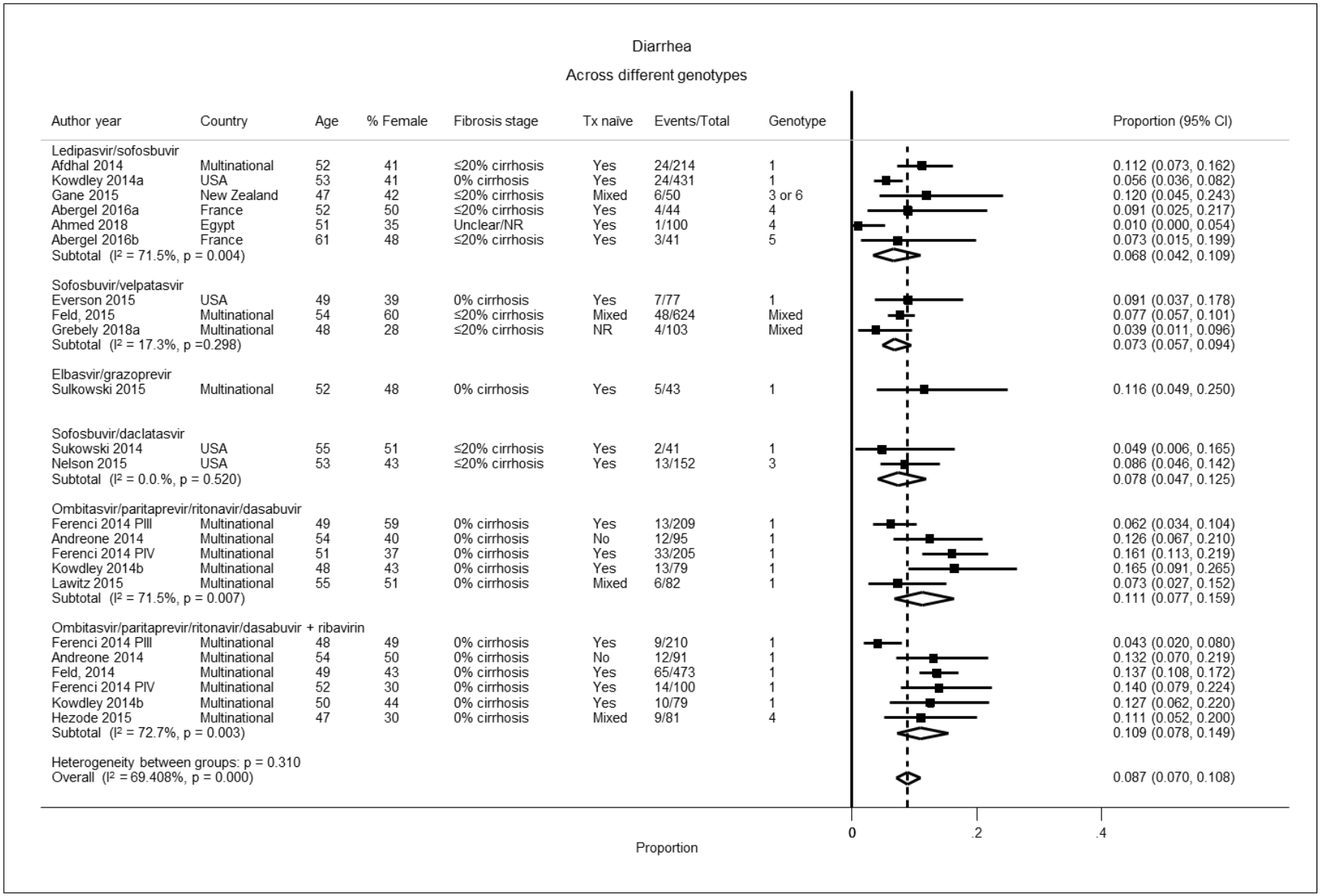
Abbreviations: CI = confidence interval; Tx = treatment; U.S. = United States.

Figure 31. Key Question 8: Direct Acting Antiviral Regimens and Pooled Rates for Nausea



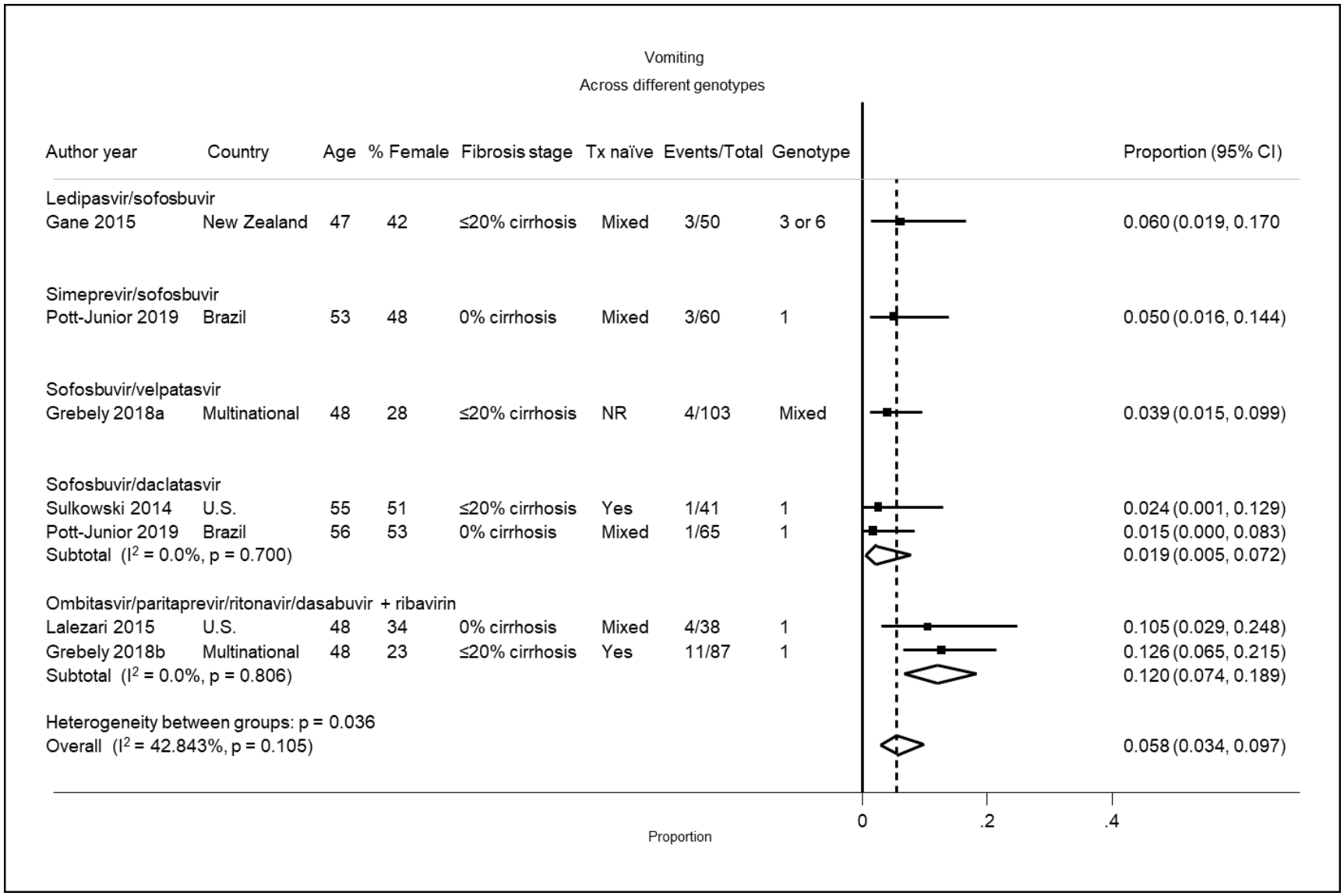
Abbreviations: CI = confidence interval; NR = not reported; Tx = Treatment; U.S. = United States.

Figure 32. Key Question 8: Direct Acting Antiviral Regimens and Pooled Rates for Diarrhea



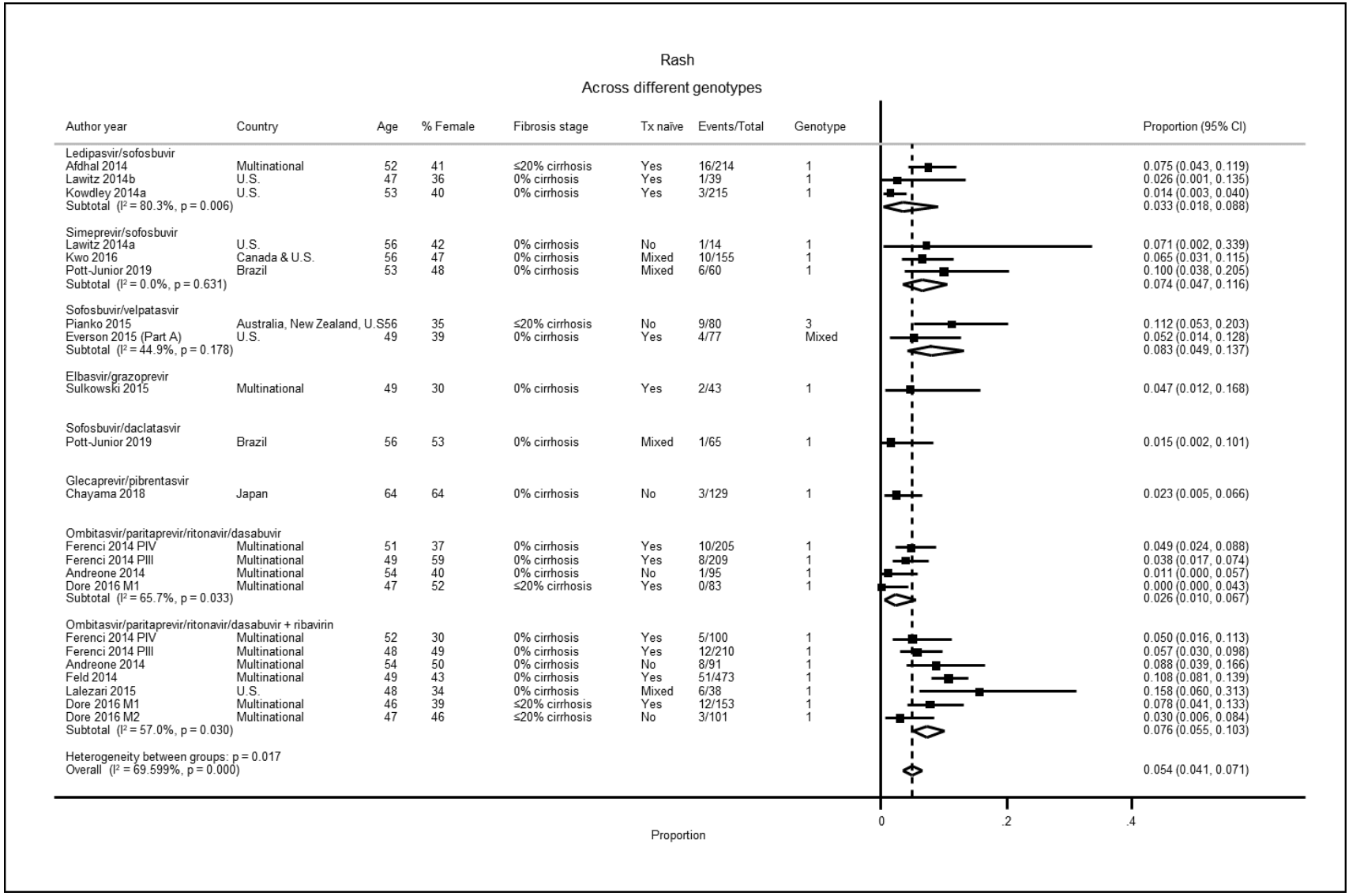
Abbreviations: CI = confidence interval; NR = not reported; Tx = treatment; U.S. = United States.

Figure 33. Key Question 8: Direct Acting Antiviral Regimens and Pooled Rates for Vomiting



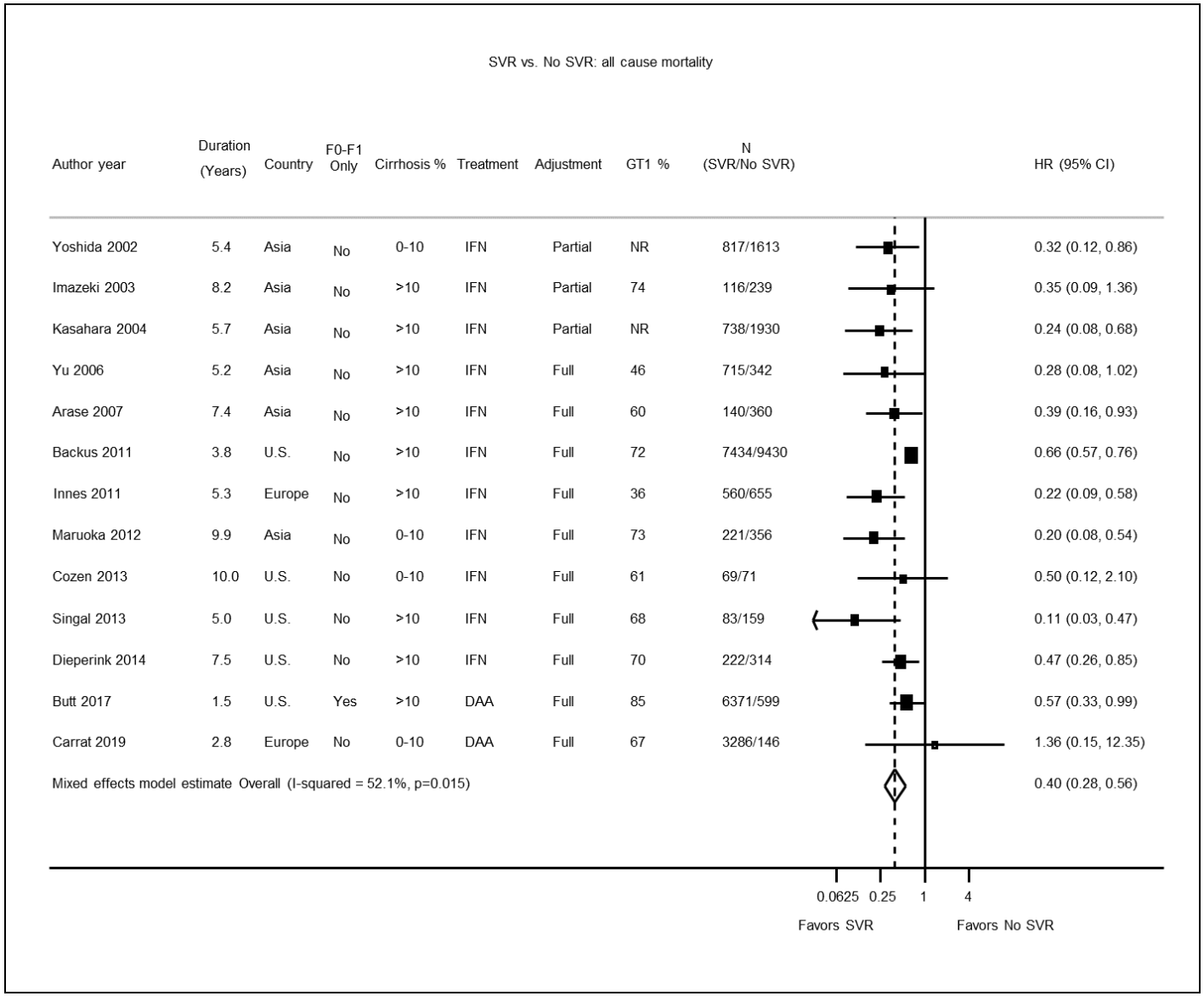
Abbreviations: CI = confidence interval; NR = not reported; Tx = treatment; U.S. = United States.

Figure 34. Key Question 8: Direct Acting Antiviral Regimens and Pooled Rates for Rash



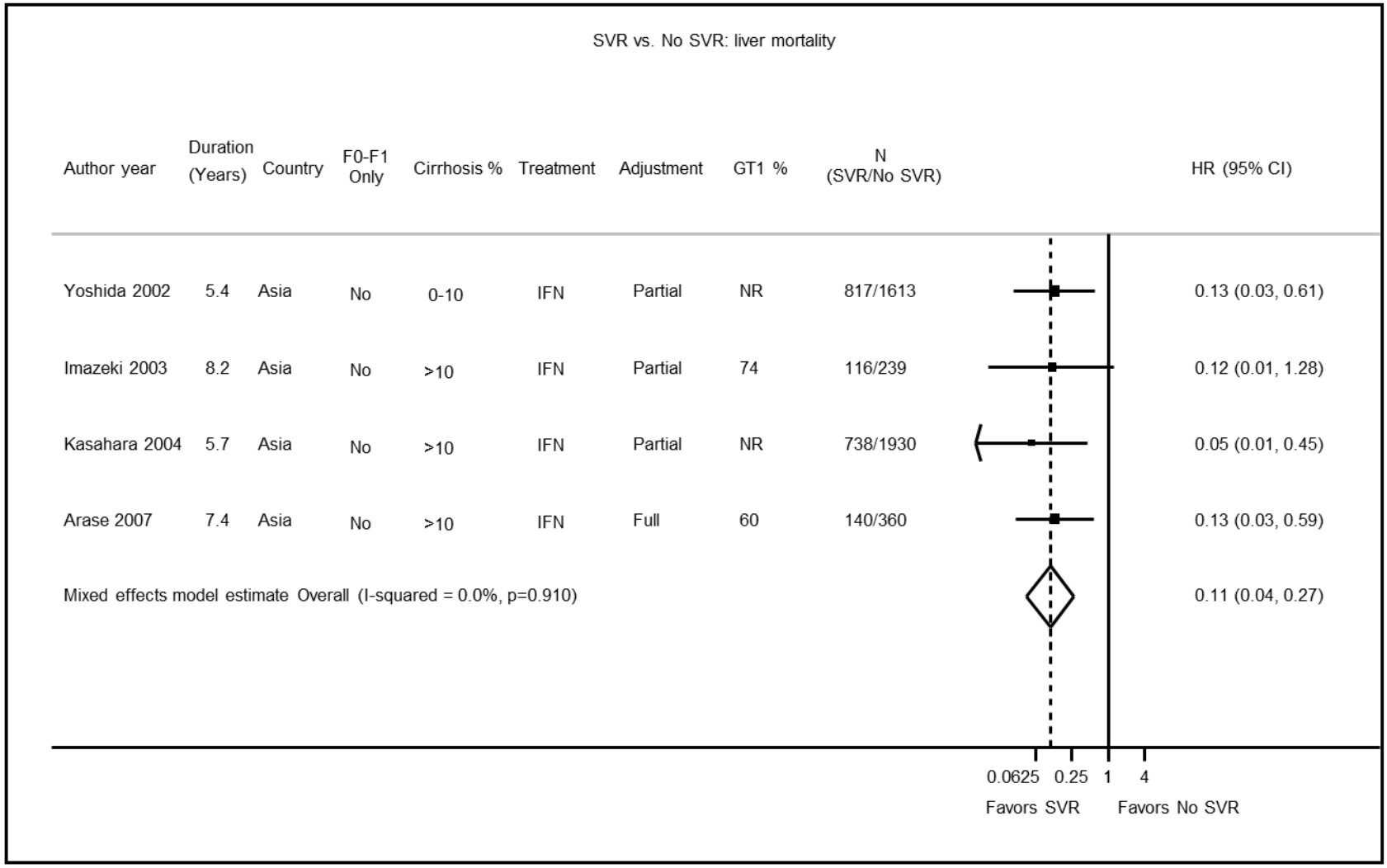
Abbreviations: CI = confidence interval; Tx = treatment; U.S. = United States.

Figure 35. Key Question 9: Association of Sustained Virologic Response With All-Cause Mortality



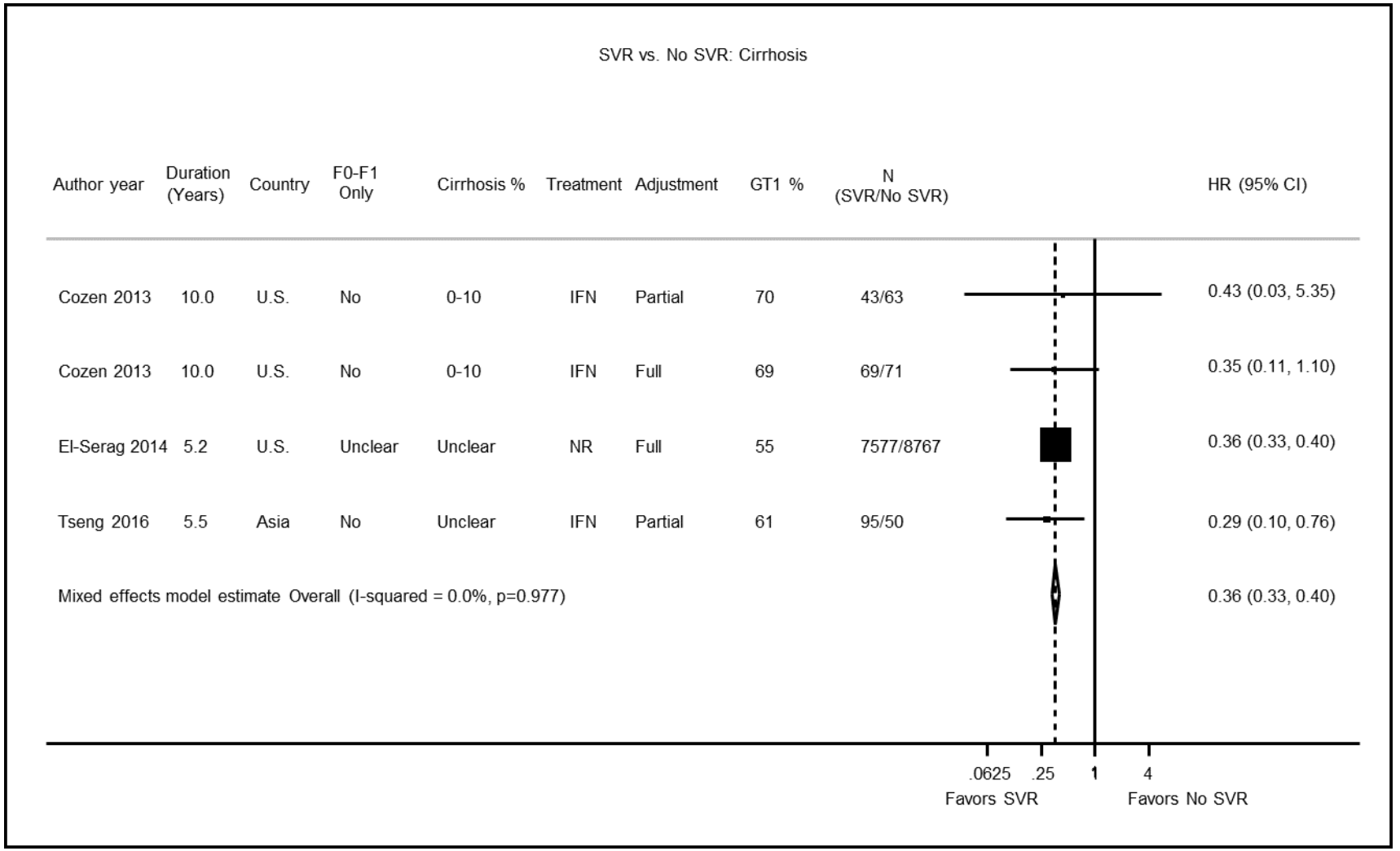
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; HR = hazard ratio; IFN = interferon; NR = not reported; SVR = sustained virologic response; U.S. = United States.

Figure 36. Key Question 9: Association of Sustained Virologic Response With Liver Mortality



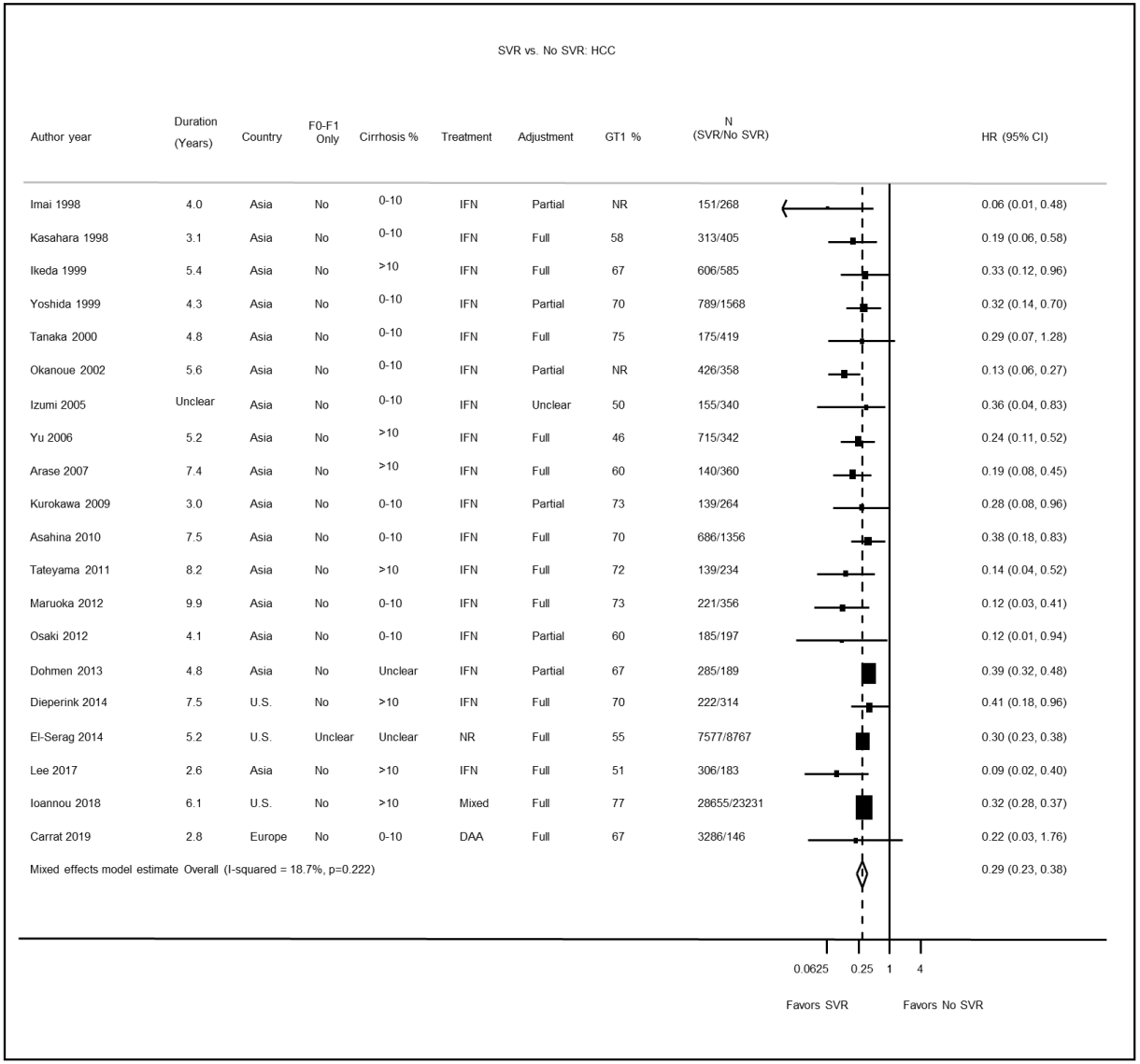
Abbreviations: CI = confidence interval; GT1 = genotype 1; HR = hazard ratio; IFN = interferon; NR = not reported; SVR = sustained virologic response.

Figure 37. Key Question 9: Association of Sustained Virologic Response With Cirrhosis



Abbreviations: CI = confidence interval; HR = hazard ratio; IFN = interferon; NR = not reported; SVR = sustained virologic response; U.S. = United States.

Figure 38. Key Question 9: Association of Sustained Virologic Response With Hepatocellular Carcinoma



Abbreviations: CI = confidence interval; DAA = direct acting antiviral; HCC = hepatocellular carcinoma; HR = hazard ratio; IFN = interferon; NR = not reported; SVR = sustained virologic response; U.S. = United States.

Table 1. Sustained Virologic Response Rates in Older Antiviral Regimens

Treatment	Sustained virologic response rate
Placebo	<2
Interferon monotherapy	6 to 16
Interferon plus ribavirin	33 to 41
Pegylated interferon alone	25 to 39
Pegylated interferon plus ribavirin	39 to 43 (genotypes 1 and 4) 76 to 83 (genotypes 2 and 3)
Boceprevir or telaprevir plus pegylated interferon and ribavirin	68 to 72 (genotype 1)

Source:[91,277]

Table 2. Currently Recommended Direct Acting Antivirals and Alternative Regimens for Treatment Naïve Adults With HCV Infection Without Cirrhosis

Recommended or Alternative	Regimen	Duration of Treatment (weeks)	Genotype
Recommended Regimens	Glecaprevir 300 mg + pibrentasvir 120 mg	8	1a, 1b, 2, 3, 4, 5, 6
	Ledipasvir 90 mg + sofosbuvir 400 mg	8	1a, 1b
	Ledipasvir 90 mg + sofosbuvir 400 mg	12	1a, 1b, 4, 5, 6
	Elbasvir 50 mg + grazoprevir 100 mg	12	1a, 1b, 4
	Sofosbuvir 400 mg + velpatasvir 100 mg	12	1a, 1b, 2, 3, 4, 5, 6
Alternative Regimens	Daclatasvir 60 mg + sofosbuvir 400 mg	12	1a, 1b, 2, 3
	Paritaprevir 150 mg + ritonavir 100 mg + ombitasvir 25 mg + weight-based ribavirin	12	4
	Simeprevir 150 mg + sofosbuvir 400 mg	12	1a, 1b
	Elbasvir 50 mg + grazoprevir 100 mg + weight-based ribavirin	16	1a
	Paritaprevir 150 mg + ritonavir 100 mg + ombitasvir 25 mg + dasabuvir ER 600 mg or dasabuvir 250 mg 2x/day + weight-based ribavirin	12	1a
	Paritaprevir 150 mg + ritonavir 100 mg + ombitasvir 25 mg + dasabuvir ER 600 mg or dasabuvir 250 mg 2x/day	12	1b

Source: AASLD/IDSA, available at: https://www.hcvguidelines.org/treatment-naive
Note: Recommended regimens are those that are favored for most patients in a given group, based on optimal efficacy, favorable tolerability and toxicity profiles, and treatment duration. Alternative regimens are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data than recommended regimens. In certain situations, an alternative regimen may be an optimal regimen for an individual patient.
Abbreviations: AASLD = American Association for the Study of Liver Diseases; ER = extended release; IDSA = Infectious Disease Society of America.

Table 3. Currently Recommended Antiviral Regimens for Treatment-Experienced Adults With HCV Infection Without Cirrhosis

Recommended or Alternative	Regimen	Duration of treatment (weeks)	Genotype
Recommended Regimens	Glecaprevir 300 mg + pibrentasvir 120 mg	8	1a, 1b, 2, 4, 5, 6
	Same as above	12	1
	Elbasvir 50 mg + grazoprevir 100 mg	12	1a, 1b, 4
	Ledipasvir 90 mg + sofosbuvir 400 mg	12	1a, 1b, 4, 5, 6
	Sofosbuvir 400 mg + velpatasvir 100 mg	12	1a, 1b, 2, 3, 4, 5, 6
	Sofosbuvir 400 mg + velpatasvir 100mg + voxilaprevir 100mg	12	1a
Alternative Regimens	Daclatasvir 60 mg + sofosbuvir 400 mg	12	1a, 1b, 2, 3
	Elbasvir 50 mg + grazoprevir 100 mg + ribavirin	12	1b
	Same as above	12 to 16	1a
	Same as above	16	1a, 4
	Ledipasvir 90 mg + sofosbuvir 400 mg + ribavirin	12	1a, 1b
	Simeprevir 150 mg + sofosbuvir 400 mg	12	1a, 1b
	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir ER 600 mg or dasabuvir 250 mg 2x/day	12	1b
	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir ER 600 mg or dasabuvir 250 mg 2x/day + weight-based ribavirin	12	1a
	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + weight-based ribavirin	12	4
	Sofosbuvir 400 mg + velpatasvir 100mg + voxilaprevir 100mg	12	3
	Glecaprevir 300 mg + pibrentasvir 120 mg	16	3

Source: AASLD/IDSA, available at: https://www.hcvguidelines.org/treatment-experienced, up to date as of June 1, 2019.
Note 1: Recommended regimens are those that are favored for most patients in a given group, based on optimal efficacy, favorable tolerability and toxicity profiles, and treatment duration. Alternative regimens are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data than recommended regimens. In certain situations, an alternative regimen may be an optimal regimen for an individual patient.
Note 2: Table does not list regimens for those with prior DAA treatment experience.
Abbreviations: AASLD = American Association for the Study of Liver Diseases; ER = extended release; IDSA = Infectious Disease Society of America.

Table 4. Currently Recommended Antiviral Regimens for Adolescents Age ≥12 Years or Weighing at Least 35 kg, Without Cirrhosis or With Compensated Cirrhosis

Regimen*	Duration of treatment (weeks)	Genotype
Ledipasvir 90 mg + sofosbuvir 400 mg for patients who are treatment-naive without cirrhosis or with compensated cirrhosis, or treatment-experienced without cirrhosis	12	1
Sofosbuvir 400 mg + weight-based ribavirin for patients who are treatment-naive or treatment-experienced without cirrhosis or with compensated cirrhosis	12	2
Sofosbuvir 400 mg + weight-based ribavirin for patients who are treatment-naive or treatment-experienced† without cirrhosis or with compensated cirrhosis	24	3
Ledipasvir 90 mg + sofosbuvir 400 mg for patients who are treatment-naive or treatment-experienced without cirrhosis or with compensated cirrhosis	12	4, 5, 6

Source: AASLD/IDSA https://www.hcvguidelines.org/unique-populations/children
Note: Recommended regimens are those that are favored for most patients in a given group, based on optimal efficacy, favorable tolerability and toxicity profiles, and treatment duration.

* Glecaprevir + pibrentasvir approved by the U.S. Food and Drug Administration in April 2019 for children 12 to 17 years of age for genotypes 1 through 6, but has not been incorporated in the AASLD recommendations as of June 1, 2019.

Abbreviations: AASLD = American Association for the Study of Liver Diseases; IDSA = Infectious Disease Society of America.

Table 5. United States Screening Guidelines

Group	Recommendation
AASLD-IDSA[65]	One-time HCV testing is recommended for persons born between 1945 and 1965 (regardless of country of birth) without prior ascertainment of risk. Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection All persons with active HCV infection should be linked to a clinician who is prepared to provide comprehensive management
CDC[87]	Persons for whom HCV testing Is recommended: Adults born from 1945 through 1965 should be tested once (without prior ascertainment of HCV risk factors) HCV testing is recommended for those who: • Currently inject drugs • Ever injected drugs, including those who injected once or a few times many years ago • Have certain medical conditions, including persons: o who received clotting factor concentrates produced before 1987 o who were ever on long-term hemodialysis o with persistently abnormal ALT levels o who have HIV infection • Were prior recipients of transfusions or organ transplants, including persons who: o were notified that they received blood from a donor who later tested positive for HCV infection o received a transfusion of blood, blood components, or an organ transplant before July 1992 • HCV- testing based on a recognized exposure is recommended for: o Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood o Children born to HCV-positive women Note: For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended.

Abbreviations: AASLD-IDSA = American Association for the Study of Liver Diseases-Infectious Diseases Society of America; ALT = alanine aminotransferase; CDC = Centers for Disease Control and Prevention; HCV = hepatitis C virus; RNA = ribonucleic acid.

Table 6. Mode of Delivery and Mother-to-Infant Transmission of HCV Infection

Author year *Quality*	N	Elective Cesarean or Cesarean not specified	Vaginal/ Emergent Cesarean	Comments/Results (95% CI)
Ceci 2001[108] *Fair*	78*	No association (data NR)	No association (data NR)	No significant association in multivariate analysis (data NR)
Gibb 2000[105] Fair	424†	0/31 (0%)	29/393 (7.4%)	OR 0 (0 to 0.87), p=0.04, adjusted for HIV status and breastfeeding
Mast 2005[104] *Good*	188*	0/12 (0%)	7/169 (4.1%)	RR 0.87 (0.05 to 14) Excluded from multivariate analyses due to lack of significance in univariate analysis
Resti 2002[107] *Good*	1,301‡	22/337 (5.8%)	73/924 (7.9%)	OR for vaginal delivery 1.17 (0.92 to 1.41), unadjusted§ OR for vaginal delivery 1.20 (0.93 to1.55), adjusted for maternal HCV RNA status, maternal HIV status, injection drug use, type of feeding§
Tovo 2005[106] EPHN *Good*	1,034*	NR	NR	OR 1.57 (0.88 to 2.83), p=0.13, unadjusted OR 1.59 (0.88 to 2.86), p=0.13 adjusted for sex, mode of delivery, prematurity, and breastfeeding
Total	3,025	--	--	--

* 0% HIV coinfected.
† 5% HIV coinfected.
‡ 14% HIV coinfected.
§ Study appears to have reversed reference standard; Calculation to adjust reference standard gives unadjusted OR for vaginal delivery (ref): 0.85 (0.71 to 1.09); Adjusted OR for vaginal delivery (ref): 0.83 (0.65 to 1.08).
Abbreviations: CI = confidence interval; EPHN = European Paediatric Hepatitis C Virus Network; HCV = hepatitis C virus; NR = not reported; OR = odds ratio; RR = relative risk.

Table 7. Duration of Membrane Rupture and Mother-to-Infant Transmission of HCV Infection

Author year *Quality*	N	Duration of Membrane Rupture (hours)	Comments/Results (95% CI)
Mast 2005[104] *Good*	189*	<1 vs. 1 to 5 vs. 6 to 12 vs. ≥13: 0/53 vs. 1/59 (1.7%) vs. 4/40 (10%) vs. 2/30 (6.7%), p=0.02	Membrane rupture >6 hours OR, 9.3 (1.5 to 179.7), adjusted for maternal demographic characteristics, HCV RNA level, fetal monitoring, history of IVDU, and cigarette smoking during pregnancy.
Total	189	--	--

* 0% HIV coinfected.

Abbreviations: CI = confidence interval; HCV = hepatitis c virus; IVDU = intravenous drug use; OR = odds ratio; RNA = ribonucleic acid.

Table 8. Fetal Monitoring and Risk of Mother-to-Infant Transmission of HCV Infection

Author year *Quality*	N	Fetal Monitoring During Delivery	Comments/ Results (95% CI)
Mast 2005[104] *Good*	188*	Internal vs. external: 3/16 (18.8%) vs. 4/165 (2.4%),	RR 7.7 (1.9 to 31.6), p=0.02, unadjusted Internal fetal monitoring, OR 6.7 (1.1 to 35.9), adjusted for maternal demographic characteristics, HCV RNA level, history of IVDU, and cigarette smoking during pregnancy.
Total	188	--	--

* 0% HIV coinfected.

Abbreviations: CI = confidence interval; IVDU = intravenous drug use; HCV = hepatitis C virus; OR = odds ratio; RNA = ribonucleic acid; RR = relative risk.

Table 9. Breastfeeding and Risk of Mother-to-Infant Transmission of HCV Infection

Author year *Quality*	N	Breast Fed	Formula Fed	Comments/Results (95% CI)
Gibb 2000[105] *Fair*	414*	7.7% (2.2 to 17.8)	6.7% (3.7 to 10.6)	OR 1.52 (0.35 to 5.12), adjusted for HIV status and mode of delivery
Resti 2002[107] *Good*	1,281†	22/360 (6.1%)	73/921 (7.9%)	OR 0.86 (0.61 to 1.10) OR 0.95 (0.58 to 1.40), adjusted for maternal HCV RNA status, maternal HIV-1 status, maternal IVDU, type of feeding, mode of delivery
Tovo 2005[106] EPHN *Good*	1,034‡	NR	NR	OR 0.88 (0.48 to 1.61), unadjusted OR 0.92 (0.50 to 1.70), adjusted for sex, prematurity, and mode of delivery
Total	3,645	--	--	--

* 5% HIV coinfected.
† 14% HIV coinfected.
‡ 0% HIV coinfected.
Abbreviations: CI = confidence interval; EPHN = European Paediatric Hepatitis C Virus Network; HCV = hepatitis C virus; IVDU = intravenous drug use; NR = not reported; OR = odds ratio; RNA = ribonucleic acid.

Table 10. Trials of Sustained Virologic Response With Direct Acting Antiviral Regimens in Adults

Author year Study name	Treatment Regimen	Primary genotype(s)	Mean age (years)	Proportion female gender	Proportion with cirrhosis	Proportion treatment-naïve	SVR
Chayama 2018[197] CERTAIN-1	Glecapravir + pibrentasvir	1	64	64%	Unclear	73%	99% (128/129)
Poordad 2017[194] MAGELLAN-1	Glecapravir + pibrentasvir	1	58	18%	0%	0%	92% (46/50)
Zeuzem 2018[167] ENDURANCE-1	Glecapravir + pibrentasvir	1	53	51%	0%	62%	99% (663/667)
Kumada 2017[152] (Part 2 only)	Grazoprevir + elbasvir	1	61	62%	0%*	66%	97% (219/227)
Sulkowski 2015[160] C-WORTHY	Grazoprevir + elbasvir	1	51	51%	0%	100%	95% (122/129)
Zeuzem 2015[166] C-EDGE	Grazoprevir + elbasvir	1	52	46%	22%	100%	95% (273/288)
Kowdley 2014a[190] ION-3	Ledipasvir + sofosbuvir	1	53	41%	0%	100%	95% (408/431)
Afdhal 2014[185] ION-1	Ledipasvir + sofosbuvir	1	52	41%	0%*	100%	100% (357/357)
Chuang 2016[145]	Ledipasvir + sofosbuvir	1	55	58%	12%	49%	98% (83/85)
Lawitz 2014b[193] LONESTAR	Ledipasvir + sofosbuvir	1	48	38%	0%	100%	97% (58/60)
Lim 2016[156]	Ledipasvir + sofosbuvir	1	54	61%	9%	100%	100% (46/46)
Wei 2018[163]	Ledipasvir + sofosbuvir	1	47	50%	16%	52%	100% (206/206)
Grebely 2018b[149] D3FEAT	Ombitasvir + paritaprevir + ritonavir + dasabuvir	1	48	23%	0%*	100%	91% (73/80)
Lalezari 2015[192]	Ombitasvir + paritaprevir + ritonavir + dasabuvir	1	48	34%	0%	95%	97% (37/38)
Kwo 2016[153] OPTIMIST-1	Simeprevir + sofosbuvir	1	56	47%	0%	74%	97% (150/155)
Lawitz 2014a[154] COSMOS	Simeprevir + sofosbuvir	1	56	29%	0%	0%	95% (61/64)
Pott-Junior 2019[159]	Simeprevir + sofosbuvir	1	53	48%	0%	60%	93% (56/60)
Pott-Junior 2019[159]	Sofosbuvir + daclatasvir	1	56	52%	0%	60%	100% (65/65)
Sulkowski 2014[161] A1444040 Study	Sofosbuvir + daclatasvir	1	55	50%	13%	100%	98% (80/82)
Everson 2015[146]	Sofosbuvir + velpatasvir	1	49	39%	0%	100%	100% (28/28)
Feld 2015[139] ASTRAL-1	Sofosbuvir + velpatasvir	1	54	40%	0%*	68%	98% (251/255)
Ferenci 2014[188] PEARL IV	Ombitasvir + paritaprevir + ritonavir + dasabuvir	1a	51	35%	0%	100%	92% (282/305)

Table 10. Trials of Sustained Virologic Response With Direct Acting Antiviral Regimens in Adults

Author year Study name	Treatment Regimen	Primary genotype(s)	Mean age (years)	Proportion female gender	Proportion with cirrhosis	Proportion treatment-naïve	SVR
Kowdley 2014b[191] AVIATOR	Ombitasvir + paritaprevir + ritonavir + dasabuvir	1a	50	42%	0%	75%	86% (183/212)
Feld 2014[187] SAPPHIRE-1	Ombitasvir + paritaprevir + ritonavir + dasabuvir	1a	49	43%	Unclear	100%	95% (307/322)
Lawitz 2015[155] PEARL-1	Ombitasvir + paritaprevir + ritonavir	1b	55	51%	0%	51%	93% (76/82)
Andreone 2014[186] PEARL-II	Ombitasvir + paritaprevir + ritonavir + dasabuvir	1b	54	46%	0%	0%	98% (176/179)
Feld, 2014[187] SAPPHIRE-1	Ombitasvir + paritaprevir + ritonavir + dasabuvir	1b	49	43%	Unclear	100%	98% (148/151)
Ferenci 2014[188] PEARL III	Ombitasvir + paritaprevir + ritonavir + dasabuvir	1b	48	54%	0%	100%	99% (416/419)
Kowdley 2014b[191] AVIATOR	Ombitasvir + paritaprevir + ritonavir + dasabuvir	1b	50	47%	0%	68%	100% (113/113)
Kumada 2015[151] GIFT-1	Ombitasvir + paritaprevir + ritonavir	1b	61	63%	0%	65%	94.9% (204/215)
Toyoda 2018[199] CERTAIN-2	Glecapravir + pibrentasvir	2	57	53%	0%	83%	98% (88/90)
Feld 2015[139] ASTRAL-1	Sofosbuvir + velpatasvir	2	54	60%	0%*	68%	100% (93/93)
Foster 2015[147] ASTRAL-2	Sofosbuvir + velpatasvir	2	57	36%	14%	86%	99% (133/134)
Zeuzem 2018[167] ENDURANCE-3	Glecapravir + pibrentasvir	3	47	41%	0%	100%	95% (149/157)
Nelson 2015[157] ALLY-3	Sofosbuvir + daclatasvir	3	55	41%	0%	59%	96% (105/109)
Zeuzem 2018[167] ENDURANCE-3	Sofosbuvir + daclatasvir	3	49	55%	0%	100%	97% (111/115)
Everson 2015[146]	Sofosbuvir + velpatasvir	3	50	37%	0%	100%	93% (25/27)
Foster 2015[147] ASTRAL-3	Sofosbuvir + velpatasvir	3	49	39%	0%*	74%	97% (191/197)
Pianko 2015[158]	Sofosbuvir + velpatasvir	3	55	34%	0%	0%	100% (53/53)
Brown 2018[144] C-SCAPE	Grazoprevir + elbasvir	4	52	58%	0%	100%	90% (9/10)
Zeuzem 2015[166] C-EDGE	Grazoprevir + elbasvir	4	52	46%	20%	100%	100% (18/18)
Abergel 2016a[142]	Ledipasvir + sofosbuvir	4	52	50%	5%	100%	96% (21/22)
Ahmed 2018[195]	Ledipasvir + sofosbuvir	4	51	35%	Unclear	100%	99% (99/100)
Hezode 2015[189] PEARL I	Ombitasvir + paritaprevir + ritonavir + dasabuvir	4	48	29%	0%	46%	100% (91/91)

Table 10. Trials of Sustained Virologic Response With Direct Acting Antiviral Regimens in Adults

Author year Study name	Treatment Regimen	Primary genotype(s)	Mean age (years)	Proportion female gender	Proportion with cirrhosis	Proportion treatment-naïve	SVR
Waked 2016[162] AGATE-II	Ombitasvir + paritaprevir + ritonavir + dasabuvir	4	49	30%	2%	100%	94% (94/100)
Feld 2015[139] ASTRAL-1	Sofosbuvir + velpatasvir	4	54	60%	0%*	68%	100% (89/89)
Asselah 2019[143] ENDURANCE-5	Glecapravir + pibrentasvir	5	68	57%	13%	83%	96% (22/23)
Abergel 2016b[141]	Ledipasvir + sofosbuvir	5	61	48%	14%	100%	95% (20/21)
Feld 2015[139] ASTRAL-1	Sofosbuvir + velpatasvir	5	54	60%	0%*	68%	97% (28/29)
Asselah 2019[143] ENDURANCE-6	Glecapravir + pibrentasvir	6	54	52%	10%	93%	98% (60/61)
Gane 2015[148]	Ledipasvir + sofosbuvir	6	51	36%	Unclear	92%	96% (24/25)
Feld 2015[139] ASTRAL-1	Sofosbuvir + velpatasvir	6	54	60%	0%*	68%	100% (35/35)
Grebely 2018a[150] SIMPLIFY	Sofosbuvir + velpatasvir	1, 3	48	28%	0%*	NR	95% (82/86)
Wei 2019b[165]	Sofosbuvir + velpatasvir	1, 3, 6	45	47%	18%	82%	97% (362/375)
Wei 2019a[164] C-CORAL	Grazoprevir + elbasvir	1, 4	48	56%	19%	100%	94% (459/486)
Sperl 2016[198] C-EDGE	Grazoprevir + elbasvir	1, 4, 6	48	57%	17%	78%	99% (128/129)
Asselah 2018[196] SURVEYOR II Part 4	Glecapravir + pibrentasvir	2, 4-6	52	52%	0%	87%	97% (196/203)
Everson 2015[146]	Sofosbuvir + velpatasvir	2; 4-6	54	32%	0%	100%	95% (21/22)

*Results for subgroup with no cirrhosis.

Abbreviations: NR = not reported; SVR = sustained virologic response. Study names are not acronyms.

Table 11. Sustained Virologic Response in Comparative Trials of Direct Acting Antiviral Regimens in Adults

Comparison	Author year Study name	Treatment Regimen	Primary genotype(s)	Mean age (years)	Proportion female gender	Proportion with cirrhosis	Proportion treatment-naïve	SVR
DAA vs. Placebo	Feld 2015[139] ASTRAL-1	Sofosbuvir + velpatasvir Placebo	Mixed	54	60%	19%	72%	99% (618/624) vs. 0% (0/116); RR 232 (95% CI, 14.6 to 3680)
DAA vs. Telaprevir-containing Regimens	Dore 2016[137] MALACHITE-1	Ombitasvir + paritaprevir + ritonavir + dasabuvir Telaprevir + pegylated interferon + ribavirin	1	46	55%	0%	100%	98% (81/83) vs. 80% (60/75); RR 1.22 (95% CI, 1.08 to 1.37)
	Dore 2016[137] MALACHITE-1	Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin Telaprevir + pegylated interferon + ribavirin	1	46	47%	0%	100%	98% (150/153) vs. 80% (60/75); RR 1.23 (95% CI, 1.09 to 1.38)
	Dore 2016[137] MALACHITE-2	Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin Telaprevir + pegylated interferon + ribavirin	1	47	46%	0%	0%	99% (100/101) vs. 66% (31/47); RR 1.50 (95% CI, 1.22 to 1.85)
DAA vs. Non-recommended DAA	Foster 2015[147] ASTRAL-2	Sofosbuvir + velpatasvir Sofosbuvir + ribavirin	2	57	41%	14%	85%	99% (133/134) vs. 94% (124/132); RR 1.06 (95% CI, 1.01 to 1.11)
	Foster 2015[147] ASTRAL-3	Sofosbuvir + velpatasvir Sofosbuvir + ribavirin	3	49	38%	0%*	74%	97% (191/197) vs. 87% (163/187); RR 1.11 (95% CI, 1.05 to 1.18)

Abbreviations: CI = confidence interval; DAA = direct acting antiviral; SVR = sustained virologic response; RR = relative risk. Study names are not acronyms.

Table 12. Sustained Virologic Response Rates With Direct Acting Antiviral Regimens in Adults by Genotype

Analysis	Number of trials	Pooled sustained virologic response rate (95% CI)	I^2	p for interaction
Genotype 1 infection	32 (in 30 publications)*[137,139,145,146,149,151-156,159-161,163-167,185-188,190-194,197,198]	97.7% (96.6% to 98.4%)	82%	--
• Ledipasvir / sofosbuvir	6[145,156,163,185,190,193]	99.4% (95.2% to 99.9%)	89%	0.005 (regimens)
• Simeprevir / sofosbuvir	3[153,154,159]	95.7% (92.6% to 97.5%)	0%	--
• Sofosbuvir / velpatasvir	3[139,146,165]	99.0% (95.4% to 99.8%)	27%	--
• Sofosbuvir / daclatasvir	2[159,161]	98.6% (94.7% to 99.7%)	45%	--
• Glecaprevir / pibrentasvir	3[167,194,197]	98.6% (94.1% to 99.7%)	78%	--
• Elbasvir / grazoprevir	5[152,160,164,166,198]	96.7% (95.0% to 97.8%)	55%	--
• Ombitasvir / paritaprevir / ritonavir / dasabuvir (genotype 1, not sub-typed)	2[149,192]	93.2% (87.0% to 96.6%)	27%	--
• Ombitasvir / paritaprevir / ritonavir / dasabuvir† (genotype 1a)	5 (in 4 publications)[137,187,188,191]	93.7% (89.0% to 96.5%)	77%	--
• Ombitasvir / paritaprevir / ritonavir / dasabuvir‡ (genotype 1b)	8 (in 7 publications)[137,151,155,186-188,191]	98.2% (96.4% to 99.1%)	68%	--
• Good quality	12* (in 10 publications)[137,139,146,152,159,164,166,187,188,191]	97.2% (95.2% to 98.4%)	82%	0.42 (quality)
• Fair quality	20[145,149,151,153-156,160,161,163,165,167,185,186,190,192-194,197,198]	97.9% (96.7% to 98.7%)	76%	--
• Cirrhosis excluded	22 (in 20 publications)§[137,139,146,149,151-155,159,160,167,185,186,188,190-194]	97.1% (95.7% to 98.1%)	82%	0.22 (cirrhosis)
• Some cirrhosis (<20% of population)	8[145,156,161,163-166,198]	98.7% (97.1% to 99.4%)	38%	--
• U.S. or Canada	8[146,153,154,161,190,192-194]	96.6% (93.1% to 98.4%)	82%	0.48 (geographic setting)
• Multinational	17†[137-139,149,151,155,160,164-167,185-188,191,198]	97.7% (96.4% to 98.6%)	89%	--
• Other geographic setting	7[145,151,152,156,159,163,197]	98.3% (96.1% to 99.2%)	28%	--
Use of ribavirin and/or dasabuvir as recommended‖	26 (in 25 publications)*[137,139,145,146,152-154,156,159-161,163-166,185,187,188,190-193,197,198]	98.3% (97.4% to 98.9%)	60%	--
• Treatment-naïve	24 (in 23 publications)*[137,139,145,146,151-156,159-161,163,164,166,185,187,188,190-193]	97.4% (96.1% to 98.3%)	80%	--
Genotype 2 infection	5[139,147,165,196,199]	98.9% (97.5% to 99.5%)	4%	--
• Sofosbuvir / velpatasvir	3[139,147,165]	99.6% (97.6% to 99.95%)	0%	0.06 (regimens)
• Glecaprevir / pibrentasvir	2[196,199]	97.9% (95.0% to 99.1%)	0%	
• Good quality	1[139]	100% (96.1% to 100%)	--	0.99 (quality)
• Fair quality	4[147,164,196,199]	98.6% (97.0% to 99.4%)	0%	
• Cirrhosis excluded	3[139,196,199]	98.5% (96.4% to 99.4%)	36%	0.37 (cirrhosis)
• Some cirrhosis (<20% of population)	2[147,164]	99.5% (96.5% to 99.9%)	0%	
• U.S. or Canada	1[147]	99.2% (94.9% to 99.9%)	--	0.62 (geographic setting)
• Multinational	3[139,164,196]	99.0% (97.0% to 99.7%)	33%	--
• Other geographic setting	1[199]	97.8% (91.6% to 99.4%)	4%	--
• Treatment-naïve	1[139]	100% (95.4% to 100%)	--	--

Table 12. Sustained Virologic Response Rates With Direct Acting Antiviral Regimens in Adults by Genotype

Analysis	Number of trials	Pooled sustained virologic response rate (95% CI)	I^2	p for interaction
Genotype 3 infection	6[146,147,157,158,165,167]	95.5% (91.6% to 97.7%)	66%	--
• Sofosbuvir / velpatasvir‖	4[146,147,158,165]	95.6% (87.1% to 98.6%)	82%	0.78 (regimens)
• Sofosbuvir / daclatasvir	2[157,167]	96.4% (93.0% to 98.2%)	0%	--
• Glecaprevir / pibrentasvir	1[167]	94.9% (90.2% to 97.8%)	--	
• Good quality	1[146]	93.2% (66.8% to 99.0%)	--	0.66 (quality)
• Fair quality	5[147,157,158,164,167]	95.7% (91.6% to 97.8%)	70%	--
• Cirrhosis excluded	5[146,147,157,158,167]	96.4% (94.6% to 97.5%)	14%	0.01 (cirrhosis)
• Some cirrhosis (<20% of population)	1[165]	85.7% (76.5% to 91.7%)	--	--
• U.S. or Canada	3[146,147,157]	96.3% (91.4% to 98.4%)	0%	0.55 (geographic setting)
• Multinational	3[158,164,167]	94.5% (88.2% to 97.6%)	80%	
• Use of ribavirin as recommended	5[146,147,157,164,167]	95.2% (91.4% to 97.3%)	0%	--
• Treatment-naïve	5 (in 4 publications)[146,147,157,167]	96.1% (94.5% to 97.3%)	14%	--
Genotype 4 infection	10[139,142,144,162,164,166,189,195,196,198]	98.2% (94.7% to 99.4%)	50%	--
• Ledipasvir / sofosbuvir	2[142,195]	98.4% (93.7% to 99.6%)	25%	0.14 (regimens)
• Sofosbuvir / velpatasvir	1[139]	100% (95.9% to 100%)	--	--
• Elbasvir / grazoprevir	4[144,164,166,198]	97.3% (83.2% to 99.6%)	0%	--
• Glecaprevir / pibrentasvir	1[196]	93.5% (82.1% to 98.6%)	--	--
• Ombitasvir / paritaprevir / ritonavir / dasabuvir	2[162,189]	98.7% (72.7% to 99.95%)	88%	--
• Good quality	5[139,162,164,166,189]	99.1% (94.0% to 99.9%)	72%	0.31 (quality)
• Fair quality	5[142,144,195,196,198]	97.0% (89.1% to 99.2%)	--	--
• Cirrhosis excluded	4[139,144,189,196]	98.3% (94.4% to 99.5%)	0%	0.52 (cirrhosis)
• Some cirrhosis (<20% of population)	5[142,162,164,166,198]	96.5% (86.5% to 99.2%)	0%	--
• U.S. or Canada	0	--	--	--
• Europe / Australia / New Zealand	1[142]	96.3% (61.1% to 99.8%)	--	0.67 (geographic setting)
• Multinational	7[139,144,164,166,189,196,198]	98.8% (94.6% to 99.7%)	45%	--
• Other	2[162,195]	97.3% (88.0% to 99.4%)	73%	--
• Treatment-naïve	8[139,142,144,162,164,166,189,195]	98.3% (94.5% to 99.5%)	52%	--
Genotype 5 infection	4[139,141,143,196]	96.0% (88.3% to 98.7%)	0%	--
• Ledipasvir / sofosbuvir	1[141]	95.2% (76.2% to 99.9%)	--	0.99 (regimens)
• Sofosbuvir / velpatasvir	1[139]	96.6% (82.2% to 99.9%)	--	--
• Glecaprevir / pibrentasvir	2[143,196]	96.0% (76.4% to 99.4%)	0%	--
• Good quality	2[139,141]	96.0% (85.4% to 99.0%)	0%	1.00 (quality)
• Fair quality	2[143,196]	96.0% (76.4% to 99.4%)	0%	--
• Cirrhosis excluded	2[139,196]	96.8% (80.4% to 99.6%)	0%	0.79 (cirrhosis)
• Some cirrhosis (<20% of population)	2[141,143]	95.4% (83.6% to 98.9%)	0%	--
• U.S. or Canada	0	--	--	--
• Europe / Australia / New Zealand	1[141]	95.2% (72.9% to 99.3%)	--	0.85 (geographic setting)
• Multinational	3[139,143,196]	96.3% (86.4% to 99.1%)	0%	--

Table 12. Sustained Virologic Response Rates With Direct Acting Antiviral Regimens in Adults by Genotype

Analysis	Number of trials	Pooled sustained virologic response rate (95% CI)	I^2	p for interaction
• Treatment-naïve	2[139,141]	95.6% (83.9% to 98.9%)	0%	--
Genotype 6 infection	5[139,143,148,165,196]	98.2% (95.4% to 99.3%)	0%	
• Ledipasvir / sofosbuvir	1[148]	96.0% (79.6% to 99.9%)	--%	0.37 (regimens)
• Sofosbuvir / velpatasvir	2[139,165]	99.2% (94.9% to 99.9%)	0%	--
• Glecaprevir / pibrentasvir	2[143,196]	97.2% (89.4% to 99.3%)	42%	--
• Good quality	1[139]	100% (90% to 100%)	--	<0.001 (quality)
• Fair quality	4[143,148,164,196]	97.9% (94.6% to 99.2%)	4%	--
• Cirrhosis excluded	2[139,196]	97.8% (85.8% to 99.7%)	63%	0.66 (cirrhosis)
• Some cirrhosis (<20% of population)	2[143,164]	98.7% (95.1% to 99.7%)	0%	--
• Cirrhosis status unclear/not reported	1[148]	96.0% (76.4% to 99.4%)	--	--
• U.S. or Canada	0	--	--	--
• Europe / Australia / New Zealand	1[148]	96.0% (76.4% to 99.4%)	--	0.43 (geographic setting)
• Multinational	4[139,143,165,196]	98.5% (95.5% to 99.5%)	0%	--
• Treatment-naïve	2[139,148]	98.4% (89.6% to 99.8%)	35%	--
Mixed genotype[¶]	2[146,150]	95.4% (89.4% to 98.1%)	0%	--
• Sofosbuvir / velpatasvir	2[146,150]	95.4% (89.4% to 98.1%)	0%	--

*Two trials reported results for genotype 1a and 1b separately (Feld 2014[187], Kowdley 2014b[191]).
†One trial omitted dasabuvir (Kowdley 2014b[191]).
‡Two trials omitted dasabuvir (Kowdley 2014b[191], Lawitz 2015[155]).
§One trial reported results for genotype 1a and 1b separately (Kowdley 2014b[191]).
‖Regimens administered with or without ribavirin.
¶All patients were treatment-naïve.
Abbreviations: CI = confidence interval; U.S. = United States.

Table 13. Sustained Virologic Response Rates With Direct Acting Antiviral Regimens in Adults in Subgroups

Author year Study name	Intervention(s)	Age	Sex/Gender	Race/Ethnicity	Other characteristics
Afdhal 2014[185] ION-1	A. Ledipasvir + sofosbuvir B. Ledipasvir + sofosbuvir + ribavirin	<65 years: 99% (196/197) vs. 100% (189/189) ≥65 years: 100% (15/15) vs. 100% (22/22)	Male gender: 99% (125/126) vs. 100% (124/124) Female gender: 100% (86/86) vs. 100% (87/87)	Black: 100% (24/24) vs. 100% (26/26) Non-Black: 99.5% (187.188) vs. 100% (184/184) Hispanic: 100% (26/26) vs. 100% (19/19)	NR
Andreone 2014[186] PEARL-2	A. Ombitasvir + paritaprevir + ritonavir + dasabuvir B. Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	NR	Male gender: 100% (54/54) vs. 95% (41/43) Female gender: 100% (37/37) vs. 98% (44/45)	Black: 100% (5/5) vs. 100% (3/3) Other: 100% (86/86) vs. 97% (82/85)	NR
Chuang 2016[145]	Ledipasvir + sofosbuvir	<65: 100% (35/35) ≥65: 100% (7/7)	Male gender: 100% (13/13) Female gender: 100% (29/29)	NR	BMI <25: 100% (26/26) ≥25: 100% (16/16)
Feld 2014[187] SAPPHIRE-1	A. Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin B. Placebo followed by open-label ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	<55 years: 97% (280/290) ≥55 years: 96% (175/183)	Male gender: 95% (258/271) Female gender: 98% (197/202)	Black: 96% (27/28) Non-Black: 96% (428/445)	BMI <30: 97% (390/402) ≥30: 92% (65/71) Diabetes Yes: 100% (19/19) No: 96% (436/454)
Feld 2015 ASTRAL-1[139]	Sofosbuvir + velpatasvir	<65 years: 99% (609/615) ≥65 years: 100% (113/113)	Male gender: 99% (426/431) Female gender: 99.7% (296/297)	Black: 98% (64/65) White: 99% (570/575) Other: 100% (84/84)	BMI <30: 99% (568/573) ≥30: 99% (154/155)
Foster 2015[147] ASTRAL-3	A. Sofosbuvir + velpatasvir B. Sofosbuvir + ribavirin	<65 years: 95% (257/270) vs. 81% (210/261) ≥65 years: 100% (7/7) vs. 79% (11/14)	Male gender: 94% (159/170) vs. 76% (132/175) Female gender: 98% (105/107) vs. 88% (89/101)	Black: 100% (3/3) vs. 100% (1/1) White: 95% (238/250) vs. 78% (187/239) Other: 96% (23/24) vs. 94% (32/34)	NR
Grebely 2018a[150] SIMPLIFY	Sofosbuvir + velpatasvir	≤41 years: 93% (26/28) >41 years: 95% (71/75)	Male gender: 92% (68/74) Female gender: 100% (29/29)	NR	No current opioid substitution therapy: 93% (54/58) Current opioid substitution therapy: 96% (43/45)
Grebely 2018b[149] D3FEAT	Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	≤54 years: 89% (59/66) >54 years: 95% (20/21)	Male gender: 91% (61/67) Female gender: 90% (18/20)	NR	No current opioid substitution therapy: 96% (25/26) Current opioid substitution therapy: 89% (54/61)

Table 13. Sustained Virologic Response Rates With Direct Acting Antiviral Regimens in Adults in Subgroups

Author year Study name	Intervention(s)	Age	Sex/Gender	Race/Ethnicity	Other characteristics
Kowdley 2014a[190] ION-3	Ledipasvir + sofosbuvir	8-week intervention group <65 years: 94% (185/196) ≥65 years: 90% (17/19) 12-week intervention group <65 years: 95% (189/199) ≥65 years: 100% (17/17)	8-week intervention group Male: 92% (119/130) Female: 98% (83/85) 12-week intervention group Male gender: 95% (122/128) Female gender: 96% (84/85)	8-week intervention group Black: 91% (41/45) Non-black: 95% (161/170) Hispanic: 100% (13/13) Non-Hispanic: 94% (187/200) 12-week intervention group Black: 95% (40/42) Non-black: 95% (165/173) Hispanic: 93% (13/14) Non-Hispanic: 96% (193/202)	NR
Kowdley 2014b[191] AVIATOR	A. Ombitasvir + paritaprevir + ritonavir + dasabuvir B. Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	NR	NR	Black: 100% (13/13) vs. 100% (13/13) Non-black: 86% (57/66) vs. 96% (63/66)	NR
Kumada 2017[152]	Elbasvir + grazoprevir	<65 years: 99% (122/123) 65-74 years: 93% (70/75) ≥75 years: 93% (27/29)	Male gender: 98% (85/87) Female gender: 96% (134/140)	NR	NR
Lim 2016[156]	Ledipasvir + sofosbuvir	<65 years: 100% (33/33) ≥65 years: 10% (13/13)	NR	NR	NR
Nelson 2015[157] ALLY-3	Daclatasvir + sofosbuvir	<65 years: 90% (128/142) ≥65 years: 70% (7/10)	Male gender: 86% (77/90) Female gender: 94% (58/62)	NR	NR
Sperl 2016[198] C-EDGE H2H	Elbasvir + grazoprevir	≤40 years: 100% (37/37) 41-50 years: 100% (31/31) 51-60 years: 98% (40/41) 61-70 years: 100% (20/20)	Male gender: 100% (55/55) Female gender: 99% (73/74)	NR	NR
Wei 2019a[164] C-CORAL	Elbasvir + grazoprevir	<65 years: 95% (420/444) ≥65 years: 93% (39/42)	Male gender: 96% (207/216) Female gender: 93% (252/270)	Hispanic/Latino: 100% (5/5) Non-Hispanic/Latino: 94% (454/481)	NR
Wei 2019b[165]	Sofosbuvir + velpatasvir	<65 years: 96% (340/353) ≥65 years: 100% (22/22)	Male gender: 94% (186/197) Female gender: 99% (176/178)	NR	NR

Table 13. Sustained Virologic Response Rates With Direct Acting Antiviral Regimens in Adults in Subgroups

Author year Study name	Intervention(s)	Age	Sex/Gender	Race/Ethnicity	Other characteristics
Zeuzem 2015 C-EDGE [166]	Grazoprevir + elbasvir	<65: 94% (270/287) ≥65: 100% (29/29)	Male gender: 93% (159/171) Female gender: 97% (140/145)	Asian: 94% (51/54) Black: 97% (57/59) White: 94% (180/191) Other: 92% (11/12)	NR
Zeuzem 2018[167] ENDURANCE-1	Glecaprevir + pibrentasvir	8-week intervention group <65 years: 99% (306/309) ≥65 years: 100% (42/42) 12-week intervention group <65 years: 99.7% (316/317) ≥65 years: 100% (35/35)	8-week intervention group Male gender: 99% (165/167) Female gender: 99% (183/184) 12-week intervention group Male gender: 100% (176/176) Female gender: 99% (175/176)	8-week intervention group Black race: 100% (14/14) Other race: 99% (334/337) 12-week intervention group Black race: 92% (12/13) Other race: 100% (339/339)	8-week intervention group No current opioid substitution therapy: 99% (336/339) Current opioid substitution therapy: 100% (12/12) 12-week intervention group No current opioid substitution therapy: 100% (336/336) Current opioid substitution therapy: 94% (15/16)
Zeuzem 2018[167] ENDURANCE-3	A. Glecaprevir 300 mg + pibrentasvir 120 mg, 8 weeks B. Glecaprevir 300 mg + pibrentasvir 120 mg, 12 weeks 3. Sofosbuvir 400 mg + daclatasvir 60 mg. 12 weeks	Age <65 years: 95% (144/152) vs. 95% (213/224) vs. 96% (107/111) Age ≥65 years: 100% (5/5) vs. 100% (9/9) vs. 100% (4/4)	Male gender: 93% (86/92) vs. 93% (112/121) vs. 92% (48/52) Female gender: 97% (63/65) vs. 98% (110/112) vs. 100% (63/63)	Black race: 100% (3/3) vs. 100% (4/4) vs. 75% (3/4) Not Black race: 95% (146/154) vs. (218/229) vs. 97% (108/111)	No current opioid substitution therapy: 94% (119/126) vs. 96% (188/195) vs. 96% (94/98) Current opioid substitution therapy: 97% (30/31) vs. 90% (34/38) vs. 100% (17/17)

Abbreviations: BMI = body mass index; CI = confidence interval; NR = not reported. Study names are not acronyms.

Table 14. Sustained Virologic Response Rates With Direct Acting Antiviral Regimens in Adolescents With HCV Infection

Author year Country *Quality*	Population characteristics	Antiviral treatment regimen	SVR, total population	SVR, subgroups
Abdel Ghaffar 2019[201] Egypt *Fair*	n=40 Mean age 12 years 38% female Race NR Fibrosis stage F0: 35%; F1: 38%; F2 and F3: 15% Genotype 4: 100% (mixed 4 and 1a: 13%; mixed 4 and 1b: 15%) Treatment naïve: 100%	Sofosbuvir 200 to 400 mg + daclatasvir 30 to 60 mg	98% (39/40)	NR
Balistreri 2017[175] Multinational *Fair*	n=100 Mean age 15 years 63% female 90% white; 7% black; 2% Asian; 1% NR Fibrosis stage F0-F3: 42%; F4:1%; NR/unknown: 57% Genotype 1a: 81%; 1b: 19% Treatment naïve: 80% Treatment experienced 20% (prior treatment unclear; presumably IFN or pegylated IFN + ribavirin)	Ledipasvir 90 mg + sofosbuvir 400 mg*	98% (98/100)	Treatment-naïve: 98% (78/80) Treatment-experienced: 100% (20/20)
El-Karaksy[202] 2018 Egypt *Fair*	n=40 Mean age 14 years 35% female Race NR Fibrosis stage F0: 55%; F0 and F1: 13%; F1: 13%; F1 and F2: 5%; F3: 10%; F4: 5% Genotype 4: 100% Treatment-naïve: 75%	Ledipasvir 90 mg + sofosbuvir 400 mg*	100% (40/40)	NR
Jonas 2019[171] DORA Multinational *Fair*	n=48 Median age 14 years 55% female 75% white; 9% black; 13% Asian; 4% mixed race Fibrosis stage F0-F1: 96%; F2: 2%; F3: 2% Genotype 1a: 51%; 1b: 28%; 2: 6%; 3: 9%; 4: 6%; no genotype 5 or 6 enrolled HIV coinfection: 4% Treatment-naïve: 77% Treatment-experienced: 23% (pegylated IFN + ribavirin)	Glecaprevir 300 mg + pibrentasvir 120 mg	100% (47/47)	NR
Leung 2018[203] Multinational *Fair*	n=38 Median age 15 years 66% female 76% white; 13% black; 8% Asian; 3% mixed race Fibrosis stage (30/38 patients): F0 and F1: 90%; F2: 3%; F3: 3%; F4: 3% Genotype 1a: 42%; 1b: 40%; 4: 18% Treatment naïve: 66%	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + weight-based ribavirin	100% (38/38)	Genotype 1a: 100% (16/16) Genotype 1b: 100% (15/15) Genotype 4: 100% (7/7) Treatment naïve: 100% (25/25) Treatment experienced: 100% (13/13)

Table 14. Sustained Virologic Response Rates With Direct Acting Antiviral Regimens in Adolescents With HCV Infection

Author year Country *Quality*	Population characteristics	Antiviral treatment regimen	SVR, total population	SVR, subgroups
Wirth 2017[173] Multinational *Fair*	n=52 Median age 15 years 40% female 90% white; 4% black; 2% Asian; 2% Hawaiian/Pacific Islander; 2% other Fibrosis stage NR; 40% no cirrhosis; 60% cirrhosis presence unknown Genotype 2: 25% Genotype 3: 75% Treatment-naive: 83%	Sofosbuvir 400 mg + weight-based ribavirin*	98% (51/52)	Genotype 2: 100% (13/13) Genotype 3: 97% (38/39)
Yakoot 2018[176] Egypt *Good*	n=30 Mean age 13 years 43% female Race NR Fibrosis stage F0: 17%; F1: 53%; F2: 27%; F3: 3% Genotype 4: 100% Treatment naïve: 73%	Sofosbuvir + daclatasvir	97% (29/30)	NR

Abbreviations: IFN = interferon; NR = not reported; SVR = sustained virologic response.

Table 15. Adverse Events With Direct Acting Antiviral Regimens in Adults

Author year	Treatment Regimen(s)	Comparison	Any adverse event	Serious adverse events*	Withdrawal due to adverse events	Headache	Fatigue	Gastrointestinal	Anemia	Insomnia	Rash
Feld 2014[139] SAPPHIRE-1	Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	DAA vs. Placebo	86% (414/473) vs. 73% (116/158); RR 1.19 (95% CI, 1.08 to 1.32)	2% (10/473) vs. 0% (0/158); RR 7.04 (95% CI, 0.42 to 120)	0.6% (3/473) vs. 0.6% (1/158); RR 1.00 (95% CI, 0.10 to 9.56)	33% (156/473) vs. 27% (42/158); RR 1.24 (95% CI, 0.93 to 1.66)	35% (164/473) vs. 28% (45/158); RR 1.22 (95% CI, 0.92 to 1.60)	Nausea: 24% (112/473) vs. 13% (21/158); RR 1.78 (95% CI, 1.16 to 2.74) Diarrhea: 14% (65/473) vs. 7% (11/158); RR 1.97 (95% CI, 1.07 to 3.64)	NR	14% (66/473) vs. 8% (12/158); RR 1.84 (95% CI, 1.02 to 3.31)	11% (51/473) vs. (9/158); RR 1.89 (95% CI, 0.95 to 3.76)
Feld 2015[139] ASTRAL-1	Sofosbuvir + velpatasvir	DAA vs. Placebo	78% (485/624) vs. 77% (89/116); RR 1.01 (95% CI, 0.91 to 1.13)	2% (15/624) vs. 0% (0/116); RR 5.80 (95% CI, 0.35 to 96)	0.2% (1/624) vs. 2% (2/116); RR 0.09 (95% CI, 0.01 to 1.02)	29% (182/624) vs. 28% (33/116); RR 1.03 (95% CI, 0.75 to 1.40)	20% (126/624) vs. 20% (23/116); RR 1.02 (95% CI, 0.68 to 1.52)	Nausea: 12% (75/624) vs. 11% (13/116); RR 1.07 (95% CI, 0.62 to 1.87) Diarrhea: 8% (48/624) vs. 7% (8/116); RR 1.12 (95% CI, 0.54 to 2.30)	NR	8% (50/624) vs. 9% (11/116); RR 0.84 (95% CI, 0.45 to 1.57	NR
Kumada 2015[151] GIFT-1 (Substudy 1)	Ombitasvir + paritaprevir + ritonavir	DAA vs. Placebo	69% (148/215) vs. 57% (60/106); RR 1.22 (95% CI, 1.01 to 1.47)	3% (7/215) vs. 2% (2/106); RR 1.73 (95% CI, 0.36 to 8.16)	0.9% (2/215) vs. 0% (0/106); RR 2.48 (95% CI, 0.12 to 51)	9% (19/215) vs. 9% (10/106); RR 0.94 (95% CI, 0.45 to 1.94)	NR	Nausea: 4% (9/215) vs. 4% (4/106); RR 1.11 (95% CI, 0.35 to 3.52)	NR	NR	NR
Wei 2019a[164] C-CORAL	Elbasvir + grazoprevir	DAA vs. Placebo	47% (230/486) vs. 50% (62/123)	2% (8/486) vs. 2% (2/123)	0.6% (3/486) vs. 2% (2/123)	6% (27/486) vs. 5% (6/123)	5% (22/486) vs. 7% (9/123)	NR	NR	NR	NR

Table 15. Adverse Events With Direct Acting Antiviral Regimens in Adults

Author year	Treatment Regimen(s)	Comparison	Any adverse event	Serious adverse events*	Withdrawal due to adverse events	Headache	Fatigue	Gastrointestinal	Anemia	Insomnia	Rash
Dore 2016[137] MALACHITE-1	Ombitasvir + paritaprevir mg + ritonavir + dasabuvir	DAA vs. telaprevir / pegylated interferon / ribavirin	49% (41/83) vs. 100% (37/37); RR 0.50 (95% CI, 0.40 to 0.62)	0% (0/83) vs. 11% (4/37); RR 0.05 (95% CI, 0.003 to 0.91)	0% (0/83) vs. (3/37); RR 0.07 (95% CI, 0.003 to 1.25)	19% (16/83) 30% (11/37); RR 0.65 (95% CI, 0.33 to 1.26)	5% (4/83) vs. 30% (11/37); RR 0.16 (95% CI, 0.06 to 0.48)	Nausea: 8% (7/83) vs. 41% (15/37); RR 0.21 (95% CI, 0.09 to 0.47)	1% (1/83) vs. 46% (17/37); RR 0.03 (95% CI, 0.004 to 0.19)	NR	0% (0/83) vs. (8/37); RR 0.03 (95% CI, 0.002 to 0.45)
Dore 2016[137] MALACHITE-1	Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	DAA vs. telaprevir / pegylated interferon / ribavirin	75% (115/153) 97% vs. (37/38); RR 0.77 (95% CI, 0.69 to 0.86)	0.7% (1/153) vs. (5/38); RR 0.05 (95% CI, 0.01 to 0.41)	1% (1/153) vs. (3/38); RR 0.08 (95% CI, 0.01 to 0.75)	27% (41/153) vs. 32% (12/38); RR 0.85 (95% CI, 0.50 to 1.45)	14% (21/153) vs. 32% (12/38); RR 0.43 (95% CI, 0.24 to 0.80)	Nausea: 21% (32/153) vs. 39% (15/38); RR 0.53 (95% CI, 0.32 to 0.87)	7% (10/153) vs. 45% (17/38); RR 0.15 (95% CI, 0.07 to 0.29)	NR	8% (12/153) vs. (9/38); RR 0.33 (95% CI, 0.15 to 0.73)
Dore 2016[137] MALACHITE-2	Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	DAA vs. telaprevir / pegylated interferon / ribavirin	62% (63/101) vs. (43/47); RR 0.68 (95% CI, 0.57 to 0.81)	1% (1/101) vs. (2/47); RR 0.23 (95% CI, 0.02 to 2.50)	0% (0/101) vs. 11% (5/47); RR 0.04 (95% CI, 0.002 to 0.76)	29% (29/101) vs. 45% (21/47); RR 0.64 (95% CI, 0.41 to 1.00)	12% (12/101) vs. 25% (12/47); RR 0.47 (95% CI, 0.23 to 0.96)	Nausea: 10% (10/101) vs. 43% (20/47); RR 0.23 (95% CI, 0.12 to 0.46)	3% (3/101) vs. 34% (16/47); RR 0.09 (95% CI, 0.03 to 0.38)	6% (6/101) vs. 21% (10/47); RR 0.28 (95% CI, 0.11 to 0.72)	3% (3/101) vs. (8/47); RR 0.17 (95% CI, 0.05 to 0.63)
Abergel 2016a[142]	Ledipasvir + sofosbuvir	NA	71% (31/44)	0% (0/44)	0% (0/44)	25% (11/44)	20% (9/44)	Nausea: 9% (4/44) Diarrhea: 9% (4/44)	NR	NR	NR
Abergel 2016b[141]	Ledipasvir + sofosbuvir	NA	80% (33/41)	2% (1/41)	0% (0/41)	27% (11/41)	10% (4/41)	Diarrhea: 7% (3/41)	NR	NR	NR
Afdhal 2014[185] ION-1	Ledipasvir + sofosbuvir	NA	79% (169/214)	0.5% (1/214)	0% (0/214)	25% (53/214)	21% (44/214)	Nausea: 11% (24/214) Diarrhea: 11% (24/214)	0%	8% (17/214)	7% (16/214)
Ahmed 2018[195] Egypt	Ledipasvir + sofosbuvir	NA	26% (26/100)	NR	NR	2% (2/100)	18% (18/100)	Diarrhea: 1% (1/100)	NR	2% (2/100)	NR

Table 15. Adverse Events With Direct Acting Antiviral Regimens in Adults

Author year	Treatment Regimen(s)	Comparison	Any adverse event	Serious adverse events*	Withdrawal due to adverse events	Headache	Fatigue	Gastrointestinal	Anemia	Insomnia	Rash
Andreone 2014[186] PEARL II	Ombitasvir + paritaprevir + ritonavir + dasabuvir	NA	77.9% (74/95)	3% (3/95)	0% (0/95)	23% (22/95)	16% (15/95)	Nausea: 6% (6/95) Diarrhea: 13% (12/95)	0% (0/95)	NR	1% (1/95)
Asselah 2018[196] SURVEYOR	Glecaprevir + pibrentasvir	NA	63% (128/203)	1% (2/203)	0% (0/203)	18% (37/203)	14% (28/203)	Nausea: 11% (23/203)	NR	NR	NR
Asselah 2019[143] ENDURANCE 5 and 6	Glecaprevir + pibrentasvir	NA	55% (46/84)	6% (5/84)	0% (0/84)	13% (11/84)	13% (11/84)	NR	NR	NR	NR
Brown 2018[144] C-SCAPE	Elbasvir + grazoprevir	NA	79% (15/19)	0% (0/19)	5% (1/19)	26% (5/19)	16% (3/19)	Nausea: 5% (1/19)	NR	NR	NR
Chayama 2018[197]	Glecaprevir + pibrentasvir	NA	57% (74/129)	0% (0/129)	0% (0/129)	5% (6/129)	NR	NR	NR	NR	2% (3/129)
Chuang 2016[145]	Ledipasvir + sofosbuvir	NA	60% (51/60)	NR	1% (1/85)	14% (12/85)	9% (8/85)	Nausea: 6% (5/85)	NR	NR	NR
Everson 2015[146] (Part A)	Sofosbuvir + velpatasvir	NA	70% (54/77)	1% (1/77)	0% (0/77)	18% (14/77)	18% (14/77)	Nausea: 10% (8/77) Diarrhea: 9% (7/77)	NR	6% (5/77)	5% (4/77)
Ferenci 2014[188] PEARL III	Ombitasvir + paritaprevir + ritonavir + dasabuvir	NA	67% (140/209)	2% (4/209)	0% (0/209)	23% (49/209)	23% (48/209)	Nausea: 4% (9/209) Diarrhea: 6% (13/209)	NR	NR	3% (8/209)
Ferenci 2014[188] PEARL IV	Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	NA	92% (92/100)	3.0% (3/100)	0% (0/100)	25% (25/100)	46% (46/100)	Nausea: 21% (21/100) Diarrhea: 14% (14/100)	NR	NR	5% (5/100)
Foster 2015[147] ASTRAL-2 and ASTRAL-3	Sofosbuvir + velpatasvir	NA	82% (337/411)	2% (7/411)	0.2% (1/411)	28% (114/411)	22% (91/411)	Nausea: 15% (60/411)	NR	9% (37/411)	NR

Table 15. Adverse Events With Direct Acting Antiviral Regimens in Adults

Author year	Treatment Regimen(s)	Comparison	Any adverse event	Serious adverse events*	Withdrawal due to adverse events	Headache	Fatigue	Gastrointestinal	Anemia	Insomnia	Rash
Gane 2015[148]	Ledipasvir + sofosbuvir	NA	92% (46/50)	10% (5/50)	2% (1/50)	24% (12/50)	22% (11/50)	Nausea: 18% (9/50) Diarrhea: 12% (6/50) Vomiting: 6% (3/50)	NR	NR	NR
Grebely 2018a[150] SIMPLIFY	Sofosbuvir + velpatasvir	NA	83% (85/103)	7% (7/103)	1% (1/103)	18% (19/103)	22% (23/103)	Nausea: 14% (14/103) Vomiting: 4% (4/103) Diarrhea: 4% (4/103)	NR	9% (9/103)	NR
Grebely 2018b[149] D3FEAT	Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	NA	61% (53/87)	6% (5/87)	0% (0/87)	5% (12/87)	10% (25/87)	Nausea: 8% (20/87) Vomiting: 4% (11/87)	5% (12/87)	4% (11/87)	NR
Hezode 2015[189] PEARL I	Ombitasvir + paritaprevir + ritonavir + ribavirin	NA	88% (80/91)	0%	0% (0/87)	31% (28/91)	15% (14/91)	Nausea: 14% (13/91) Diarrhea: 11% (9/81)	NR	13% (12/91)	NR
Kowdley 2014b[191] AVIATOR	Ombitasvir + paritaprevir + ritonavir + dasabuvir	NA	NR	3% (2/79)	0% (0/79)	19% (15/79)	20% (16/79)	Nausea: 3% (2/79) Diarrhea: 16% (13/79)	9% (7/79)	NR	NR
Kowdley 2014b[191] AVIATOR	Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	NA	NR	1% (1/79)	3% (2/79)	27% (21/79)	28% (22/79)	Nausea: % 1% (1/79) Diarrhea: 13% (10/79)	9% (7/79)	NR	NR

Table 15. Adverse Events With Direct Acting Antiviral Regimens in Adults

Author year	Treatment Regimen(s)	Comparison	Any adverse event	Serious adverse events*	Withdrawal due to adverse events	Headache	Fatigue	Gastrointestinal	Anemia	Insomnia	Rash
Kowdley 2014a[190] ION-3	Ledipasvir + sofosbuvir	NA	67% (355/431)	2% (9/431)	0.5% (2/431)	15% (63/431)	22% (94/431)	Nausea: 9% (39/431) Diarrhea: 6% (24/431)	0.7% (3/431)	6% (26/431)	1% (3/215)
Kumada 2015[151]	Ombitasvir + paritaprevir + ritonavir	NA	69% (148/215)	3% (7/215)	0.9% (2/215)	9% (19/215)	NR	Nausea: 4% (9/215)	NR	NR	NR
Kumada 2017[152] (Part 2 only)	Elbasvir + grazoprevir	NA	96% (219/227)	5% (11/227)	1% (3/227)	NR	NR	NR	NR	NR	NR
Kwo 2016[153] OPTIMIST-1	Simeprevir + sofosbuvir	NA	66% (103/155)	1% (1/155)	0% (0/155)	14% (22/155)	12% (19/155)	15% (23/155)	NR	NR	6% (10/155)
Lalezari 2015[192]	Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	NA	92% (35/38)	8% (3/38)	3% (1/38)	32% (12/38)	47% (18/38)	Nausea: 50% (19/38) Vomiting: 11% (4/38)	11% (4/38)	19% (7/38)	16% (6/38)
Lawitz 2014a[154] COSMOS	Simeprevir + sofosbuvir	NA	79% (11/14)	0% (0/14)	0% (0/14)	NR	NR	NR	0% (0/14)	NR	7% (1/14)
Lawitz 2014b[193] LONESTAR	Ledipasvir + sofosbuvir	NA	45% (17/39)	3% (1/39)	0% (0/39)	5% (2/39)	NR	Nausea: 8% (3/39)	NR	NR	3% (1/39)
Lawitz 2015[155] PEARL 1	Ombitasvir + paritaprevir + ritonavir	NA	93% (76/82)	2% (2/82)	0% (0/82)	29% (24/82)	7% (6/82)	Nausea: 10% (8/82) Diarrhea: 7% (6/82)	NR	NR	NR
Lim 2016[156]	Ledipasvir + sofosbuvir	NA	49% (46/93)	3% (3/93)	1% (1/93)	8% (7/93)	8% (7/93)	NR	NR	NR	NR
Nelson 2015[157] ALLY-3	Sofosbuvir + daclatasvir	NA	NR	0.7% (1/152)	NR	20% (30/152)	19% (29/152)	Nausea: 12% (18/152) Diarrhea: 9% (13/152)	NR	6% (9/152)	NR
Poordad 2017[194] MAGELLAN-1	Glecapravir + pibrentasvir	NA	82% (23/28)	4% (1/28)	0% (0/28)	32% (9/28)	18% (5/28)	Nausea: 18% (5/28)	NR	0% (0/28)	NR
Pott-Junior 2019[159] Group A	Sofosbuvir + daclatasvir	NA	NR	NR	NR	15% (10/65)	23% (15/65)	Nausea: 6% (4/65) Vomiting: 2% (1/65)	NR	6% (4/65)	2% (1/65)

Table 15. Adverse Events With Direct Acting Antiviral Regimens in Adults

Author year	Treatment Regimen(s)	Comparison	Any adverse event	Serious adverse events*	Withdrawal due to adverse events	Headache	Fatigue	Gastrointestinal	Anemia	Insomnia	Rash
Pott-Junior 2019[159] Group B	Simeprevir + sofosbuvir	NA	NR	NR	NR	28% (17/60)	28% (17/60)	Nausea: 13% (8/60) Vomiting: 5% (3/60)	NR	10% (6/60)	10% (6/60)
Sperl 2016[198] C-EDGE Head-2-Head	Elbasvir + grazoprevir	NA	52% (67/129)	0.8% (1/129)	0.8% (1/129)	NR	NR	NR	NR	NR	NR
Sulkowski 2014[161] A1444040 Study	Sofosbuvir + daclatasvir	NA	93% (38/41)	2% (1/41)	0% (0/141)	34% (14/41)	39% (16/41)	Nausea: 20% (8/41) Vomiting: 2% (1/41) Diarrhea: 5% (2/41)	NR	10% (4/41)	NR
Sulkowski 2015[160] C-WORTHY	Elbasvir + grazoprevir	NA	56% (24/43; drug-related adverse events)	0% (0/44)	0% (0/44)	35% (15/43)	23% (10/43)	Nausea: 16% (7/43) Diarrhea: 12% (5/43)	NR	NR	NR
Toyoda 2018[199] CERTAIN-2	Glecaprevir + pibrentasvir	NA	48% (43/90)	2% (2/90)	1% (1/90)	7% (6/90)	NR	Nausea: 3% (3/90)	0% (0/90)	NR	NR
Waked 2016[162] AGATE-II	Ombitasvir + paritaprevir + ritonavir + ribavirin	NA	80% (80/100)	2% (2/100)	0% (0/100)	41% (41/100)	35% (35/100)	Dyspepsia: 17% (17/100)	NR	9% (9/100)	NR
Wei 2018[163]	Ledipasvir + sofosbuvir	NA	58% (120/206)	1% (3/206)	0% (0/206)	NR	NR	NR	NR	NR	NR
Wei 2019b[165]	Sofosbuvir + velpatasvir	NA	50% (189/375)	1% (3/375)	0% (0/375)	5% (18/375)	NR	NR	NR	NR	NR
Zeuzem 2015[166] C-EDGE	Elbasvir + grazoprevir	NA	71% (175/246)	3% (7/246)	0.8% (2/246)	NR	NR	NR	NR	NR	NR
Zeuzem 2018[167] ENDURANCE-1	Glecaprevir + pibrentasvir	NA	64% (450/703)	1% (9/703)	0.1% (1/703)	18% (130/703)	11% (74/703)	Nausea: 7% (48/703)	NR	NR	NR
Zeuzem 2018[167] ENDURANCE-3 (Glecaprevir + pibrentasvir arm)	Glecaprevir + pibrentasvir	NA	71% (275/390)	2% (8/390)	0.8% (3/390)	23% (91/390)	16% (64/390)	Nausea: 13% (51/390)	NR	NR	NR

Table 15. Adverse Events With Direct Acting Antiviral Regimens in Adults

Author year	Treatment Regimen(s)	Comparison	Any adverse event	Serious adverse events*	Withdrawal due to adverse events	Headache	Fatigue	Gastrointestinal	Anemia	Insomnia	Rash
Zeuzem 2018[167] ENDURANCE-3 (Sofosbuvir + daclatasvir arm)	Sofosbuvir + daclatasvir	NA	70% (80/115)	2% (2/115)	0.9% (1/115)	20% (23/115)	14% (16/115)	Nausea: 13% (15/115)	NR	NR	NR

*Serious adverse events listed in Appendix B Table 12

Abbreviations: CI = confidence interval; DAA = direct acting antiviral; NA = not applicable; NR = not reported; RR = relative risk. Study names are not acronyms.

Table 16. Pooled Rates With Direct Acting Antiviral Regimens in Adults for Any Adverse Event, Serious Adverse Events, and Withdrawals Due to Adverse Events

Analysis	Any adverse event: Pooled rate (95% CI); I^2; number of studies (k)	Serious adverse events: Pooled rate (95% CI); I^2; number of studies (k)	Withdrawal due to adverse event: Pooled rate (95% CI): I^2; number of studies (k)
All studies	73.3% (68.0% to 78.1%); I^2=95%; k=44[137,139,141-156,159-167,185-190,192-199]	1.9% (1.5% to 2.4%); I^2=33%; k=44[137,139,141-144,146-157,160-167,185-194,196-199]	0.4% (0.3% to 0.6%); I^2=0%; k=44[137,139,141-156,160,161,163-167,185-194,196-199]
• Ledipasvir / sofosbuvir	69.4% (54.8% to 80.9%); I^2=95%; k=10[141,142,145,148,156,163,185,190,193,195]	2.0% (1.0% to 3.9%); I^2=47%; k=8[141,142,148,156,163,185,190,193]	0.4% (0.2% to 1.0%); I^2=0%; k=9[141,142,145,148,156,163,185,190,193]
• Simeprevir / sofosbuvir	67.5% (60.0% to 74.1%); I^2=0%; k=2[153,156]	0.6% (0.1% to 4.1%); I^2=0%; k=2[153,156]	0% (0% to 21.6%); I^2=0%; k=2*[153,156]
• Sofosbuvir / daclatasvir	82.7% (58.5% to 94.2%); I^2=90%; k=2[161,167]	1.3% (0.5% to 3.4%); I^2=0%; k=3[157,161,167]	0.6% (0.1% to 4.4%); I^2=0%; k=2[161,167]
• Sofosbuvir / velpatasvir	74.6% (63.5% to 83.2%); I^2=96%; k=6[139,146,147,150,165]	1.9% (0.1% to 4.1%); I^2=57%; k=6[139,146,147,150,165]	0.2% (0.1% to 0.6%); I^2=0%; k=6[139,146,147,150,165]
• Glecaprevir / pibrentasvir	62.3% (56.1% to 68.1%); I^2=78%; k=7[143,167,194,196,197,199]	1.7% (1.0% to 2.8%); I^2=51%; k=7[143,167,194,196,197,199]	0.3% (0.1% to 0.9%); I^2=0%; k=7[143,167,194,196,197,199]
• Elbasvir / grazoprevir	79.1% (50.0% to 86.8%); I^2=98%; k=6[144,152,160,164,166,198]	2.1% (1.1% to 3.9%); I^2=42%; k=6[144,152,160,164,166,198]	0.9% (0.5% to 1.6%); I^2=0%; k=6[144,152,160,164,166,198]
• Ombitasvir / paritaprevir / ritonavir / dasabuvir	75.1% (62.3% to 84.6%); I^2=92%; k=6[137,151,155,186,188]	1.9% (1.2% to 3.2%); I^2=31%; k=7[137,151,155,186,188,191]	0.1% (0% to 4.0%); I^2=0%; k=7[137,151,155,186,188,191]
• Ombitasvir / paritaprevir / ritonavir / dasabuvir/ ribavirin	81.1% (74.2% to 86.5%); I^2=87%; k=10[137,149,162,186-189,192]	2.1% (1.5% to 3.0%); I^2=26%; k=11[137,149,162,186-189,191,192]	0.6% (0.3% to 1.1%); I^2=11%; k=11[137,149,162,186-189,191,192]
• Patients with cirrhosis excluded	75.5% (69.0% to 81.1%); I^2=94%; k=24[137,144,146,151-155,160,167,186-190,192-194,196,197,199]	1.8% (1.3% to 2.5%); I^2=22%; k=23[144,146,151-154,160,167,186-194,196,197,199]	0.5% (0.3% to 0.7%); I^2=14%; k=23[144,146,151-155,160,167,186-194,196,197,199]
• Some patients (<20% of sample) with cirrhosis	72.4% (64.6% to 79.0%); I^2=95%; k=19[139,141-143,145,147-150,156,161-166,185,198]	2.0% (1.4% to 2.7%); I^2=51%; k=21[137,139,141-143,147-150,156,157,161-166,185,198]	0.3% (0.2% to 0.6%); I^2=0%; k=21[137,139,141,143,145,147-150,156,161,162,164-166,185,198]
• Treatment-naïve	74.0% (66.6% to 80.2%); I^2=95%; k=23[137,141,142,144-146,148,149,156,160-162,164,166,167,185,187-190,193,195]	1.8% (1.4% to 2.4%); I^2=16%; k=24[137,141,142,144,146,148,149,156,157,160-162,164,166,167,185,187-191,193]	0.5% (0.3% to 0.8%); I^2=0%; k=23[137,141,142,144-146,148,149,156,160-162,164,166,167,185,187-191,193]
• Treatment-experienced	76.6% (61.5% to 87.0%); I^2=72%; k=5[137,154,186,189,194]	1.7% (0.7% to 4.0%); I^2=0%; k=5[137,154,186,189,194]	0.5% (0.1% to 2.1%); I^2=0%; k=5*[137,154,186,189,194]
• Mixed treatment-naïve and experienced	71.0% (62.0% to 78.6%); I^2=96.0%; k=17[139,143,147,148,151-153,155,163,165,192,196-199]	1.9% (1.4% to 2.6%); I^2=51%; k=17[139,143,147,148,151-153,155,163,165,192,196-199]	0.3% (0.2% to 0.5%); I^2=8%; k=17[139,143,147,148,151-153,155,163,165,167,192,196-199]

*No events reported

Abbreviation: CI = confidence interval.

Table 17. Pooled Rates With Direct Acting Antiviral Regimens in Adults for Anemia, Fatigue, Headache, and Insomnia

Analysis	Anemia: Pooled rate (95% CI); I^2; number of studies (k)	Fatigue: Pooled rate (95% CI); I^2; number of studies (k)	Headache: Pooled rate (95% CI): I^2; number of studies (k)	Insomnia: Pooled rate (95% CI); I^2; number of studies (k)
All studies	2.4% (0.9% to 6.3%); I^2=85%; k=13[137,149,154,185,186,190-192,199]	18.4% (15.6% to 21.7%); I^2=90%; k=37[137,139,141-150,153,155-157,159-162,164,167,185-192,194-196]	18.7% (15.6% to 22.2%); I^2=90%; k=42[137,139,141-151,153,155-157,159-162,164,165,167,185-197,199]	8.1% (6.7% to 9.9%); I^2=60%; k=18[139,146,147,149,150,157,159-162,185,187,189,190,192,194,195]
• Ledipasvir / sofosbuvir	0.5% (0.2% to 1.4%); I^2=44%; k=2[185,190]	16.2% (12.2% to 21.0%); I^2=67%; k=8[141,142,145,148,156,185,190,195]	13.7% (8.4% to 21.5%); I^2=85%; k=9[141,142,145,148,156,185,190,193,195]	6.0% (4.5% to 8.0%); I^2=58%; k=3[185,190,195]
• Simeprevir / sofosbuvir	0% (0% to 23.2%); k=1*[154]	18.4% (9.8% to 31.8%; I^2=86%); k=2[153,159]	19.5% (11.7% to 30.8%); I^2=81%; k=2[153,159]	10.0% (3.8% to 20.5%); k=1[159]
• Sofosbuvir / velpatasvir	--	20.8% (17.9% to 24.0%); I^2=44%; k=5[139,146,147,150]	18.0% (10.8% to 28.5%); I^2=96%; k=6[139,146,147,150,165]	8.3% (6.7% to 10.2%); I^2=32%; k=5[139,146,147,150]
• Sofosbuvir / daclatasvir	--	21.7% (14.9% to 30.7%); I^2=72%; k=4[157,159,160,167]	20.6% (16.8% to 25.1%); I^2=41%; k=4[157,159,161,167]	6.6% (4.1% to 10.3%); I^2=0%; k=3[157,159,161]
• Glecaprevir / pibrentasvir	0% (0% to 4.0%); k=1[199]	13.3% (10.8% to 16.3%; I^2=54%); k=5[143,167,194,196]	14.7% (9.4% to 22.2%) I^2=87%; k=7[143,167,194,196,197,199]	0% (0% to 12.3%); k=1[194]
• Elbasvir / grazoprevir	--	10.9% (4.3% to 25.1%; I^2=88%); k=3[144,160,164]	17.1% (6.1% to 39.5%) I^2=94%; k=3[144,160,164]	7.0% (2.3% to 19.5%); k=1[160]
• Ombitasvir / paritaprevir / ritonavir / dasabuvir	0.8% (0.2% to 3.1%); I^2=0%%; k=3[137,186,191]	15.8% (9.1% to 26.1%); 91%; k=6[137,155,186,188,191]	20.7% (15.6% to 26.9%); I^2=83%; k=7[137,151,155,186,188,191]	--
• Ombitasvir / paritaprevir / ritonavir / dasabuvir / ribavirin	8.3% (5.8% to 11.8%); I^2=49%; k=6[137,149,186,191,192]	26.9% (20.5% to 34.4%); I^2=88%; k=11[137,149,162,186-189,191,192]	27.7% (24.0% to 31.6%); I^2=62%; k=11[137,149,162,187-189,191,192]	12.2% (9.4% to 15.7%); I^2=37%; k=6[137,149,162,187,189,192]
• Patients with cirrhosis excluded	2.2% (0.6% to 7.3%); I^2=81%; k=6[154,186,190-192,199]	20.2% (16.0% to 25.3%); I^2=92%; k=18[144,146,153,155,159,160,167,186-192,194,196]	19.6% (15.6% to 24.4%); I^2=87%; k=22[144,146,151,153,155,159,160,167,186-194,196,197,199]	8.9% (7.0% to 11.4%); I^2=70%; k=10[146,157,159,161,162,187,189,190,192,194]
• Some cirrhosis (≤20%)	2.9% (0.7% to 11.0%); I^2=92%; k=4[137,149,185]	16.7% (13.1% to 21.2%); I^2=90%; k=18[137,139,141-143,145,147-150,156,157,161,162,164,185]	19.1% (14.9% to 24.1%); I^2=94%; k=19[137,139,141-143,145,147-150,156,157,161,162,164,165,185]	8.2% (6.3% to 10.5%); I^2=16%; k=8[139,147,149,150,160,185,194]
• Treatment-naïve	2.2% (0.7% to 6.7%); I^2=90%; k=6[137,149,185,190,191]	18.1% (14.5% to 22.2%); I^2=92%; k=24[141,142,144-146,148,149,156,157,160-162,164,167,185,187-191,195]	21.1% (16.8% to 26.2%); I^2=92%; k=24[137,141,142,144-146,148,149,156,157,160,162,164,167,185,187-191,193,195]	8.0% (5.9% to 10.7%); I^2=71.5%; k=9[146,149,160,162,185,187,189,190,195]
• Treatment-experienced	3.6% (0.8% to 14.5%); I^2=0%; k=3[137,154,186]	23.2% (14.7% to 34.6%); I^2=51%; k=4[137,186,189,194]	23.5% (14.4% to 35.8%); I^2=0%; k=4[137,186,189,194]	8.1% (4.6% to 13.7%); I^2=66%; k=4[137,161,189,194]
• Mixed treatment-naïve and experienced	2.1% (0.2% to 18.1%); I^2=89%; k=2[192,199]	17.6% (12.8% to 23.7%) I^2=87%; k=11[139,143,147,148,153,155,159,164,192,196]	14.5% (10.6% to 19.5%); I^2=93%; k=15[139,143,147,148,151,153,155,159,167,192,196,197,199]	8.3% (5.9% to 11.4%); I^2=53%; k=6[139,147,157,159,192]

Abbreviation: CI = confidence interval.
*No events reported

Table 18. Pooled Rates With Direct Acting Antiviral Regimens in Adults for Nausea, Diarrhea, Vomiting, and Rash

Analysis	Nausea: Pooled rate (95% CI); I^2; number of studies (k)	Diarrhea: Pooled rate (95% CI); I^2; number of studies (k)	Vomiting: Pooled rate (95% CI); I^2; number of studies (k)	Rash: Pooled rate (95% CI): I^2; number of studies (k)
All studies	11.1% (9.1% to 13.5%); I^2=82%; k=36[137,139,142,144-151,153,157,159-162,167,185,186,188-196,199]	8.9% (7.0% to 10.8%); I^2=69%; k=19[139,141,142,146,148,150,155,157,160,161,185-191,195]	5.8% (3.4% to 9.7%); I^2=43%; k=6[148-150,159,161,192]	5.4% (4.1% to 7.1%); I^2=70%, k=17[137,146,153,154,158-160,185-188,190,192,193,197]
• Ledipasvir / sofosbuvir	8.4% (5.7% to 12.1%); I^2=60%; k=7[142,145,148,185,190,193,195]	6.8% (4.2% to 10.9%); I^2=72%; k=6[141,142,148,185,190,195]	6.0% (1.9% to 17.0%); k=1[148]	3.3% (1.8% to 8.8%); I^2=80%; k=3[185,190,193]
• Simeprevir / sofosbuvir	14.4% (10.3% to 19.8%); I^2=0%; k=2[153,159]	--	5.0% (1.6% to 14.4%); k=1[159]	7.4% (4.7% to 11.6%); I^2=0%; k=3[153,154,159]
• Sofosbuvir / daclatasvir	12.1% (9.1% to 15.8%); I^2=32%; k=4[157,159,161,167]	7.8% (4.7% to 12.5%); I^2=0%; k=2[157,161]	1.9% (0.5% to 7.2%); I^2=0%; k=2[159,161]	1.5% (0.2% to 10.1%); k=1[159]
• Sofosbuvir / velpatasvir	12.9% (11.0% to 15.0%); I^2=13%; k=5[139,146,147,150]	7.3% (5.7% to 9.4%); I^2=17%; k=3[139,146,150]	3.9% (1.5% to 9.9%); k=1[150]	8.3% (4.9% to 13.7%); I^2=45%; k=2[146,158]
• Glecaprevir / pibrentasvir	9.3% (6.4% to 13.4%); I^2=79%; k=5[167,194,196,199]	--	--	2.3% (0.5% to 6.6%); k=1[197]
• Elbasvir / grazoprevir	12.9% (6.6% to 23.7%); I^2=19%; k=2[144,160]	11.6% (4.9% to 25.0%); k=1[160]	--	4.7% (1.2% to 16.8%); k=1[160]
• Ombitasvir / paritaprevir / ritonavir / dasabuvir	6.5% (4.3% to 9.7%); I^2=70%; k=7[137,151,155,186,188,191]	11.1% (7.7% to 15.9%); I^2=72%; k=5[155,186,188,191]	--	2.6% (1.0% to 6.7%); I^2=66%; k=4[137,186,188]
• Ombitasvir / paritaprevir / ritonavir / dasabuvir/ ribavirin	15.2% (9.6% to 23.2%); I^2=90%; k=11[137,149,162,186-189,191,192]	10.9% (7.8% to 14.9%); I^2=73%; k=6[186-189,191]	12.0% (7.4% to 18.9%); I^2=0%; k=2[149,192]	7.6% (5.5% to 10.3%); I^2=57%; k=7[137,186-188,192]
• Patients with cirrhosis excluded	10.6% (8.2% to 13.5%); I^2=89%; k=21[144,146,151,153,155,160,167,186-194,196,199]	10.1% (7.9% to 12.8%); I^2=80%; k=10[146,155,160,186-191]	5.2% (2.1% to 12.4%); I^2=65%; k=2[159,192]	5.2% (3.8% to 7.0%); I^2=68%; k=13[146,153,154,159,160,186-188,190,192,193,197]
• Some patients (<20% of sample) with cirrhosis	12.9% (9.6% to 17.1%); I^2=43%; k=14[137,139,142,145,147-150,157,161,162,185]	8.0% (5.8% to 10.9%); I^2=0.8%; k=8[139,141,142,148,150,157,161,185]	6.1% (3.2% to 11.4%); I^2=51%; k=4[148-150,161]	6.2% (3.7% to 10.1%); I^2=49%; k=4[137,158,185]
• Treatment-naïve	11.8% (9.0% to 15.2%); I^2=86%; k=22[137,142,144-146,148,149,157,160-162,167,185,187-191,193,195]	9.0% (7.0% to 11.3%); I^2=77%; k=15[141,142,146,148,157,160,161,185,187-191,195]	9.6% (5.3% to 16.8%); I^2=51%; k=3[148,149,161]	5.2% (3.6% to 7.3%); I^2=74%; k=9[137,146,154,160,185,187,188,190]
• Treatment-experienced	12.2% (7.2% to 20.1%); I^2=0%; k=4[137,186,189,194]	10.2% (5.3% to 18.7%); I^2=0%; k=2[186,189]	--	4.8% (2.8% to 8.2%); I^2=50%; k=5[137,154,158,186,197]
• Mixed treatment-naïve and experienced	9.6% (6.6% to 13.6%); I^2=86%; k=12[139,147,148,151,153,155,159,167,192,196,199]	8.60% (5.0% to 14.6%); I^2=4.8%; k=3[139,148,155]	4.2% (2.1% to 8.6%); I^2=54%; k=3[148,159,192]	7.6% (4.2% to 13.6%); I^2=47%; k=3[153,159,192]

Abbreviation: CI = confidence interval.

Table 19. Adverse Events With Direct Acting Antiviral Regimens in Adolescents

Author, year Country *Quality*	Antiviral treatment regimen	Any adverse event	Serious adverse events	Withdrawal due to adverse events	Headache	Fatigue	Gastrointestinal	Insomnia
Abdel Ghaffar 2019[201] Egypt *Fair*	Sofosbuvir 200-400 mg + daclatasvir 30-60 mg	NR	NR	NR	3% (1/40)	5% (2/40)	Vomiting: 3% (1/40)	NR
Balistreri 2017[175] Multinational *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg*	71% (71/100)	0% (0/100)	0% (0/100)	27% (27/100)	13% (13/100)	Nausea: 11% (11/100) Vomiting: 11% (11/100)	NR
El-Karaksy 2018[202] Egypt *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg*	NR	NR	NR	48% (19/40)	53% (21/40)	Nausea: 28% (11/40) Diarrhea: 23% (9/40)	23% (9/40)
Jonas 2019[171] DORA Multinational *Fair*	Glecaprevir 300 mg + pibrentasvir 120 mg	87% (41/47)	0% (0/47)	0% (0/47)	17% (8/47)	11% (5/47)	NR	NR
Leung 2018[203] Multinational *Fair*	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + weight-based ribavirin	84% (32/38)	0% (0/38)	0% (0/38)	21% (8/38)	18% (7/38)	NR	NR
Wirth 2017[173] Multinational *Fair*	Sofosbuvir 400 mg + weight-based ribavirin*	81% (41/52)	2% (1/52)	0% (0/52)	23% (12/52)	12% (6/52)	Nausea: 27% (14/52) Diarrhea: 6% (3/52)	NR
Yakoot 2018[176] Egypt *Good*	Sofosbuvir + daclatasvir	27% (8/30)	0% (0/30)	0% (0/30)	10% (3/30)	13% (4/30)	Nausea: 10% (3/30)	NR

*Currently recommended regimen.
Abbreviation: NR = not reported.

Table 20. Studies on the Association Between Sustained Virologic Response After Antiviral Therapy vs. No Sustained Virologic Response and Clinical Outcomes

Author year Country	Duration of followup	N, by treatment response	Percent with Cirrhosis	Percent with Genotype 1	Statistical adjustments for age, sex, fibrosis, genotype
Arase 2007[204] Japan*	7.4 years (mean)	SVR: 140 No SVR: 360	14%	60%	Yes
Asahina 2010[217] Japan†	7.5 years (mean)	SVR: 686 No SVR: 1,356	5%	70%	Yes
Backus 2011[69] U.S.‡	3.8 years (median)	SVR: 7,434 No SVR: 9,430	13%	72%	Yes
Butt 2017[205] U.S.‡	1.5 years	SVR: 6,371 No SVR: 599	15%	85%	Yes
Carrat 2019[168]	2.8 years (median)	SVR: 3,286 No SVR: 146 Unknown SVR: 1,089	0% (subgroup)	67%	Yes
Cozen 2013[206] U.S.‡	10 years (mean)	SVR: 112 No SVR: 91 Relapse: 43 Early treatment discontinuation or unknown: 44	5%	67%	Yes in San Francisco VA cohort Partial in UCSF cohort
Dieperink 2014[207] U.S.‡	7.5 years (median)	SVR: 222 No SVR: 314	21%	70%	Yes
Dohmen 2013[218] Japan	4.8 years (median)	SVR: 285 No SVR: 189	NR	67%	Partial
El-Serag 2014[215] U.S.‡	5.2 years (mean)	SVR: 7,577 No SVR: 8,767	NR	55%	Yes
Ikeda 1999[219] Japan*	5.4 years (median)	SVR: 606 No SVR: 585	0%	67%	Yes
Imai 1998[220] Japan	4 years (median)	SVR: 151 Relapse: 120 No SVR: 148	8%	NR	Partial
Imazeki 2003[208] Japan§	8.2 years (mean)	SVR: 116 No SVR: 239	13%	74%	Partial
Innes 2011[209] U.K.	5.3 years (mean)	SVR: 560 No SVR: 655	14%	36%	Yes
Ioannou 2018[221] U.S.‖	6.1 years (mean)	SVR: 28,655 No SVR: 23,231	17%	77%	Yes
Izumi 2005[222] Japan†	Unclear	SVR: 155 No SVR: 340	1%	50%	Unclear
Kasahara 1998[223] Japan¶	3.1 years (mean)	SVR: 313 Relapse: 304 No SVR: 405	0%	58%	Yes
Kasahara 2004[210] Japan¶	5.7 years (mean)	SVR: 738 No SVR: 1,930	4%	NR	Partial
Kurokawa 2009[224] Japan¶	3 years (median)	SVR: 139 No SVR: 264	2%	73%	Partial
Lee 2017[225] South Korea	2.6 years (median)	SVR: 306 No SVR: 183	13%	51%	Yes
Maruoka 2012[211] Japan§	9.9 years (mean)	SVR: 221 No SVR: 356	10%	73%	Yes
Okanoue 2002[226] Japan	5.6 years (mean)	SVR: 426 Relapse: 358 No SVR: 586	4%	NR	Partial
Osaki 2012[227] Japan	4.1 years (median)	SVR: 185 No SVR: 197	0%	60%	Partial
Singal 2013[212] U.S.	5 years (median)	SVR: 83 No SVR: 159	21%	68%	Yes
Sinn 2008[231] South Korea	4.6 years (median)	SVR: 296 No SVR: 194	Unclear	46%	No

Table 20. Studies on the Association Between Sustained Virologic Response After Antiviral Therapy vs. No Sustained Virologic Response and Clinical Outcomes

Author year Country	Duration of followup	N, by treatment response	Percent with Cirrhosis	Percent with Genotype 1	Statistical adjustments for age, sex, fibrosis, genotype
Tanaka 2000[228] Japan	4.8 years (mean)	SVR: 175 Relapse: 165 No SVR: 254	3%	75%	Yes
Tateyama 2011[229] Japan	8.2 years (mean)	SVR: 139 No SVR: 234	17%	72%	Yes
Tseng 2016[216] Taiwan	5.5 years (mean)	SVR: 95 No SVR: 50	NR	61%	Partial
Yoshida 1999[230] Japan#	4.3 years (mean)	SVR: 789 No SVR: 1,568	10%	70%	Partial
Yoshida 2002[213] Japan#	5.4 years (mean)	SVR: 817 No SVR: 1,613	10%	NR	Partial
Yu 2006[214] Taiwan	5.2 years (mean)	SVR: 715 No SVR: 342	16%	46%	Yes

* Study populations overlap.
† Study populations overlap.
‡ Study population appears to overlap with Ioannou 2018.
§ Study populations overlap.
‖ Study population appears to overlap with Backus 2011, Butt 2017, Cozen 2013, Dieperink 2014, and El-Serag 2014.
¶ Study populations likely overlap.
# Study populations appear to overlap.
Abbreviations: NR = not reported; SVR = sustained virologic response; UCSF = University of California, San Francisco; U.K. = United Kingdom; U.S. = United States; VA = Veterans Affairs.

Table 21. Pooled Estimates on the Association Between Sustained Virologic Response After Antiviral Therapy vs. No Sustained Virologic Response and Clinical Outcomes

Outcome	Adjusted HR (95% CI)	I^2	Number of studies	p for interaction
All-cause mortality	0.40 (0.28 to 0.56)	52%	13[69,168,204-214]	--
• Exclude overlapping studies	0.37 (0.25 to 0.56)	62%	10[69,168,204,205,209-214]	--
• Fully adjusted*	0.42 (0.29 to 0.62)	55%	10[69,168,204-207,209,211,212,214]	0.34
• Partially adjusted	0.29 (0.15 to 0.55)	0%	3[208,210,213]	--
• Duration >5 years	0.33 (0.24 to 0.46)	0%	9[204,206-211,213,214]	0.003
• Duration <5 years	0.64 (0.56 to 0.74)	58%	4[69,168,205,212]	--
• U.S./Europe	0.50 (0.32 to 0.8)	54%	7[69,168,205-207,209,212]	0.10
• Asia	0.29 (0.19 to 0.45)	0%	6[204,208,210,211,213,214]	--
• Cirrhosis 0-10%	0.32 (0.18 to 0.60)	0%	4[168,206,211,213]	0.58
• Cirrhosis >10%	0.41 (0.28 to 0.62)	56%	9[69,204,205,207-210,212,214]	--
Liver mortality†	0.11 (0.04 to 0.27)	0%	4[204,208,210,213]	--
• Fully adjusted*	0.13 (0.03 to 0.59)	--	1[204]	0.79
• Partially adjusted	0.10 (0.03 to 0.30)	0%	3[208,210,213]	--
• Cirrhosis 0-10%	0.13 (0.03 to 0.61)	--	1[213]	0.82
• Cirrhosis >10%	0.10 (0.03 to 0.30)	0%	3[204,208,210]	--
Cirrhosis‡	0.36 (0.33 to 0.40)	0%	4[206,215,216]	--
• Exclude overlapping studies	0.36 (0.33 to 0.40)	0%	3[206,215,216]	--
• Fully adjusted*	0.36 (0.33 to 0.40)	0%	2[206,215]	0.76
• Partially adjusted	0.31 (0.12 to 0.78)	0%	2[206,216]	--
• U.S./Europe	0.36 (0.33 to 0.40)	0%	3[206,215]	0.71
• Asia	0.29 (0.10 to 0.76)	--	1[216]	--
• Cirrhosis 0 to 10%	0.36 (0.13 to 1.03)	0%	2[206]	0.99
• Cirrhosis unclear	0.36 (0.33 to 0.40)	0%	2[215,216]	--
Hepatocellular carcinoma	0.29 (0.23 to 0.38)	19%	20[168,204,207,211,214,215,217-230]	--
• Exclude overlapping studies	0.25 (0.18 to 0.34)	34%	16[168,204,211,214,217,218,220,221,223-230]	--
• Fully adjusted*	0.30 (0.27 to 0.34)	0%	13[168,204,207,211,214,215,217,219,221,223,225,228,229]	0.26
• Partially adjusted	0.26 (0.16 to 0.42)	51%	7[218,220,222,224,226,227,230]	--
• Duration >5 years	0.30 (0.27 to 0.34)	23%	10[204,207,211,214,215,217,221,226,229]	0.18
• Duration <5 years	0.29 (0.16 to 0.52)	17%	9[168,218,220,223-225,227,228,230]	--
• U.S./Europe	0.32 (0.28 to 0.36)	0%	4[168,207,215,221]	0.37
• Asia	0.24 (0.18 to 0.33)	34%	16[204,211,214,217-220,222-230]	--
• Cirrhosis 0 to 10%	0.22 (0.16 to 0.31)	0%	11[168,211,217,220,222-224,226-228,230]	0.08
• Cirrhosis >10%	0.31 (0.27 to 0.35)	7%	7[204,207,214,219,221,225,229]	--

*Study accounted for age, sex, fibrosis stage, and HCV genotype in analysis.
†All studies conducted in Asia and had duration >5 years.
‡All studies had duration >5 years.
Abbreviations: CI = confidence interval; HR = hazard ratio; U.S. = United States.

Table 22. Hepatitis C Cost-Effectiveness Analyses

Screening population	Author year	Screening strategies	HCV prevalence (range)	Background testing rates	Antiviral therapy costs (range)	HCV infection utilities (range)	Rates of linkage to care	Incremental cost-effectiveness ratios	Comments
General adult population	Barocas 2018[247]	A: ≥18 years B: ≥30 years C: ≥40 years D: Birth cohort	NR (incidence in PWID 12 cases/100 person-years)	Per 100 person-years PWID: 33.1 Non-PWID: 2.6 to 2.7	$69,078 ($0 to $114,000)	F0 to F3: 0.94 (0.0 to 1.0) F4: 0.75 (0.6 to 0.9) Decompensated: 0.60 (0.48 to 0.75)	<30 years: 17.9% ≥30 years: 28.9%	A: $28,000/QALY B: Dominated C: Dominated D: Reference	HCV Cost-Effectiveness model. All screening strategies included risk-based screening; model included reinfection
	Eckman 2018[248]	A: ≥18 years B: Birth cohort C: No screening	Birth cohort: 2.6% Non-birth cohort: 0.29%	Not included in model	$24,270 ($24,270 to $74,760)	F0 to F3: 0.79 (NR) F4: 0.79 (NR) Decompensated: 0.72 (NR) Post-transplant: 0.75 (NR) HCC: 0.72 (NR)	100%	A: $11,378/QALY B: Reference C: Dominated	Screening strategies did not include risk-based screening; model did not include reinfection
15 to 30 years old	Assoumou 2018[249]	9 1-time HCV screening strategies in 15 to 30 year olds vs. risk-based testing	NR (incidence 15.6/100 person-years)	PWID: 5% Non-PWID: 3%	$71,950 to $137,820 ($26,480 to $206,730)	F0 to F3: NR F4: 0.62 (0.55 to 0.75) Decompensated: 0.48 (0.40-0.60)	53%	Counselor-initiated, routine rapid testing: $71,000/QALY Physician-ordered, counselor-performed targeted rapid testing: $40,000/QALY Counselor-initiated, targeted rapid testing: $44,000/QALY Other screening strategies: Dominated Risk-based testing: Reference	Hepatitis C Cost-Effectiveness model. Screening strategies varied with respect to routine vs. expanded targeted vs. current risk-based screening; counselor/tester vs. physician-initiated; rapid vs. standard test. Counselor-initiated, routine rapid testing associated with greater average QALY gain (0.007 to 0.11) compared with the other two non-dominated strategies and below $100,000/QALY willingness-to-pay threshold

Table 22. Hepatitis C Cost-Effectiveness Analyses

Screening population	Author year	Screening strategies	HCV prevalence (range)	Background testing rates	Antiviral therapy costs (range)	HCV infection utilities (range)	Rates of linkage to care	Incremental cost-effectiveness ratios	Comments
Prenatal screening	Chaillon 2019[250]	A: Prenatal screening B: Risk-based screening	0.73%	5% per year	$25,000 (no range reported)	F0: 0.93 (0.83 to 1.0) F1, F2: 0.86 (0.78 to 0.94) F3: 0.83 (0.78 to 0.89) F4: 0.81 (0.68 to 0.89) Decompensated cirrhosis: 0.70 (0.56 to 0.79) HCC: 0.67 (0.56 to 0.78) Post-transplant: 0.71 (0.69 to 0.79)	Appears to be 100%	A: $2,826/QALY B: Reference	Costs and effects on neonate not modelled; antiviral therapy administered postpartum; model did not appear to include reinfection
	Tasillo 2019[251]	A: Prenatal screening B: Current practice	0.38%	During pregnancy: 14% No risk behaviors: 4 per 100 person-years With risk behavior: 40 per 100 person-years	No cirrhosis: $39,600 ($19,800 to $59,400) Cirrhosis: $68,773 ($47,833 to $89,712)	F0 to F3: 0.94 (0.94 to 1.0) F4: 0.75 (NR) Decompensated cirrhosis: 0.60 (NR)	Linked to care: 25% Initiated treatment if linked: 92%	A: $41,000/QALY B: Reference	HCV Cost-Effectiveness model. Costs and effects on neonate not modelled; antiviral therapy offered 6 months postpartum

Abbreviations: HCC = hepatocellular carcinoma; HCV = hepatitis C virus; NR = not reported; PWID = people who inject drugs; QALY = quality-adjusted life year.

Table 23. Summary of Evidence

KQ	Number of Studies (k) Number of participants (n) Study Designs	Summary of Findings	Consistency and Precision	Overall quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
KQ 1a. Benefits of screening	No studies	---	---	---	---	---	---
KQ 1b. Prenatal screening and vertical transmission	No studies	---	---	---	---	---	---
KQ 2.Screening strategies	No studies	---	---	---	---	---	---
KQ 3. Screening strategies and yield	Prior review: k=5 studies (n=8,044) New evidence: k=1 study (n=5,917)	The prior review included 5 studies that found risk-based screening associated with sensitivities of >90% and numbers needed to screen to identify 1 case of HCV infection of <20. One new study found that perfect application of risk-based guidelines would identify 82% of HCV cases with a number needed to screen to identify one case of HCV infection of 14.6, while applying a birth cohort strategy would result in 76% of cases identified a number needed to screen of 28.7.	Reasonable consistent and precise.	Fair	Studies were retrospective and in some studies significant proportions of patients were not tested. No studies of the yield of one-time versus repeat screening, alternative screening strategies in different risk groups, or the yield of currently recommended screening versus expanded screening strategies.	Low	Most studies conducted in high-prevalence settings. One study assumed perfect application of risk-based screening, which has not been attainable.
KQ 4. Harms of screening	Prior review: k=5 studies (n=288) New evidence: No new studies	Poor-quality evidence from the prior review suggested potential negative psychological and social effects of screening. No new studies on harms of screening were identified.	Low consistency and precision	Poor	Small sample sizes, no unscreened comparison group, reliance on retrospective recall, poorly defined outcomes.	Low	Studies were conducted in the era of interferon-based treatments

Table 23. Summary of Evidence

KQ	Number of Studies (k) Number of participants (n) Study Designs	Summary of Findings	Consistency and Precision	Overall quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
KQ 5. Effectiveness of interventions to prevent vertical transmission	Prior review: k=4 studies (n=1,724) New evidence: k=1 study (n=1,301)	Mode of delivery and risk of mother-to-infant transmission (5 studies, 1 new): No clear association Prolonged rupture of membrane (1 study from prior review): Adjusted OR 9.3, 95% CI, 1.5 to 180 Internal fetal monitoring (1 study from prior review): Adjusted OR 6.7, 95% CI, 1.1 to 35.9 Breastfeeding (3 studies, 1 new): No clear association	Mode of delivery: Inconsistent; some imprecision Rupture of membranes and fetal monitoring: Unable to assess consistency, imprecise Fetal monitoring: NA; imprecise Breastfeeding: Inconsistent; some imprecision	Fair	All studies were observational. Most studies from prior review were poor-quality and didn't perform statistical adjustment for potential confounders and were excluded. Prolonged rupture of membranes and internal monitoring only evaluated in 1 study each.	Low	Studies were conducted in the U.S. or Europe One study excluded women who were HIV positive; in the remaining 4 studies, HIV infection rates ranged from 5% to 15%

Table 23. Summary of Evidence

KQ	Number of Studies (k) Number of participants (n) Study Designs	Summary of Findings	Consistency and Precision	Overall quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
KQ 6. Effect of treatment on health outcomes - Adults	Prior review: NA (outdated regimens) New evidence: k=37 (34 trials [n=4,434], 2 pooled analyses [n=2,706], and 3 observational studies [n=58,892])	Two pooled analyses of 3 and 4 trials each and data from 3 other trials not included in pooled analyses found small, short-term improvements in quality of life scale scores after compared with before DAA therapy. In 31 DAA trials reporting short-term (<1 year) mortality, there were no deaths in 21 trials; mortality was low in the remaining 10 trials (0.4% [17/3,848] overall.) Two large observational studies found use of both DAA associated with lower rates of cardiovascular events and hepatocellular cancer. These associations were not found in a third, smaller observational study with shorter duration of followup.	Consistent, imprecise	Fair	Trials reporting quality of life and function were not randomized, used an open-label design, and did not have a non-DAA comparison group. Trials provided short-term followup, and were not designed to assess health outcomes. Event rates for mortality were low across studies, and other health outcomes were not widely reported. Evidence on long-term clinical outcomes was limited to 3 observational studies.	Low	Trials did not enroll a high proportion of patients with cirrhosis at baseline and evaluated current DAA regimens. Evidence on effects on hepatocellular cancer and cardiovascular events was primarily derived from a VA database that included few female subjects (3-4%).
KQ 6. Effect of treatment on health outcomes - Adolescents	k=3 (3 trials [n=230] in 5 publications)	There were no deaths in 3 trials of DAA regimens reporting short-term mortality. Sofosbuvir with ledipasvir or ribavirin and glecaprevir with pibrentasvir were associated with small improvements in Pediatric Quality of Life Inventory scores compared to baseline.	Cannot determine (for quality of life); imprecise	Fair	Trials were not designed to assess long-term health outcomes. The only evidence on quality of life outcomes is based on a post-hoc analysis of trial data.	Low	One trial evaluated a DAA regimen not FDA-approved for use in adolescents.

Table 23. Summary of Evidence

KQ	Number of Studies (k) Number of participants (n) Study Designs	Summary of Findings	Consistency and Precision	Overall quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
KQ 7. Effect of treatment on SVR - Adults	Prior review: NA (outdated regimens) New evidence: k=49 trials (n=10,181; 27 multi-arm trials and 22 single arm trials)	DAA vs. placebo (1 RCT): SVR 99% vs. 0%, RR 231.6, 95% CI, 14.6 to 3680 DAA vs. telaprevir (2 RCTs): SVR 98% vs. 80%, RR 1.22 (95% CI, 1.09 to 1.37) and 99% vs. 66%, RR 1.50 (95% CI, 1.22 to 1.85) In 49 trials, SVR rates with DAA therapies ranged from 95% to 100% across genotypes. Estimates were consistent in subgroup analyses based on study quality, geographic setting, fibrosis status, prior treatment experience, and other factors. Results were also similar in trials that stratified patients according to age, sex, race or ethnicity, or treatment-experience.	Consistent; precise	Good	All studies were industry-funded. Most DAA trials did not include a non-DAA comparison group. Evidence was most robust for genotype 1 and more limited for genotypes 2 through 6.	High	SVR rates based on currently recommended DAA regimens. Trials did not enroll a high proportion of patients with cirrhosis at baseline. Most trials enrolled predominantly white participants. Persons with current or recent drug use excluded from most trials. Most trials were conducted in the U.S. or Europe or were multinational.
KQ 7. Effect of treatment on SVR - Adolescents	Prior review: NA k=7 single arm trials (n=348)	In seven trials, the SVR rate ranged from 97% to 100%. Rates were similar when stratified according to DAA treatment regimen, genotype and treatment history.	Consistent; imprecise	Fair	Evidence in adolescents with genotype 2 and 4 infection was very limited (n=20) Four trials were industry funded.	Fair	Three trials evaluated DAA regimens not FDA-approved for use in adolescents. Four trials were multinational (primarily U.S. and Europe) and three were conducted in Egypt.

Table 23. Summary of Evidence

KQ	Number of Studies (k) Number of participants (n) Study Designs	Summary of Findings	Consistency and Precision	Overall quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
KQ 8. Harms – Adults: DAA vs. placebo	k=4 trials (n=2,113)	Pooled adverse event rates, DAA versus placebo: • Any adverse event (4 trials): RR 1.12, 95% CI, 1.02 to 1.24, I^2=46 • Serious adverse events (4 trials): RR 1.90, 95% CI, 0.73 to 4.95, I^2=0% • Withdrawal due to adverse events (4 trials): RR 0.47, 95% CI, 0.14 to 1.58, I^2=14% • Headache (4 trials): RR 1.12, 95% CI, 0.91 to 1.37, I^2=0% • Nausea (3 trials): RR 1.42, 95% CI, 1.00 to 2.03, I^2=10% • Diarrhea (2 trials): RR 1.53, 95% CI, 0.88 to 2.68, I^2=29% • Fatigue (3 trials): RR 1.05, 95% CI, 0.78 to 1.40; I^2=32% • Anemia (1 trial): RR 2.21, 95% CI, 0.11 to 46	Consistent; precise	Fair	Most trials did not have a non-DAA comparison group. Reporting of methods used to assess and define was suboptimal. Trials did not report long-term follow-up.	Moderate	See KQ 7

Table 23. Summary of Evidence

KQ	Number of Studies (k) Number of participants (n) Study Designs	Summary of Findings	Consistency and Precision	Overall quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
KQ 8. Harms – Adults: DAA vs. other treatment	k=2 trials (n=459)	Pooled adverse event rates, DAA versus other treatment: • Any adverse event (2 trials): RR 0.65, 95% CI, 0.50 to 0.84, I^2=87% • Serious adverse events (2 trials): RR 0.08, 95% CI, 0.02 to 0.34, I^2=0% • Headache (2 trials): RR 0.78, 95% CI, 0.58 to 1.04; I^2=0% • Withdrawal due to adverse events (2 trials): RR 0.06, 95% CI, 0.01 to 0.29, I^2=0% • Fatigue (2 trials): RR 0.37, 95% CI, 0.21 to 0.63, I^2=32% • Headache (2 trials): RR 0.70, 95% CI, 0.52 to 0.95; I^2=0% • Nausea (2 trials): RR 0.31, 95% CI, 0.16 to 0.59, I2=65% • Anemia (2 trials): RR 0.09, 95% CI, 0.04 to 0.23, I^2=41% • Rash (2 trials): RR 0.19, 95% CI, 0.06 to 0.58, I^2=48%	Consistent; precise	Fair	Most trials did not have a non-DAA comparison group. Reporting of methods used to assess and define was suboptimal. Trials did not report long-term follow-up.	Moderate	See KQ 7

Table 23. Summary of Evidence

KQ	Number of Studies (k) Number of participants (n) Study Designs	Summary of Findings	Consistency and Precision	Overall quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
KQ 8. Harms of treatment – Adults: Overall	Prior review: NA (outdated regimens) New evidence: k=49 trials (n=10,181)	Pooled adverse events rates for currently recommended DAA regimens were: • Any adverse event (44 trials): 73.3%, 95% CI, 68.0% to 78.1%; I^2=95% • Serious adverse events (44 trials): 1.9%, 95% CI, 1.5% to 2.4%; I^2=33% • Withdrawal due to adverse events (44 trials): 0.4%, 95% CI, 0.3% to 0.6%; I^2=0% • Anemia (13 trials): 2.4%, 95% CI, 0.9% to 6.3%; I^2=85% • Fatigue (37 trials): 18.4%, 95% CI, 15.6% to 21.7%; I^2=90% • Headache (42 trials): 18.7%, 95% CI, 15.6% to 22.2%; I^2=90% • Insomnia (18 trials): 8.1%, 95% CI, 6.7% to 9.9%; I^2=58% • Nausea (36 trials): 11.1%; 95% CI, 9.1% to 13.5%, I^2=82% • Diarrhea (19 trials): 8.7%, 95% CI, 7.0% to 10.8%; I^2=69% • Vomiting (6 trials): 5.8%, 95% CI, 3.4% to 9.7%; I^2=43% • Rash (17 trials): 5.4%, 95% CI, 4.1% to 7.1%; I^2=70%	Consistent; precise	Fair	Estimates were without a non-DAA comparison group. Reporting of methods used to assess and define was suboptimal. Trials did not report long-term follow-up.	Moderate	See KQ 7

Table 23. Summary of Evidence

KQ	Number of Studies (k) Number of participants (n) Study Designs	Summary of Findings	Consistency and Precision	Overall quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
KQ 8. Harms of treatment – Adolescents	Prior review: NA New evidence: k=7 trials (n=348)	Five trials reported no withdrawals due to adverse events. There was one serious adverse event (grade 3 joint injury) in 1 trial. The rate of any adverse event was 27% in one trial and 71 to 87% in four trials. Specific adverse event rates were: • Headache (7 trials): 3 to 48% • Fatigue (7 trials): 5 to 53% • Gastrointestinal adverse events (5 trials): 3 to 28% • Insomnia (1 trial): 23%	Inconsistent; imprecise	Fair	Trials did not have a non-DAA comparison group. There was high variability in adverse event rates, with no clear trends when results were stratified according to regimen. Reporting of methods used to assess harms was suboptimal and long-term followup (>48 weeks) was not reported	Fair	See KQ 6 - Adolescents

Table 23. Summary of Evidence

KQ	Number of Studies (k) Number of participants (n) Study Designs	Summary of Findings	Consistency and Precision	Overall quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
KQ 9. Association between SVR and health outcomes	Prior review: 19 studies (n=30,692) New evidence: k=30 (n=116,659 [n=26,191 from studies included in the prior report + n=90,468 from new studies])	Pooled estimates for health outcomes for SVR versus no SVR, in studies in which <25% of the population had cirrhosis at baseline: • All-cause mortality (13 studies, 5 new): HR 0.40, 95% CI, 0.28 to 0.56; I^2=52% • Liver mortality (4 studies, 0 new): HR 0.11, 95% CI, 0.04 to 0.27; I^2=0% • Cirrhosis (4 cohorts reported in 3 studies, all new): HR 0.36, 95% CI, 0.33 to 0.40; I^2=0%) • Hepatocellular carcinoma (20 studies, 16 new): HR 0.29, 95% CI, 0.23 to 0.38; I^2=19% Estimates were consistent in analyses stratified according to duration of follow-up, geographic setting, and level of statistical adjustment for potential confounders.	Consistent, precise	Fair	Studies are observational and susceptible to confounding. Some studies appeared to evaluate overlapping patient populations. About half (k=13) of the studies did not address four pre-specified potential confounders in analyses (age, sex, fibrosis stage, and genotype).	Fair	Most studies evaluated SVR after interferon-based therapy; evidence on SVR after DAA therapy was limited to two studies, one of which reported imprecise estimates. Studies did not enroll a high proportion of patients with cirrhosis at baseline. Patients primarily received interferon-containing therapy. Six of seven U.S. studies conducted in VA populations. Over half of studies conducted in Asia, though results similar in U.S./Europe studies.

Abbreviations: ARD = adjusted risk difference; CI = confidence interval; DAA = direct acting antiviral; EPC = Evidence-based Practice Center; FDA = US Food and Drug Administration; HCV = hepatitis C virus; HR = hazard ratio; KQ = Key Question; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SVR = sustained virologic response; U.S. = United States; VA = Veterans Affairs

Appendix A1. Search Strategies

Key Questions 1-4

Database: Ovid MEDLINE(R) 1996 to February Week 1 2019

1. Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/
2. ("Hepatitis C" or hepacivirus* or HCV).ti,ab.
3. 1 or 2
4. Mass Screening/ or Population Surveillance/ or Sentinel Surveillance/ or Seroepidemiologic Studies/ or Prenatal Diagnosis/ or Neonatal Screening/ or Infectious Disease Transmission, Vertical/ or Disease Transmission, Infectious/ or tm.fs. or transmi*.ti,ab. or ((public* or communit* or universal* or widespread or open* or unrestricted or group* or adult* or adolescen* or pregnan* or antibod*) adj3 (screen* or test* or surveillance)).ti,ab.
5. 3 and 4
6. limit 5 to yr="2012 -Current"
7. 6 and (random* or control* or trial or cohort or group*).ti,ab.
8. limit 6 to (clinical trial, all or comparative study or randomized controlled trial)
9. 7 or 8
10. limit 9 to (english language and humans)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials February 2019

1. Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/
2. ("Hepatitis C" or hepacivirus* or HCV).ti,ab.
3. 1 or 2
4. Mass Screening/ or Population Surveillance/ or Sentinel Surveillance/ or Seroepidemiologic Studies/ or Prenatal Diagnosis/ or Neonatal Screening/ or Infectious Disease Transmission, Vertical/ or Disease Transmission, Infectious/ or tm.fs. or transmi*.ti,ab. or ((public* or communit* or universal* or widespread or open* or unrestricted or group* or adult* or adolescen* or pregnan* or antibod*) adj3 (screen* or test* or surveillance)).ti,ab.
5. 3 and 4
6. limit 5 to yr="2012 -Current"

Key Question 5

Database: Ovid MEDLINE(R) 1996 to February Week 1 2019

1. Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/
2. ("Hepatitis C" or hepacivirus* or HCV).ti,ab.
3. 1 or 2
4. Infectious Disease Transmission, Vertical/ or Pregnancy Complications, Infectious/
5. Maternal-Fetal Exchange/
6. exp Breast Feeding/ or (breastfeed or breast feed* or breastfed or breast fed or breast milk).ti,ab.
7. (pregnan* or mother or maternal or child* or infan* or neonat* or prenatal or perinatal).ti,ab.
8. and tm.fs.
9. 3 and (4 or 5 or 6 or 8)
10. (random$ or control$ or trial or cohort or group* or compar*).ti,ab.
11. limit 9 to (clinical trial, all or comparative study or randomized controlled trial)
12. 9 and 10
13. 11 or 12
14. limit 13 to yr="2012 -Current"
15. limit 14 to (english language and humans)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials Feburary 2019

1. Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/
2. ("Hepatitis C" or hepacivirus* or HCV).ti,ab.
3. 1 or 2
4. Infectious Disease Transmission, Vertical/ or Pregnancy Complications, Infectious/
5. Maternal-Fetal Exchange/
6. exp Breast Feeding/ or (breastfeed or breast feed* or breastfed or breast fed or breast milk).ti,ab.

7. (pregnan* or mother or maternal or child* or infan* or neonat* or prenatal or perinatal).ti,ab.
8. 7 and tm.fs.
9. 3 and (4 or 5 or 6 or 8)
10. limit 9 to yr="2012 -Current"

Key Questions 6-7

Database: Ovid MEDLINE(R) 1946 to February Week 1 2019

1 (Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/) and dt.fs.
2 ("Hepatitis C" or hepacivirus* or HCV).ti,ab.
3 1 or 2
4 Antiviral Agents/ad, tu
5 (daclatasvir or dasabuvir or elbasvir or glecaprevir or grazoprevir or ledipasvir or ombitasvir or paritaprevir or pibrentasvir or ribavirin or simeprevir or sofosbuvir or velpatasvir or voxilaprevir).ti,ab,kw
6 4 or 5
7 3 and 6
8 7 not (transplant* or HIV or "hepatitis B").ti.
9 limit 8 to yr="2012 -Current"
10 9 and exp Clinical Studies as Topic/
11 limit 9 to (clinical trial, all or meta analysis or randomized controlled trial or systematic reviews)
12 9 and (random* or control* or trial or "systematic review" or "meta-analysis" or metaanalysis).ti,ab.
13 10 or 11 or 12
14 limit 13 to (english language and humans)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials February 2019

1. (Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/) and dt.fs.
2. ("Hepatitis C" or hepacivirus* or HCV).ti,ab.
3. 1 or 2
4. Antiviral Agents/ad, tu [Administration & Dosage, Therapeutic Use]
5. (daclatasvir or dasabuvir or elbasvir or glecaprevir or grazoprevir or ledipasvir or ombitasvir or paritaprevir or pibrentasvir or ribavirin or simeprevir or sofosbuvir or velpatasvir or voxilaprevir).mp.
6. 4 or 5
7. 3 and 6
8. 7 not (transplant* or HIV or "hepatitis B").ti.
9. limit 8 to yr="2012 -Current"

Key Question 8

Database: Ovid MEDLINE(R) 1996 to February Week 1 2019

1. (Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/) and dt.fs.
2. ("Hepatitis C" or hepacivirus* or HCV).ti,ab.
3. 1 or 2
4. Antiviral Agents/ad, tu [Administration & Dosage, Therapeutic Use]
5. (daclatasvir or dasabuvir or elbasvir or glecaprevir or grazoprevir or ledipasvir or ombitasvir or paritaprevir or pibrentasvir or ribavirin or simeprevir or sofosbuvir or velpatasvir or voxilaprevir).mp.
6. 4 or 5
7. 3 and 6
8. 7 not (transplant* or HIV or "hepatitis B").ti.
9. limit 8 to yr="2012 -Current"
10. 9 and exp Clinical Studies as Topic/
11. limit 9 to (clinical trial, all or meta analysis or randomized controlled trial or systematic reviews)
12. 9 and (random* or control* or trial or "systematic review" or "meta-analysis" or metaanalysis).ti,ab.
13. 10 or 11 or 12
14. limit 13 to (english language and humans)
15. 9 not 14
16. 15 and (ae or co or mo or po or to or ct).fs.
17. 15 and (adverse or safety or harm* or complication* or "side-effect*" or "treatment emerg*").ti,ab.

18. 16 or 17
19. limit 18 to (english language and humans)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials February 2019
10. (Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/) and dt.fs.
11. ("Hepatitis C" or hepacivirus* or HCV).ti,ab.
12. 1 or 2
13. Antiviral Agents/ad, tu [Administration & Dosage, Therapeutic Use]
14. (daclatasvir or dasabuvir or elbasvir or glecaprevir or grazoprevir or ledipasvir or ombitasvir or paritaprevir or pibrentasvir or ribavirin or simeprevir or sofosbuvir or velpatasvir or voxilaprevir).mp.
15. 4 or 5
16. 3 and 6
17. 7 not (transplant* or HIV or "hepatitis B").ti.
18. limit 8 to yr="2012 -Current"

Key Question 9

Database: Ovid MEDLINE(R) 1996 to February Week 1 2019
1. (Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/) and dt.fs.
2. ("Hepatitis C" or hepacivirus* or HCV).ti,ab.
3. 1 or 2
4. Antiviral Agents/ad, tu [Administration & Dosage, Therapeutic Use]
5. (daclatasvir or dasabuvir or elbasvir or glecaprevir or grazoprevir or ledipasvir or ombitasvir or paritaprevir or pibrentasvir or ribavirin or simeprevir or sofosbuvir or velpatasvir or voxilaprevir).mp.
6. 4 or 5
7. 3 and 6
8. sustained virologic response/
9. ("sustained virologic response" or svr).ti,ab.
10. 8 or 9
11. 7 and 10
12. Liver Cirrhosis/
13. Liver Transplantation/
14. (cirrho* or transplant* or decompensat* or morbidity or mortality or death*).ti,ab.
15. 11 and (12 or 13 or 14)
16. limit 15 to yr="2012 -Current"
17. limit 16 to (english language and humans)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials February 2019
1. (Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/) and dt.fs.
2. ("Hepatitis C" or hepacivirus* or HCV).ti,ab.
3. 1 or 2
4. Antiviral Agents/ad, tu [Administration & Dosage, Therapeutic Use]
5. (daclatasvir or dasabuvir or elbasvir or glecaprevir or grazoprevir or ledipasvir or ombitasvir or paritaprevir or pibrentasvir or ribavirin or simeprevir or sofosbuvir or velpatasvir or voxilaprevir).mp.
6. 4 or 5
7. 3 and 6
8. sustained virologic response/
9. ("sustained virologic response" or svr).ti,ab.
10. 8 or 9
11. 7 and 10
12. Liver Cirrhosis/
13. Liver Transplantation/
14. (cirrho* or transplant* or decompensat* or morbidity or mortality or death*).ti,ab.
15. 11 and (12 or 13 or 14)
16. limit 15 to yr="2012 -Current"

All Key Questions

Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to February 6, 2019

1. ("Hepatitis C" or hepacivirus* or HCV).ti.
2. (daclatasvir or dasabuvir or elbasvir or glecaprevir or grazoprevir or ledipasvir or ombitasvir or paritaprevir or pibrentasvir or ribavirin or simeprevir or sofosbuvir or velpatasvir or voxilaprevir).ti,ab.
3. 1 and 2
4. screen*.mp. [mp=title, short title, abstract, full text, keywords, caption text]
5. 1 and 4
6. 3 or 5
7. limit 6 to full systematic reviews

Appendix A2. Inclusion and Exclusion Criteria

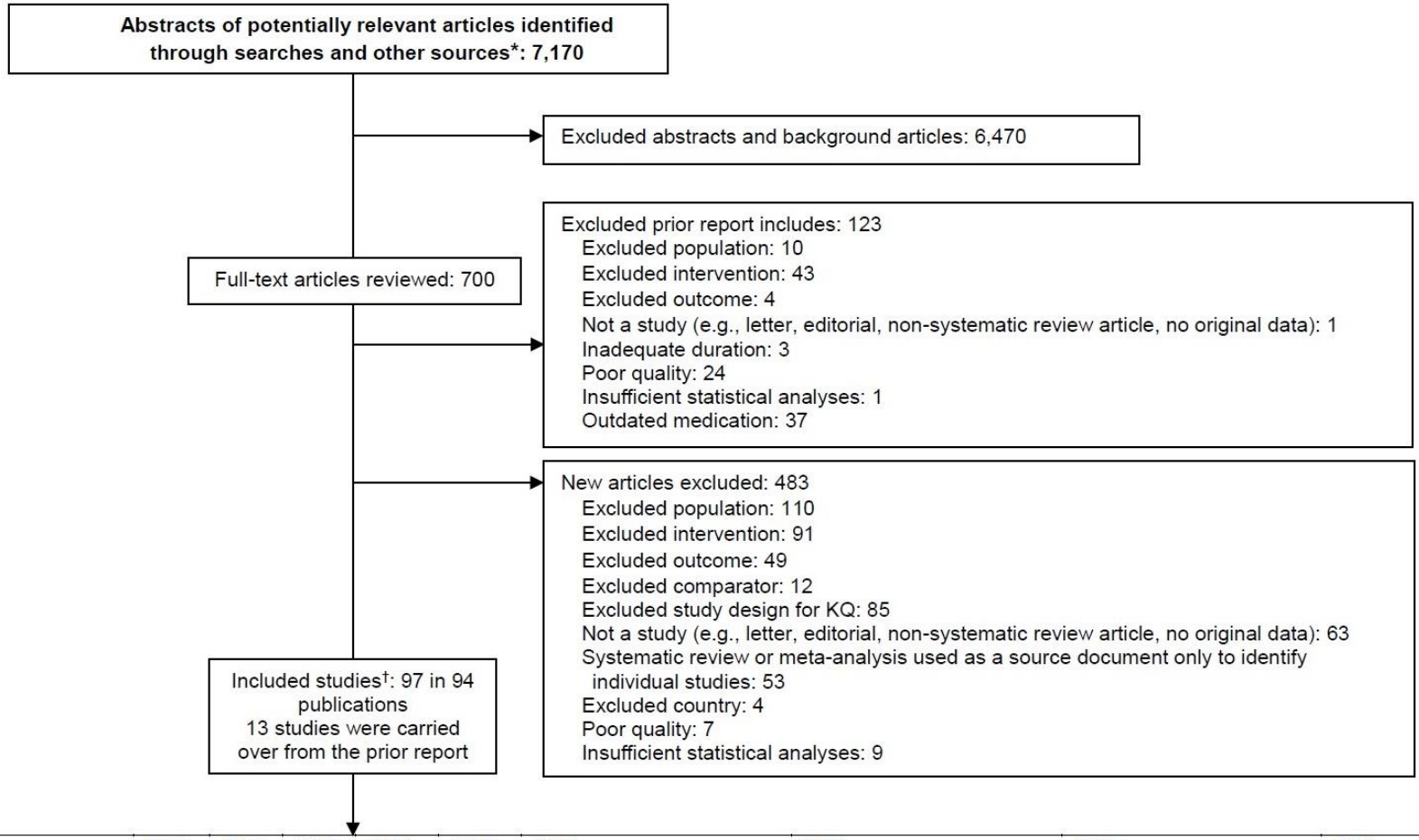
PICOTS	Inclusion Criteria	Exclusion Criteria
Populations	**Screening in nonpregnant adolescents and adults (KQs 1a, 2–4) Screening in pregnant adolescents and adults (KQs 1–4)** Asymptomatic, pregnant and nonpregnant adolescents (ages 12 to 17 years) and adults without prior HCV infection **Labor and delivery and perinatal interventions (KQ 5)** Pregnant adolescents and adults with HCV infection **Antiviral treatment (KQs 6–8)** Persons with screen-detected or asymptomatic HCV infection (patients with a METAVIR fibrosis stage of 0–3, if symptom status is NR); persons with no prior antiviral treatment; includes pregnant women **Association between improvements in sustained virologic response and clinical outcomes (KQ 9)** Persons with HCV infection being treated with antiviral therapy	**Screening in nonpregnant adolescents and adults (KQs 1a, 2–4)** Persons with known abnormal liver function tests, hepatitis B virus infection, or HIV infection; children age <12 years **Screening in pregnant adolescents and adults (KQs 1–4)** Persons with known abnormal liver function tests, hepatitis B virus infection, or HIV infection **Labor and delivery and perinatal interventions (KQ 5)** Other populations **Antiviral treatment (KQs 6–8) Association between improvements in sustained virologic response and clinical outcomes (KQ 9)** Persons who are coinfected with the hepatitis B virus or HIV, transplant patients, persons with renal failure
Interventions	**Screening in nonpregnant adolescents and adults (KQs 1a, 2–4) Screening in pregnant adolescents and adults (KQs 1–4)** Screening **Labor and delivery and perinatal interventions (KQ 5)** Mode of delivery, labor management strategies, breastfeeding practices **Antiviral treatment (KQs 6–8)** Currently recommended direct acting antiviral regimens* **Association between improvements in sustained virologic response and clinical outcomes (KQ 9)** Direct acting antiviral regimens or other antiviral treatment	**Screening in nonpregnant adolescents and adults (KQs 1a, 2–4) Screening in pregnant adolescents and adults (KQs 1–4) Labor and delivery and perinatal interventions (KQ 5)** Other interventions **Antiviral treatment (KQs 6–8)** Interferon-based treatment and other nonrecommended regimens*
Comparisons	**Screening in nonpregnant adolescents and adults (KQs 1a, 2–4) Screening in pregnant adolescents and adults (KQs 1–4)** Screening vs. no screening, one screening method vs. another, screening interval comparisons **Labor and delivery and perinatal interventions (KQ 5)** Elective cesarean delivery vs. vaginal or emergency cesarean delivery, internal fetal monitoring vs. no monitoring, longer vs. shorter duration of rupture of membranes, breastfeeding vs. no breastfeeding **Antiviral treatment (KQs 6–8)** Another direct acting antiviral regimen or older antiviral regimen; includes clinical trials without a comparison group **Association between improvements in sustained virologic response and clinical outcomes (KQ 9)** Persons who experience a sustained virologic response vs. those who do not	**Screening in nonpregnant adolescents and adults (KQs 1a, 2–4) Screening in pregnant adolescents and adults (KQs 1–4) Labor and delivery and perinatal interventions (KQ 5)** Other comparisons

Appendix A2. Inclusion and Exclusion Criteria

PICOTS	Inclusion Criteria	Exclusion Criteria
Outcomes	**Screening in nonpregnant adolescents and adults (KQs 1a, 2–4)** Mortality, morbidity (e.g., cirrhosis, hepatic decompensation, liver transplant, extrahepatic manifestations of HCV infection), quality of life, HCV transmission, harms (e.g., labeling, anxiety, drug-related harms), screening yield (number of new diagnoses per tests performed) (KQ 3) **Screening in pregnant adolescents and adults (KQs 1–4)** Perinatal transmission, mortality, morbidity, quality of life, harms (e.g., labeling, anxiety, drug-related harms), screening yield (number of new diagnoses per tests performed) (KQ 3) **Labor and delivery and perinatal interventions (KQ 5)** Perinatal transmission of HCV infection **Antiviral treatment (KQs 6–8)** Sustained virologic response (KQ 7); morbidity (e.g., cirrhosis, hepatic decompensation, liver transplant, extrahepatic manifestations of HCV infection), mortality, quality of life, HCV transmission (KQ 6), harms of treatment (KQ 8); behavioral outcomes will be included for Contextual Question 3 **Association between improvements in sustained virologic response and clinical outcomes (KQ 9)** Morbidity (e.g., cirrhosis, hepatic decompensation, liver transplant), mortality	**Screening in nonpregnant adolescents and adults (KQs 1a, 2–4)** Other outcomes, including intermediate outcomes **Screening in pregnant adolescents and adults (KQs 1–4) Labor and delivery and perinatal interventions (KQ 5)** Other outcomes **Antiviral treatment (KQs 6–8) Association between improvements in sustained virologic response and clinical outcomes (KQ 9)** Histologic outcomes, liver function tests
Setting	**Screening in nonpregnant adolescents and adults (KQs 1a, 2–4) Screening in pregnant adolescents and adults (KQs 1–4)** U.S. primary care, obstetrics/gynecology, emergency department, and primary care–applicable settings, including settings that offer integrated services for primary care and behavioral health care (e.g., substance use treatment clinics) **Labor and delivery and perinatal interventions (KQ 5)** U.S. labor and delivery settings **Antiviral treatment (KQs 6–8) Association between improvements in sustained virologic response and clinical outcomes (KQ 9)** Clinical settings in which HCV antiviral treatments are prescribed	
Study design	**Screening in nonpregnant adolescents and adults (KQs 1a, 2–4) Screening in pregnant adolescents and adults (KQs 1–4) Labor and delivery and perinatal interventions (KQ 5)** RCTs, controlled observational studies **Antiviral treatment (KQs 6–8)** RCTs and uncontrolled clinical trials; for harms and clinical outcomes (KQ 6), will also include large cohort and case-control studies; will consider good-quality systematic reviews of clinical trials **Association between improvements in sustained virologic response and clinical outcomes (KQ 9)** Cohort studies	**Screening in nonpregnant adolescents and adults (KQs 1a, 2–4) Screening in pregnant adolescents and adults (KQs 1–4)** Uncontrolled studies **Labor and delivery and perinatal interventions (KQ 5) Antiviral treatment (KQs 6–8)** Case reports, studies not reporting original data **Association between improvements in sustained virologic response and clinical outcomes (KQ 9)** Case-control studies, case reports, studies not reporting original data

*For clinical outcomes (KQs 6 and 9), previously recommended regimens will be used.
Abbreviations: HCV = hepatitis C virus; KQ = Key Question; NR = not reported; PICOTS = population, interventions, comparisons, outcomes, setting, study design; RCTs = randomized controlled trials; U.S. = United States.

Appendix A3. Literature Flow Diagram



	KQ1	KQ2	KQ3	KQ4	KQ5	KQ6	KQ7	KQ8	KQ9
New studies:	0	0	1	0	1	40 (in 36 publications)	56 (in 53 publications)	56 (in 53 publications)	21
Carried forward:	0	0	0	0	4	0	0	0	9
Total includes:	0	0	1	0	5	40 (in 36 publications)	56 (in 53 publications)	56 (in 53 publications)	30

*Other sources include prior reports, reference lists of relevant articles, systematic reviews, etc.
†Some studies were included for multiple KQs.
Abbreviation: KQ = Key Question.

Appendix A4. List of Included Studies

Abdel Ghaffar TY, Naghi SE, Gawad MA, et al. Safety and efficacy of combined sofosbuvir/daclatasvir treatment of children and adolescents with chronic hepatitis C genotype 4. J Viral Hepat. 2019;26(2):263-70. doi: 10.1111/jvh.13032. PMID: 30380158.

Abergel A, Asselah T, Metivier S, et al. Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: an open-label, multicentre, single-arm, phase 2 study. Lancet Infect Dis. 2016b;16(4):459-64. doi: 10.1016/S1473-3099(15)00529-0. PMID: 26803446.

Abergel A, Metivier S, Samuel D, et al. Ledipasvir plus sofosbuvir for 12 weeks in patients with hepatitis C genotype 4 infection. Hepatology. 2016a;64(4):1049-56. doi: 10.1002/hep.28706. PMID: 27351341.

Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370(20):1889-98. doi: 10.1056/NEJMoa1402454. PMID: 24725239.

Ahmed OA, Kaisar HH, Badawi R, et al. Efficacy and safety of sofosbuvir-ledipasvir for treatment of a cohort of Egyptian patients with chronic hepatitis C genotype 4 infection. Infect Drug Resist. 2018;11:295-8. doi: 10.2147/IDR.S153060. PMID: 29535545.

Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology. 2014;147(2):359-65.e1. doi: 10.1053/j.gastro.2014.04.045. PMID: 24818763.

Arase Y, Ikeda K, Suzuki F, et al. Long-term outcome after interferon therapy in elderly patients with chronic hepatitis C. Intervirology. 2007;50(1):16-23. doi: 10.1159/000096308. PMID: 17164553.

Asahina Y, Tsuchiya K, Tamaki N, et al. Effect of aging on risk for hepatocellular carcinoma in chronic hepatitis C virus infection. Hepatology. 2010;52(2):518-27. doi: 10.1002/hep.23691. PMID: 20683951.

Asselah T, Kowdley KV, Zadeikis N, et al. Efficacy of glecaprevir/pibrentasvir for 8 or 12 weeks in patients with hepatitis C virus genotype 2, 4, 5, or 6 infection without cirrhosis. Clin Gastroenterol Hepatol. 2018;16(3):417-26. doi: 10.1016/j.cgh.2017.09.027. PMID: 28951228.

Asselah T, Lee SS, Yao BB, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients with chronic hepatitis C virus genotype 5 or 6 infection (ENDURANCE-5,6): an open-label, multicentre, phase 3b trial. Lancet Gastroenterol Hepatol. 2019;4(1):45-51. doi: 10.1016/S2468-1253(18)30341-8. PMID: 30393106.

Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol. 2011;9:509-16. doi: 10.1016/j.cgh.2011.03.004. PMID: 21397729.

Balistreri WF, Murray KF, Rosenthal P, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12-17 years old with hepatitis C virus genotype 1 infection. Hepatology. 2017;66(2):371-8. doi: 10.1002/hep.28995. PMID: 27997679.

Brown A, Hezode C, Zuckerman E, et al. Efficacy and safety of 12 weeks of elbasvir +/- grazoprevir +/- ribavirin in participants with hepatitis C virus genotype 2, 4, 5 or 6 infection: the C-SCAPE study. J Viral Hepat. 2018;25(5):457-64. doi: 10.1111/jvh.12801. PMID: 29152828.

Butt AA, Yan P, Shuaib A, et al. Direct-acting antiviral therapy for HCV Infection is associated with a reduced risk of cardiovascular disease events. Gastroenterology. 2019;156(4):987-96. doi: 10.1053/j.gastro.2018.11.022. PMID: 30445009.

Butt AA, Yan P, Simon TG, et al. Effect of paritaprevir/ritonavir/ombitasvir/dasabuvir and ledipasvir/sofosbuvir regimens on survival compared with untreated hepatitis C virus-infected persons: results from ERCHIVES. Clin Infect Dis. 2017;65(6):1006-11. doi: 10.1093/cid/cix364. PMID: 28903508.

Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet. 2019 doi: 10.1016/s0140-6736(18)32111-1. PMID: 30765123.

Ceci O, Margiotta M, Marello F, et al. Vertical transmission of hepatitis C virus in a cohort of 2,447 HIV-seronegative pregnant women: a 24-month prospective study. J Pediatr Gastroenterol Nutr. 2001;33(5):570-5. PMID: 11740231.

Chayama K, Suzuki F, Karino Y, et al. Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 1 hepatitis C virus infection with and without cirrhosis. J Gastroenterol. 2018:557-65. PMID: 28948366.

Chuang WL, Chien RN, Peng CY, et al. Ledipasvir/sofosbuvir fixed-dose combination tablet in Taiwanese patients with chronic genotype 1 hepatitis C virus. J Gastroenterol Hepatol. 2016;31(7):1323-9. PMID: 26841930.

Cozen ML, Ryan JC, Shen H, et al. Nonresponse to interferon-alpha based treatment for chronic hepatitis C infection is associated with increased hazard of cirrhosis. PLoS One. 2013;8(4):e61568. doi: 10.1371/journal.pone.0061568. PMID: 23637856.

Appendix A4. List of Included Studies

Dieperink E, Pocha C, Thuras P, et al. All-cause mortality and liver-related outcomes following successful antiviral treatment for chronic hepatitis C. Dig Dis Sci. 2014;59(4):872-80. doi: 10.1007/s10620-014-3050-5. PMID: 24532254.

Dohmen K, Kawano A, Takahashi K, et al. The incidence and risk factors for the development of hepatocellular carcinoma after peginterferon plus ribavirin therapy for chronic hepatitis C. Hepatogastroenterology. 2013;60(128):2034-8. PMID: 24719946.

Dore GJ, Conway B, Luo Y, et al. Efficacy and safety of ombitasvir/paritaprevir/r and dasabuvir compared to IFN-containing regimens in genotype 1 HCV patients: the MALACHITE-I/II trials. J Hepatol. 2016;64(1):19-28. doi: 10.1016/j.jhep.2015.08.015. PMID: 26321288.

El-Karaksy H, Mogahed EA, Abdullatif H, et al. Sustained viral response in genotype 4 chronic hepatitis C virus-infected children and adolescents treated with sofosbuvir/ledipasvir. J Pediatr Gastroenterol Nutr. 2018;67(5):626-30. doi: 10.1097/mpg.0000000000002101. PMID: 30216203.

El-Serag HB, Kramer J, Duan Z, et al. Racial differences in the progression to cirrhosis and hepatocellular carcinoma in HCV-infected veterans. Am J Gastroenterol. 2014;109(9):1427-35. doi: 10.1038/ajg.2014.214. PMID: 25070058.

Everson GT, Towner WJ, Davis MN, et al. Sofosbuvir with velpatasvir in treatment-naive noncirrhotic patients with genotype 1 to 6 hepatitis C virus infection: A randomized trial. Ann Intern Med. 2015;163(11):818-26. doi: 10.7326/M15-1000. PMID: 26551051.

Feld JJ, Jacobson IM, Hezode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med. 2015;373(27):2599-607. doi: 10.1056/NEJMoa1512610. PMID: 26571066.

Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014;370(17):1594-603. doi: 10.1056/NEJMoa1315722. PMID: 24720703.

Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med. 2014;370(21):1983-92. doi: 10.1056/NEJMoa1402338. PMID: 24795200.

Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med. 2015;373(27):2608-17. doi: 10.1056/NEJMoa1512612. PMID: 26575258.

Gane EJ, Hyland RH, An D, et al. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection. Gastroenterology. 2015;149(6):1454-61.e1. doi: 10.1053/j.gastro.2015.07.063. PMID: 26261007.

Gibb DM, Goodall RL, Dunn DT, et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. Lancet. 2000;356(9233):904-7. PMID: 11036896.

Grebely J, Conway B, Cunningham EB, et al. Paritaprevir, ritonavir, ombitasvir, and dasabuvir with and without ribavirin in people with HCV genotype 1 and recent injecting drug use or receiving opioid substitution therapy. Int J Drug Policy. 2018b;62:94-103. doi: 10.1016/j.drugpo.2018.10.004. PMID: 30384028.

Grebely J, Dalgard O, Conway B, et al. Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use (SIMPLIFY): an open-label, single-arm, phase 4, multicentre trial. Lancet Gastroenterol Hepatol. 2018a;3(3):153-61. doi: 10.1016/S2468-1253(17)30404-1. PMID: 29310928.

Hezode C, Asselah T, Reddy KR, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. Lancet. 2015;385(9986):2502-9. doi: 10.1016/S0140-6736(15)60159-3. PMID: 25837829.

Ikeda K, Saitoh S, Arase Y, et al. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: A long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. Hepatology. 1999;29(4):1124-30. doi: 10.1002/hep.510290439. PMID: 10094956.

Imai Y, Kawata S, Tamura S, et al. Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Osaka hepatocellular carcinoma prevention study group. Ann Intern Med. 1998;129(2):94-9. PMID: 9669992.

Imazeki F, Yokosuka O, Fukai K, et al. Favorable prognosis of chronic hepatitis C after interferon therapy by long-term cohort study. Hepatology. 2003;38(2):493-502. doi: 10.1053/jhep.2003.50329. PMID: 12883494.

Innes HA, Hutchinson SJ, Allen S, et al. Excess liver-related morbidity of chronic hepatitis C patients, who achieve a sustained viral response, and are discharged from care. Hepatology. 2011;54(5):1547-58. doi: 10.1002/hep.24561. PMID: 22045672.

Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol. 2018;68(1):25-32. doi: 10.1016/j.jhep.2017.08.030. PMID: 28887168.

Izumi N, Yasuhiro A, Kurosaki M, et al. Development of hepatocellular carcinoma after interferon therapy in chronic hepatitis C. Is it possible to reduce the incidence by ribanirin and IFN combination therapy? Intervirology. 2005;48(1):59-63. doi: 10.1159/000082096. PMID: 15785091.

Appendix A4. List of Included Studies

Jonas MM, Squires RH, Rhee SM, et al. Pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in adolescents with chronic HCV: part 1 of the DORA study. Hepatology. 2019 doi: 10.1002/hep.30840. PMID: 31254392.

Kasahara A, Hayashi N, Mochizuki K, et al. Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. Osaka Liver Disease Study Group. Hepatology. 1998;27(5):1394-402. doi: 10.1002/hep.510270529. PMID: 9581697.

Kasahara A, Tanaka H, Okanoue T, et al. Interferon treatment improves survival in chronic hepatitis C patients showing biochemical as well as virological responses by preventing liver-related death. J Viral Hepat. 2004;11(2):148-56. PMID: 14996350.

Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014a;370(20):1879-88. doi: 10.1056/NEJMoa1402355. PMID: 24720702.

Kowdley KV, Lawitz E, Poordad F, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. N Engl J Med. 2014b;370(3):222-32. doi: 10.1056/NEJMoa1306227. PMID: 24428468.

Kumada H, Chayama K, Rodrigues L, Jr., et al. Randomized phase 3 trial of ombitasvir/paritaprevir/ritonavir for hepatitis C virus genotype 1b-infected Japanese patients with or without cirrhosis. Hepatology. 2015;62(4):1037-46. doi: 10.1002/hep.27972. PMID: 26147154.

Kumada H, Suzuki Y, Karino Y, et al. The combination of elbasvir and grazoprevir for the treatment of chronic HCV infection in Japanese patients: a randomized phase II/III study. J Gastroenterol. 2017;52(4):520-33. doi: 10.1007/s00535-016-1285-y. PMID: 27873094.

Kurokawa M, Hiramatsu N, Oze T, et al. Effect of interferon alpha-2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with chronic hepatitis. Hepatol Res. 2009;39(5):432-8. doi: 10.1111/j.1872-034X.2008.00477.x. PMID: 19207583.

Kwo P, Gitlin N, Nahass R, et al. Simeprevir plus sofosbuvir (12 and 8 weeks) in hepatitis C virus genotype 1-infected patients without cirrhosis: OPTIMIST-1, a phase 3, randomized study. Hepatology. 2016;64(2):370-80. doi: 10.1002/hep.28467. PMID: 26799692.

Lalezari J, Sullivan JG, Varunok P, et al. Ombitasvir/paritaprevir/r and dasabuvir plus ribavirin in HCV genotype 1-infected patients on methadone or buprenorphine. J Hepatol. 2015;63(2):364-9. doi: 10.1016/j.jhep.2015.03.029. PMID: 25839406.

Lawitz E, Makara M, Akarca US, et al. Efficacy and safety of ombitasvir, paritaprevir, and ritonavir in an open-label study of patients with genotype 1b chronic hepatitis C virus infection with and without cirrhosis. Gastroenterology. 2015;149(4):971-80.e1. doi: 10.1053/j.gastro.2015.07.001. PMID: 26170136.

Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet. 2014b;383(9916):515-23. doi: 10.1016/S0140-6736(13)62121-2. PMID: 24209977.

Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet. 2014a;384(9956):1756-65. doi: 10.1016/S0140-6736(14)61036-9. PMID: 25078309.

Lee SH, Jin YJ, Shin JY, et al. Assessment of hepatocellular carcinoma risk based on peg-interferon plus ribavirin treatment experience in this new era of highly effective oral antiviral drugs. Medicine. 2017;96(1):e5321. doi: 10.1097/MD.0000000000005321. PMID: 28072684.

Leung DH, Wirth S, Yao BB, et al. Ombitasvir/paritaprevir/ritonavir with or without dasabuvir and with or without ribavirin for adolescents with HCV genotype 1 or 4. Hepatol Commun. 2018;2(11):1311-9. doi: 10.1002/hep4.1250. PMID: 30411078.

Li DK, Ren Y, Fierer DS, et al. The short-term incidence of hepatocellular carcinoma is not increased after hepatitis C treatment with direct-acting antivirals: an ERCHIVES study. Hepatology. 2018;67(6):2244-53. doi: 10.1002/hep.29707. PMID: 29205416.

Lim YS, Ahn SH, Lee KS, et al. A phase IIIb study of ledipasvir/sofosbuvir fixed-dose combination tablet in treatment-naive and treatment-experienced Korean patients chronically infected with genotype 1 hepatitis C virus. Hepatol Int. 2016;10(6):947-55. PMID: 27198664.

Maruoka D, Imazeki F, Arai M, et al. Long-term cohort study of chronic hepatitis C according to interferon efficacy. J Gastroenterol Hepatol. 2012;27(2):291-9. doi: 10.1111/j.1440-1746.2011.06871.x. PMID: 21793911.

Mast EE, Hwang LY, Seto DS, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. J Infect Dis. 2005;192(11):1880-9. doi: 10.1086/497701. PMID: 16267758.

Appendix A4. List of Included Studies

Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015;61(4):1127-35. doi: 10.1002/hep.27726. PMID: 25614962.

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Appendix A4. List of Included Studies

Waked I, Shiha G, Qaqish RB, et al. Ombitasvir, paritaprevir, and ritonavir plus ribavirin for chronic hepatitis C virus genotype 4 infection in Egyptian patients with or without compensated cirrhosis (AGATE-II): a multicentre, phase 3, partly randomised open-label trial. Lancet Gastroenterol Hepatol. 2016;1(1):36-44. PMID: 28404110.

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Wei L, Lim SG, Xie Q, et al. Sofosbuvir-velpatasvir for treatment of chronic hepatitis C virus infection in Asia: a single-arm, open-label, phase 3 trial. Lancet Gastroenterol Hepatol. 2019b;4(2):127-34. doi: 10.1016/S2468-1253(18)30343-1. PMID: 30555048.

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Zeuzem S, Ghalib R, Reddy KR, 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;163(1):1-13. doi: 10.7326/M15-0785. PMID: 25909356.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Abad S, Vega A, Hernandez E, et al. Universal sustained viral response to the combination of ombitasvir/paritaprevir/ritonavir and dasabuvir with/without ribavirin in patients on hemodialysis infected with hepatitis C virus genotypes 1 and 4. Am J Nephrol. 2017;45(3):267-72. doi: 10.1159/000454819. PMID: 28166520. Excluded for ineligible study design for Key Question.

Abad S, Vega A, Rincon D, et al. Effectiveness of direct-acting antivirals in hepatitis C virus infection in haemodialysis patients. Nefrologia. 2017;37(2):158-63. doi: 10.1016/j.nefro.2016.10.003. PMID: 27914803. Excluded for ineligible population.

Abdel-Aziz AM, Ibrahim MA, El-Sheikh AA, et al. Effect of sofosbuvir plus daclatasvir in hepatitis C virus genotype-4 patients: promising effect on liver fibrosis. J Clin Exp Hepatol. 2018;8(1):15-22. doi: 10.1016/j.jceh.2017.06.006. PMID: 29743792. Excluded for ineligible population.

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Abdel-Moneim A, Aboud A, Abdel-Gabaar M, et al. Efficacy and safety of sofosbuvir plus daclatasvir with or without ribavirin: large real-life results of patients with chronic hepatitis C genotype 4. Hepatol Int. 2018;12(4):348-55. doi: 10.1007/s12072-018-9868-8. PMID: 29754329. Excluded for ineligible population.

Abd-Elsalam S, Badawi R, Elnawasany S, et al. Sofosbuvir, pegylated interferon and ribavirin in treatment of an Egyptian cohort with hepatitis C virus infection in real life clinical practice. Infect Disord Drug Targets. 2018;12:12. doi: 10.2174/1871526518666180912121835. PMID: 30207250. Excluded for ineligible intervention.

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Abouelkheir Abdalla D, Ali Elhadidy T, Besheer T, et al. Respiratory adverse effects of sofosbuvir-based regimens for treatment of chronic hepatitis C virus. Egypt J Chest Dis Tuberc. 2016;10. Excluded for ineligible intervention.

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Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014;370(16):1483-93. doi: 10.1056/NEJMoa1316366. PMID: 24725238. Excluded for ineligible population.

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Ahn SH, Lim YS, Lee KS, et al. A phase 3b study of sofosbuvir plus ribavirin in treatment-naive and treatment-experienced Korean patients chronically infected with genotype 2 hepatitis C virus. J Viral Hepat. 2016;23(5):358-65. doi: 10.1111/jvh.12499. PMID: 26864153. Excluded for ineligible intervention.

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Akahane T, Kurosaki M, Itakura J, et al. Real-world efficacy and safety of sofosbuvir + ribavirin for hepatitis C genotype 2: a nationwide multicenter study by the Japanese Red Cross Liver Study Group. Hepatol Res. 2018;01:01. doi: 10.1111/hepr.13246. PMID: 30171740. Excluded for ineligible intervention.

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Akuta N, Kobayashi M, Suzuki F, et al. Liver fibrosis and body mass index predict hepatocarcinogenesis following eradication of hepatitis C virus RNA by direct-acting antivirals. Oncology. 2016;91(6):341-7. doi: 10.1159/000450551. PMID: 27694754. Excluded for ineligible comparator.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Akuta N, Suzuki F, Seko Y, et al. Efficacy and anticarcinogenic activity of ribavirin combination therapy for hepatitis C virus-related compensated cirrhosis. Intervirology. 2013;56(1):37-45. doi: 10.1159/000342746. PMID: 23037768. Excluded for ineligible population.

Alavi M, Spelman T, Matthews GV, et al. Injecting risk behaviours following treatment for hepatitis C virus infection among people who inject drugs: the Australian trial in acute hepatitis C. Int J Drug Policy. 2015;26(10):976-83. doi: 10.1016/j.drugpo.2015.05.003. PMID: 26115881. Excluded for ineligible study design for Key Question.

Alfaleh FZ, Alswat K, Helmy A, et al. The natural history and long-term outcomes in patients with chronic hepatitis C genotype 4 after interferon-based therapy. Liver Int. 2013;33(6):871-83. doi: 10.1111/liv.12127. PMID: 23490034. Excluded for poor quality.

Almario CV, Vega M, Trooskin SB, et al. Examining hepatitis C virus testing practices in primary care clinics. J Viral Hepat. 2012;19(2):e163-9. doi: 10.1111/j.1365-2893.2011.01539.x. PMID: 22239514. Excluded for ineligible outcome.

Alqahtani SA, Afdhal N, Zeuzem S, et al. Safety and tolerability of ledipasvir/sofosbuvir with and without ribavirin in patients with chronic hepatitis C virus genotype 1 infection: analysis of phase III ION trials. Hepatology. 2015;62(1):25-30. doi: 10.1002/hep.27890. PMID: 25963890. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

American College of Obstetricians and Gynecologists' Committee on Gynecological Practice. Committee opinion no. 655: hepatitis B, hepatitis C, and human immunodeficiency virus infections in obstetrician-gynecologists. Obstet Gynecol. 2016;127(2):e70-4. doi: 10.1097/AOG.0000000000001315. PMID: 26942390. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Ampuero J, Reddy KR, Romero-Gomez M. Hepatitis C virus genotype 3: meta-analysis on sustained virologic response rates with currently available treatment options. World J Gastroenterol. 2016;22(22):5285-92. doi: 10.3748/wjg.v22.i22.5285. PMID: 27298572. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

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Anderson ES, Pfeil SK, Deering LJ, et al. High-impact hepatitis C virus testing for injection drug users in an urban ED. Am J Emerg Med. 2016;34(6):1108-11. doi: 10.1016/j.ajem.2016.03.004. PMID: 27037135. Excluded for ineligible study design for Key Question.

Andriulli A, Cursaro C, Cozzolongo R, et al. Early discontinuation of ribavirin in HCV-2 and HCV-3 patients responding to peg-interferon alpha-2a and ribavirin. J Viral Hepat. 2009;16(1):28-35. doi: 10.1111/j.1365-2893.2008.01044.x. PMID: 18761603. Excluded for outdated medication.

Anonymous. Corrections to: "Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS)" [Lancet Infect Dis (2015), 15: 397-404]. Lancet Infect Dis. 2015;15(7):761. doi: 10.1016/S1473-3099(15)00111-5. PMID: 26122440. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Anonymous. Erratum: simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet. 2016;387(10030):1816. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Anonymous. Correction: ombitasvir, paritaprevir, and ritonavir plus ribavirin for chronic hepatitis C virus genotype 4 infection in Egyptian patients with or without compensated cirrhosis (AGATE-II): a multicentre, phase 3, partly randomised open-label trial. Lancet Gastroenterol Hepatol. 2016;1(1):e1. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Aqel B, Leise M, Vargas HE, et al. Multicenter experience using ledipasvir/sofosbuvir +/- RBV to treat HCV GT 1 relapsers after simeprevir and sofosbuvir treatment. Ann Hepatol. 2018;17(5):815-21. doi: 10.5604/01.3001.0012.3142. PMID: 30145562. Excluded for ineligible population.

Aqel BA, Pungpapong S, Leise M, et al. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 in patients with cirrhosis. Hepatology. 2015;62(4):1004-12. doi: 10.1002/hep.27937. PMID: 26096332. Excluded for ineligible population.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Arora S, O'Brien C, Zeuzem S, et al. Treatment of chronic hepatitis C patients with persistently normal alanine aminotransferase levels with the combination of peginterferon alpha-2a (40 kDa) plus ribavirin: impact on health-related quality of life. J Gastroenterol Hepatol. 2006;21(2):406-12. doi: 10.1111/j.1440-1746.2005.04059.x. PMID: 16509866. Excluded for ineligible outcome.

Asahina Y, Itoh Y, Ueno Y, et al. Ledipasvir-sofosbuvir for treating Japanese patients with chronic hepatitis C virus genotype 2 infection. Liver Int. 2018;38(9):1552-61. doi: 10.1111/liv.13685. PMID: 29297980. Excluded for ineligible population.

Ascione A, De Luca M, Tartaglione MT, et al. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. Gastroenterology. 2010;138(1):116-22. doi: 10.1053/j.gastro.2009.10.005. PMID: 19852964. Excluded for outdated medication.

Asselah T. Sofosbuvir-based interferon-free therapy for patients with HCV infection. J Hepatol. 2013;59(6):1342-5. doi: 10.1016/j.jhep.2013.07.023. PMID: 23891655. Excluded for ineligible study design for Key Question.

Asselah T, Hezode C, Qaqish RB, et al. Ombitasvir, paritaprevir, and ritonavir plus ribavirin in adults with hepatitis C virus genotype 4 infection and cirrhosis (AGATE-I): a multicentre, phase 3, randomised open-label trial. Lancet Gastroenterol Hepatol. 2016;1(1):25-35. doi: 10.1016/S2468-1253(16)30001-2. PMID: 28404108. Excluded for ineligible population.

Asselah T, Tran T, Alves K, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients with HCV genotype 5 or 6 infection: The ENDURANCE-5,6 study. J Hepatol. 2018;68:S39. doi: 10.1016/s0168-8278(18)30294-0. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Atsukawa M, Tsubota A, Toyoda H, et al. Efficacy and safety of ombitasvir/paritaprevir/ritonavir and ribavirin for chronic hepatitis patients infected with genotype 2a in Japan. Hepatol Res. 2018;28:28. doi: 10.1111/hepr.13292. PMID: 30485638. Excluded for ineligible population.

Attia D, El Saeed K, Elakel W, et al. The adverse effects of interferon-free regimens in 149 816 chronic hepatitis C treated Egyptian patients. Aliment Pharmacol Ther. 2018;47(9):1296-305. doi: 10.1111/apt.14538. PMID: 29504152. Excluded for ineligible population.

Aziz H, Aziz M, Gill ML. Analysis of host and viral-related factors associated to direct acting antiviral response in hepatitis C virus patients. Viral Immunol. 2018;31(3):256-63. doi: 10.1089/vim.2017.0124. PMID: 29664710. Excluded for ineligible intervention.

Azzaroli F, Accogli E, Nigro G, et al. Interferon plus ribavirin and interferon alone in preventing hepatocellular carcinoma: a prospective study on patients with HCV related cirrhosis. World J Gastroenterol. 2004;10(21):3099-102. PMID: 15457551. Excluded for ineligible population.

Babatin MA, AlGhamdi AS, Assiri AM, et al. Treatment efficacy of ledipasvir/sofosbuvir for 8 weeks in non-cirrhotic chronic hepatitis C genotype 4 patients. Saudi J Gastroentero. 2019;25(1):55-60. doi: 10.4103/sjg.SJG_189_18. PMID: 30117490. Excluded for ineligible intervention.

Backus LI, Belperio PS, Shahoumian TA, et al. Comparative effectiveness of ledipasvir/sofosbuvir +/- ribavirin vs. ombitasvir/paritaprevir/ritonavir + dasabuvir +/- ribavirin in 6961 genotype 1 patients treated in routine medical practice. Aliment Pharmacol Ther. 2016;44(4):400-10. doi: 10.1111/apt.13696. PMID: 27291852. Excluded for ineligible study design for Key Question.

Bang C, Song I. Impact of antiviral therapy on hepatocellular carcinoma and mortality in patients with chronic hepatitis C: systematic review and meta-analysis. BMC Gastroenterol. 2017;17(1):46. doi: 10.1186/s12876-017-0606-9. PMID: 28376711. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Barron J, Xie Y, Wu SJ, et al. Treatment of chronic hepatitis C infection with sofosbuvir-based regimens in a commercially insured patient population. Am Health Drug Benefits. 2016;9(6):327-35. PMID: 27924186. Excluded for ineligible study design for Key Question.

Bassiony MM, Yousef A, Yousef U, et al. Major depressive disorder and generalized anxiety disorder and response to treatment in hepatitis C patients in Egypt. Int J Psychiatry Med. 2015;50(2):147-62. doi: 10.1177/0091217415605029. PMID: 26405268. Excluded for ineligible intervention.

Basu P, Shah NJ, Aloysius MM, Brown RS Jr. . Interferon ineligible naïve chronic hepatitis C genotype I subjects treated with simeprevir and sofosbuvir in special population (psychiatric). A clinical pilot study; Inspire C study; interim results. HPB (Oxford). 2015;S2(17):46. Excluded for ineligible comparator.

Bell AM, Wagner JL, Barber KE, et al. Elbasvir/Grazoprevir: a review of the latest agent in the fight against hepatitis C. Int J Hepatol. 2016;2016:3852126. doi: 10.1155/2016/3852126. PMID: 27403342. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Belperio PS, Shahoumian TA, Loomis TP, et al. Real-world effectiveness of daclatasvir plus sofosbuvir and velpatasvir/sofosbuvir in hepatitis C genotype 2 and 3. J Hepatol. 2019;70(1):15-23. doi: 10.1016/j.jhep.2018.09.018. PMID: 30266283. Excluded for ineligible study design for Key Question.

Berden FA, Aaldering BR, Groenewoud H, et al. Identification of the best direct-acting antiviral regimen for patients with hepatitis C virus genotype 3 infection: a systematic review and network meta-analysis. Clin Gastroenterol Hepatol. 2017;15(3):349-59. doi: 10.1016/j.cgh.2016.10.034. PMID: 27840182. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Bernardinello E, Cavalletto L, Chemello L, et al. Long-term clinical outcome after beta-interferon therapy in cirrhotic patients with chronic hepatitis C. TVVH Study Group. Hepatogastroenterology. 1999;46(30):3216-22. PMID: 10626189. Excluded for ineligible population.

Bernstein D, Kleinman L, Barker CM, et al. Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients. Hepatology. 2002;35(3):704-8. doi: 10.1053/jhep.2002.31311. PMID: 11870387. Excluded for outdated medication.

Bezemer G, Van Gool AR, Verheij-Hart E, et al. Long-term effects of treatment and response in patients with chronic hepatitis C on quality of life. An international, multicenter, randomized, controlled study. BMC Gastroenterol. 2012;12:11. doi: 10.1186/1471-230X-12-11. PMID: 22292521. Excluded for ineligible intervention.

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Bonkovsky HL, Woolley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy. The Consensus Interferon Study Group. Hepatology. 1999;29(1):264-70. doi: 10.1002/hep.510290124. PMID: 9862876. Excluded for ineligible outcome.

Boyd SD, Harrington P, Komatsu TE, et al. HCV genotype 4, 5 and 6: Distribution of viral subtypes and sustained virologic response rates in clinical trials of approved direct-acting antiviral regimens. J Viral Hepat. 2018;25(8):969-75. doi: 10.1111/jvh.12896. PMID: 29577495. Excluded for ineligible study design for Key Question.

Braks RE, Ganne-Carrie N, Fontaine H, et al. Effect of sustained virological response on long-term clinical outcome in 113 patients with compensated hepatitis C-related cirrhosis treated by interferon alpha and ribavirin. World J Gastroenterol. 2007;13(42):5648-53. PMID: 17948941. Excluded for ineligible population.

Bronowicki JP, Ouzan D, Asselah T, et al. Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirin. Gastroenterology. 2006;131(4):1040-8. doi: 10.1053/j.gastro.2006.07.022. PMID: 17030174. Excluded for ineligible intervention.

Bronowicki JP, Pol S, Thuluvath PJ, et al. Randomized study of asunaprevir plus pegylated interferon-alpha and ribavirin for previously untreated genotype 1 chronic hepatitis C. Antivir Ther. 2013;18(7):885-93. doi: 10.3851/IMP2660. PMID: 23804631. Excluded for ineligible intervention.

Brook RA, Kleinman NL, Su J, et al. Absenteeism and productivity among employees being treated for hepatitis C. Am J Manag Care. 2011;17(10):657-64. PMID: 22106459. Excluded for ineligible outcome.

Bruix J, Poynard T, Colombo M, et al. Maintenance therapy with peginterferon alfa-2b does not prevent hepatocellular carcinoma in cirrhotic patients with chronic hepatitis C. Gastroenterology. 2011;140(7):1990-9. doi: 10.1053/j.gastro.2011.03.010. PMID: 21419770. Excluded for ineligible population.

Bruno G, Saracino A, Fabrizio C, et al. Safety and effectiveness of a 12-week course of sofosbuvir and simeprevir+/-ribavirin in HCV-infected patients with or without HIV infection: a multicentre observational study. Int J Antimicrob Agents. 2017;49(3):296-301. doi: 10.1016/j.ijantimicag.2016.11.030. PMID: 28163136. Excluded for ineligible study design for Key Question.

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Buti M, Calleja JL, Lens S, et al. Simeprevir in combination with sofosbuvir in treatment-naive and -experienced patients with hepatitis C virus genotype 4 infection: a Phase III, open-label, single-arm study (PLUTO). Aliment Pharmacol Ther. 2017;45(3):468-75. doi: 10.1111/apt.13883. PMID: 27896822. Excluded for ineligible intervention.

Buti M, Dominguez-Hernandez R, Casado MA, et al. Healthcare value of implementing hepatitis C screening in the adult general population in Spain. PLoS One. 2018;13(11):e0208036. doi: 10.1371/journal.pone.0208036. PMID: 30485377. Excluded for ineligible study design for Key Question.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Buti M, Flisiak R, Kao JH, et al. Alisporivir with peginterferon/ribavirin in patients with chronic hepatitis C genotype 1 infection who failed to respond to or relapsed after prior interferon-based therapy: FUNDAMENTAL, a Phase II trial. J Viral Hepat. 2015;22(7):596-606. doi: 10.1111/jvh.12360. PMID: 25412795. Excluded for ineligible intervention.

Butt AA, Ren Y, Marks K, et al. Do directly acting antiviral agents for HCV increase the risk of hepatic decompensation and decline in renal function? Results from ERCHIVES. Aliment Pharmacol Ther. 2017;45(1):150-9. doi: 10.1111/apt.13837. PMID: 27813162. Excluded for ineligible study design for Key Question.

Butt AA, Yan P, Marks K, et al. Adding ribavirin to newer DAA regimens does not affect SVR rates in HCV genotype 1 infected persons: results from ERCHIVES. Aliment Pharmacol Ther. 2016;44(7):728-37. doi: 10.1111/apt.13748. PMID: 27459341. Excluded for ineligible study design for Key Question.

Butt AA, Yan P, Shaikh OS, et al. Hepatitis B reactivation and outcomes in persons treated with directly acting antiviral agents against hepatitis C virus: results from ERCHIVES. Aliment Pharmacol Ther. 2018a;47(3):412-20. doi: 10.1111/apt.14426. PMID: 29181838. Excluded for ineligible study design for Key Question.

Cacoub P, Desbois AC, Comarmond C, et al. Impact of sustained virological response on the extrahepatic manifestations of chronic hepatitis C: a meta-analysis. Gut. 2018:2025-34. doi: 10.1136/gutjnl-2018-316234. PMID: 29703790. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Cacoub P, Lidove O, Maisonobe T, et al. Interferon-alpha and ribavirin treatment in patients with hepatitis C virus-related systemic vasculitis. Arthritis Rheum. 2002;46(12):3317-26. doi: 10.1002/art.10699. PMID: 12483738. Excluded for ineligible intervention.

Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol. 2010;52(5):652-7. doi: 10.1016/j.jhep.2009.12.028. PMID: 20346533. Excluded for ineligible population.

Caroleo B, Colangelo L, Perticone M, et al. Efficacy and safety of elbasvir-grazoprevir fixed dose in the management of polytreated HCV patients: evidence from real-life clinical practice. J Clin Pharmacol. 2018;58(10):1248-53. doi: 10.1002/jcph.1135. PMID: 29746724. Excluded for ineligible outcome.

Cha RR, Lee SS, Lee CM, et al. Clinical features and outcomes of patients with genotype 3 hepatitis C virus infection in Korea: a retrospective observational study. Medicine. 2016;95(6):e2755. doi: 10.1097/MD.0000000000002755. PMID: 26871824. Excluded for ineligible population.

Chahine EB, Sucher AJ, Hemstreet BA. Sofosbuvir/velpatasvir: the first pangenotypic direct-acting antiviral combination for hepatitis C. Ann Pharmacother. 2017;51(1):44-53. doi: 10.1177/1060028016668897. PMID: 27609942. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Chamorro-de-Vega E, Gimenez-Manzorro A, Rodriguez-Gonzalez CG, et al. Effectiveness and safety of ombitasvir-paritaprevir/ritonavir and dasabuvir with or without ribavirin for HCV genotype 1 infection for 12 weeks under routine clinical practice. Ann Pharmacother. 2016;50(11):901-8. doi: 10.1177/1060028016659306. PMID: 27422641. Excluded for ineligible population.

Chan HLY, Tsang OTY, Hui YT, et al. Real-life efficacy and safety of paritaprevir/ ritonavir, ombitasvir and dasabuvir combination with or without ribavirin in difficult-to-treat genotype 1 chronic hepatitis C patients in Hong Kong. J Gastroenterol Hepatol. 2016;31(378). Excluded for ineligible population.

Chang KC, Ye YH, Wu CK, et al. Risk factors for development of hepatocellular carcinoma in patients with chronic hepatitis C without sustained response to combination therapy. J Formos Med Assoc. 2018;117(11):1011-8. doi: 10.1016/j.jfma.2017.11.008. PMID: 29254684. Excluded for ineligible population.

Chang SC, Yang SS, Chang CC, et al. Assessment of health-related quality of life in antiviral-treated Taiwanese chronic hepatitis C patients using SF-36 and CLDQ. Health Qual Life Outcomes. 2014;12:97. doi: 10.1186/1477-7525-12-97. PMID: 24941994. Excluded for ineligible intervention.

Chayama K, Notsumata K, Kurosaki M, et al. Randomized trial of interferon- and ribavirin-free ombitasvir/paritaprevir/ritonavir in treatment-experienced hepatitis C virus-infected patients. Hepatology. 2015;61(5):1523-32. doi: 10.1002/hep.27705. PMID: 25644279. Excluded for ineligible intervention.

Chen J, Shi J, Xie WF, et al. Meta-analysis: amantadine may lower the efficacy of pegylated interferon plus ribavirin in treatment-naive hepatitis C genotype 1 patients. Int J Infect Dis. 2012;16(10):e748-52. doi: 10.1016/j.ijid.2012.06.002. PMID: 22836046. Excluded for ineligible intervention.

Cheng PN, Chiu YC, Chien SC, et al. Real-world effectiveness and safety of sofosbuvir plus daclatasvir with or without ribavirin for genotype 2 chronic hepatitis C in Taiwan. J Formos Med Assoc. 2018;11:11. doi: 10.1016/j.jfma.2018.09.016. PMID: 30316677. Excluded for ineligible population.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Cho Y, Cho EJ, Lee JH, et al. Sofosbuvir-based therapy for patients with chronic hepatitis C: early experience of its efficacy and safety in Korea. Clin Mol Hepatol. 2015;21(4):358-64. doi: 10.3350/cmh.2015.21.4.358. PMID: 26770924. Excluded for ineligible study design for Key Question.

Chopp S, Vanderwall R, Hult A, et al. Simeprevir and sofosbuvir for treatment of hepatitis C infection. Am J Health Syst Pharm. 2015;72(17):1445-55. PMID: 26294237. Excluded for ineligible study design for Key Question.

Chung W, Kim KA, Jang ES, et al. Cost-effectiveness of sofosbuvir plus ribavirin therapy for hepatitis C virus genotype 2 infection in South Korea. J Gastroenterol Hepatol. 2018;21:21. doi: 10.1111/jgh.14554. PMID: 30462841. Excluded for ineligible outcome.

Conte D, Fraquelli M, Prati D, et al. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. Hepatology. 2000;31(3):751-5. doi: 10.1002/hep.510310328. PMID: 10706568. Excluded for poor quality.

Cornberg M, Petersen J, Schober A, et al. Real-world use, effectiveness and safety of anti-viral treatment in chronic hepatitis C genotype 3 infection. Aliment Pharmacol Ther. 2017;45(5):688-700. doi: 10.1111/apt.13925. PMID: 28078723. Excluded for ineligible study design for Key Question.

Coughlan B, Sheehan J, Carr A, et al. Evaluation of a brief group based psychological/educational treatment programme for women with an iatrogenic chronic hepatitis C virus infection. J Clin Psychol Med Settings. 2004;11(4):303-14. Excluded for poor quality.

Coverdale SA, Khan MH, Byth K, et al. Effects of interferon treatment response on liver complications of chronic hepatitis C: 9-year follow-up study. Am J Gastroenterol. 2004;99(4):ajg2004123. doi: 10.1111/j.1572-0241.2004.04085.x. PMID: 15089895. Excluded for ineligible population.

Coyle C, Moorman AC, Bartholomew T, et al. The HCV care continuum: linkage to HCV care and treatment among patients at an urban health network, Philadelphia, PA. Hepatology. 2019 doi: 10.1002/hep.30501. PMID: 30633811. Excluded for ineligible outcome.

Cucchetti A, D'Amico G, Trevisani F, et al. Effect of direct-acting antivirals on future occurrence of hepatocellular carcinoma in compensated cirrhotic patients. Dig Liver Dis. 2018;50(2):156-62. doi: 10.1016/j.dld.2017.10.004. PMID: 29102521. Excluded for ineligible outcome.

Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med. 2015;373(27):2618-28. doi: 10.1056/NEJMoa1512614. PMID: 26569658. Excluded for ineligible population.

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Dalgard O, Bjoro K, Ring-Larsen H, et al. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. Hepatology. 2008;47(1):35-42. doi: 10.1002/hep.21975. PMID: 17975791. Excluded for outdated medication.

Dalgard O, Weiland O, Noraberg G, et al. Sofosbuvir based treatment of chronic hepatitis C genotype 3 infections-A Scandinavian real-life study. PLoS One. 2017;12(7):e0179764. doi: 10.1371/journal.pone.0179764. PMID: 28704381. Excluded for ineligible population.

Damiani G, Franchi C, Pigatto P, et al. Outcomes assessment of hepatitis C virus-positive psoriatic patients treated using pegylated interferon in combination with ribavirin compared to new direct-acting antiviral agents. World J Hepatol. 2018;10(2):329-36. doi: 10.4254/wjh.v10.i2.329. PMID: 29527268. Excluded for ineligible study design for Key Question.

Davitkov P, Chandar AK, Hirsch A, et al. Treatment selection choices should not be based on benefits or costs alone: a head-to-head randomized controlled trial of antiviral drugs for hepatitis C. PLoS One. 2016;11(10):e0163945. doi: 10.1371/journal.pone.0163945. PMID: 27741230. Excluded for ineligible intervention.

Del Rio-Valencia JC, Asensi-Diez R, Madera-Pajin R, et al. Interferon-free treatments in patients with hepatitis C genotype 3 infection in a tertiary hospital. Rev Esp Quimioter. 2018;31(1):35-42. PMID: 29376623. Excluded for ineligible study design for Key Question.

Delamare C, Carbonne B, Heim N, et al. Detection of hepatitis C virus RNA (HCV RNA) in amniotic fluid: a prospective study. J Hepatol. 1999;31(3):416-20. PMID: 10488698. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Delotte J, Barjoan EM, Berrebi A, et al. Obstetric management does not influence vertical transmission of HCV infection: results of the ALHICE group study. J Matern Fetal Neonatal Med. 2014;27(7):664-70. doi: 10.3109/14767058.2013.829813. PMID: 23971940. Excluded for insufficient statistical analysis.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Desnoyer A, Pospai D, Le MP, et al. Pharmacokinetics, safety and efficacy of a full dose sofosbuvir-based regimen given daily in hemodialysis patients with chronic hepatitis C. J Hepatol. 2016;65(1):40-7. PMID: 26952005. Excluded for ineligible population.

Deterding K, Spinner CD, Schott E, et al. Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. Lancet Infect Dis. 2017;17(2):215-22. PMID: 28029529. Excluded for ineligible intervention.

Dhiman RK, Grover GS, Premkumar M, et al. Direct-acting antiviral therapy is safe and effective in pediatric chronic hepatitis C: the public health perspective. J Pediatr Gastroenterol Nutr. 2019;68(1):74-80. doi: 10.1097/MPG.0000000000002139. PMID: 30211847. Excluded for ineligible study design for Key Question.

Di Martino V, Crouzet J, Hillon P, et al. Long-term outcome of chronic hepatitis C in a population-based cohort and impact of antiviral therapy: a propensity-adjusted analysis. J Viral Hepat. 2011;18(7):493-505. doi: 10.1111/j.1365-2893.2011.01476.x. PMID: 21692956. Excluded for insufficient statistical analysis.

Dieterich D, Nelson M, Soriano V, et al. Faldaprevir and pegylated interferon alpha-2a/ribavirin in individuals co-infected with hepatitis C virus genotype-1 and HIV. AIDS. 2015;29(5):571-81. doi: 10.1097/QAD.0000000000000579. PMID: 25710287. Excluded for ineligible intervention.

D'Offizi G, Camma C, Taibi C, et al. Clinical and virological predictors of sustained response with an interferon-based simeprevir regimen for patients with chronic genotype 1 hepatitis C virus infection. New Microbiol. 2017;40(1):19-26. PMID: 28072888. Excluded for ineligible intervention.

Dore GJ, Altice F, Litwin AH, et al. Elbasvir-grazoprevir to treat hepatitis C virus infection in persons receiving opioid agonist therapy: a randomized trial. Ann Intern Med. 2016;165(9):625-34. doi: 10.7326/M16-0816. PMID: 27537841. Excluded for ineligible population.

Dore GJ, Lawitz E, Hezode C, et al. Daclatasvir plus peginterferon and ribavirin is noninferior to peginterferon and ribavirin alone, and reduces the duration of treatment for HCV genotype 2 or 3 infection. Gastroenterology. 2015;148(2):355-66.e1. doi: 10.1053/j.gastro.2014.10.007. PMID: 25311593. Excluded for ineligible intervention.

Doss W, Shiha G, Hassany M, et al. Sofosbuvir plus ribavirin for treating Egyptian patients with hepatitis C genotype 4. J Hepatol. 2015;63(3):581-5. doi: 10.1016/j.jhep.2015.04.023. PMID: 25937436. Excluded for ineligible intervention.

Dultz G, Muller T, Petersen J, et al. Effectiveness and safety of direct-acting antiviral combination therapies for treatment of hepatitis C virus in elderly patients: results from the German hepatitis C registry. Drugs Aging. 2018;35(9):843-57. doi: 10.1007/s40266-018-0572-0. PMID: 30084012. Excluded for ineligible study design for Key Question.

Dusheiko G. The impact of antiviral therapy for hepatitis C on the quality of life: a perspective. Liver Int. 2017;37 Suppl 1:7-12. doi: 10.1111/liv.13292. PMID: 28052638. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Dusheiko GM, Manns MP, Vierling JM, et al. Safety and tolerability of grazoprevir/elbasvir in patients with chronic hepatitis C (HCV) infection: Integrated analysis of phase 2-3 trials. Hepatology. 2015;62:562A. Excluded for ineligible population.

El Kassas M, Elbaz T, Hafez E, et al. Safety of direct antiviral agents in the management of hepatitis C. Expert Opin Drug Saf. 2016;15(12):1643-52. doi: 10.1080/14740338.2017.1240781. PMID: 27661100. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

El Raziky M, Gamil M, Ashour MK, et al. Simeprevir plus sofosbuvir for eight or 12 weeks in treatment-naive and treatment-experienced hepatitis C virus genotype 4 patients with or without cirrhosis. J Viral Hepat. 2017;24(2):102-10. PMID: 27790789. Excluded for ineligible intervention.

El-Karaksy HM, Mogahed EA, El-Raziky MS, et al. Safety and efficacy of combined treatment with pegylated interferon alpha-2b and ribavirin for HCV genotype 4 in children. J Interferon Cytokine Res. 2016;36(1):1-8. doi: 10.1089/jir.2015.0066. PMID: 26406390. Excluded for ineligible intervention.

el-Khattib AA, Abdelhakam SM, Ghoraba DM, et al. Outcome of antiviral therapy in Egyptian hepatitis C virus (HCV) genotype 4 patients with advanced liver fibrosis. Eur J Intern Med. 2012;23(1):e34-5. doi: 10.1016/j.ejim.2011.10.003. PMID: 22153547. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

El-Khayat H, Kamal EM, Yakoot M, et al. Effectiveness of 8-week sofosbuvir/ledipasvir in the adolescent chronic hepatitis C-infected patients. Eur J Gastroenterol Hepatol. 2019;22:22. doi: 10.1097/MEG.0000000000001360. PMID: 30676473. Excluded for ineligible study design for Key Question.

El-Khayat HR, Kamal EM, El-Sayed MH, et al. The effectiveness and safety of ledipasvir plus sofosbuvir in adolescents with chronic hepatitis C virus genotype 4 infection: a real-world experience. Aliment Pharmacol Ther. 2018;47(6):838-44. doi: 10.1111/apt.14502. PMID: 29349793. Excluded for ineligible study design for Key Question.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

El-Serag HB, Alsarraj A, Richardson P, et al. Hepatocellular carcinoma screening practices in the Department of Veterans Affairs: findings from a national facility survey. Dig Dis Sci. 2013;58(11):3117-26. doi: 10.1007/s10620-013-2794-7. PMID: 23868438. Excluded for ineligible intervention.

Ennaifer R, Sabbah M, Hefaiedh R, et al. Antiviral therapy for hepatitis C virus infection, cryoglobulinemic glomerulonephritis and low-grade malignant lymphoma: a challenge? Tunis Med. 2015;93(3):203-4. PMID: 26367421. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Escudero A, Rodriguez F, Serra MA, et al. Pegylated alpha-interferon-2a plus ribavirin compared with pegylated alpha-interferon-2b plus ribavirin for initial treatment of chronic hepatitis C virus: prospective, non-randomized study. J Gastroenterol Hepatol. 2008;23(6):861-6. doi: 10.1111/j.1440-1746.2008.05397.x. PMID: 18422960. Excluded for outdated medication.

Esteban R, Pineda JA, Calleja JL, et al. Efficacy of sofosbuvir and velpatasvir, with and without ribavirin, in patients with hepatitis C virus genotype 3 infection and cirrhosis. Gastroenterology. 2018;155(4):1120-7.e4. doi: 10.1053/j.gastro.2018.06.042. PMID: 29958855. Excluded for ineligible population.

Everson G, Cooper C, Hezode C, et al. DAUPHINE: a randomized phase II study of danoprevir/ritonavir plus peginterferon alpha-2a/ribavirin in HCV genotypes 1 or 4. Liver Int. 2015;35(1):108-19. doi: 10.1111/liv.12471. PMID: 24517252. Excluded for ineligible intervention.

Fabris P, Tositti G, Giordani MT, et al. Assessing patients' understanding of hepatitis C virus infection and its impact on their lifestyle. Aliment Pharmacol Ther. 2006;23(8):1161-70. doi: 10.1111/j.1365-2036.2006.02882.x. PMID: 16611277. Excluded for poor quality.

Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, et al. Oral direct-acting agent therapy for hepatitis C virus infection: a systematic review. Ann Intern Med. 2017;166(9):637-48. doi: 10.7326/m16-2575. PMID: 28319996. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Fartoux L, Degos F, Trepo C, et al. Effect of prolonged interferon therapy on the outcome of hepatitis C virus-related cirrhosis: a randomized trial. Clin Gastroenterol Hepatol. 2007;5(4):502-7. doi: 10.1016/j.cgh.2006.10.016. PMID: 17261383. Excluded for ineligible population.

Fazel Y, Lam B, Golabi P, et al. Safety analysis of sofosbuvir and ledipasvir for treating hepatitis C. Expert Opin Drug Saf. 2015;14(8):1317-26. doi: 10.1517/14740338.2015.1053868. PMID: 26043900. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Feld JJ, Grebely J, Matthews GV, et al. Plasma interferon-gamma-inducible protein-10 levels are associated with early, but not sustained virological response during treatment of acute or early chronic HCV infection. PLoS One. 2013;8(11):e80003. doi: 10.1371/journal.pone.0080003. PMID: 24278230. Excluded for ineligible intervention.

Ferenci P, Brunner H, Laferl H, et al. A randomized, prospective trial of ribavirin 400 mg/day versus 800 mg/day in combination with peginterferon alfa-2a in hepatitis C virus genotypes 2 and 3. Hepatology. 2008;47(6):1816-23. doi: 10.1002/hep.22262. PMID: 18454510. Excluded for outdated medication.

Ferenci P, Caruntu FA, Lengyel G, et al. Boceprevir plus peginterferon alfa-2a/ribavirin in treatment-naive hepatitis C virus genotype 1 patients: International Phase IIIb/IV TriCo Trial. Infect Dis Ther. 2016;5(2):113-24. doi: 10.1007/s40121-016-0110-5. PMID: 27228998. Excluded for ineligible outcome.

Fernández-Rodríguez CM, Alonso S, Martinez SM, et al. Peginterferon plus ribavirin and sustained virological response in HCV-related cirrhosis: outcomes and factors predicting response. Am J Gastroenterol. 2010;105(10):2164. doi: 10.1038/ajg.2010.294. PMID: 20700116. Excluded for ineligible population.

Flamm SL, Muir AJ, Fried MW, et al. Sustained virologic response rates with telaprevir-based therapy in treatment-naive patients evaluated by race or ethnicity. J Clin Gastroenterol. 2015;49(4):336-44. doi: 10.1097/MCG.0000000000000150. PMID: 24828357. Excluded for ineligible outcome.

Flisiak R, Janczewska E, Wawrzynowicz-Syczewska M, et al. Real-world effectiveness and safety of ombitasvir/paritaprevir/ritonavir +/- dasabuvir +/- ribavirin in hepatitis C: AMBER study. Aliment Pharmacol Ther. 2016;44(9):946-56. doi: 10.1111/apt.13790. PMID: 27611776. Excluded for ineligible study design for Key Question.

Fontana RJ, Litman HJ, Dienstag JL, et al. YKL-40 genetic polymorphisms and the risk of liver disease progression in patients with advanced fibrosis due to chronic hepatitis C. Liver Int. 2012;32(4):665-74. doi: 10.1111/j.1478-3231.2011.02686.x. PMID: 22103814. Excluded for ineligible population.

Fouad HM, Ahmed Mohamed A, Sabry M, et al. The effectiveness of ledipasvir/sofosbuvir in youth with genotype 4 hepatitis C virus: a single Egyptian center study. Pediatr Infect Dis J. 2019;38(1):22-5. doi: 10.1097/INF.0000000000002189. PMID: 30234791. Excluded for ineligible study design for Key Question.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Fujii Y, Uchida Y, Mochida S. Drug-induced immunoallergic hepatitis during combination therapy with daclatasvir and asunaprevir. Hepatology. 2015;61(1):400-1. doi: 10.1002/hep.27559. PMID: 25308083. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Gamal N, Andreone P. Safety and efficacy of once daily ledipasvir/sofosbuvir fixed-dose combination in patients with chronic hepatitis C. Expert Opin Drug Saf. 2016;15(4):549-57. doi: 10.1517/14740338.2016.1157163. PMID: 26899025. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Gane EJ, Hyland RH, Yang Y, et al. Efficacy of ledipasvir plus sofosbuvir for 8 or 12 weeks in patients with hepatitis C virus genotype 2 infection. Gastroenterology. 2017;152(6):1366-71. doi: 10.1053/j.gastro.2017.01.017. PMID: 28137593. Excluded for ineligible intervention.

Gane EJ, Kowdley KV, Pound D, et al. Efficacy of sofosbuvir, velpatasvir, and GS-9857 in patients with hepatitis C virus genotype 2, 3, 4, or 6 infections in an open-label, phase 2 trial. Gastroenterology. 2016;151(5):902-9. doi: 10.1053/j.gastro.2016.07.038. PMID: 27486033. Excluded for ineligible intervention.

Gane EJ, Stedman CA, Hyland RH, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. Gastroenterology. 2014;146(3):736-43.e1. doi: 10.1053/j.gastro.2013.11.007. PMID: 24262278. Excluded for ineligible intervention.

Garland SM, Tabrizi S, Robinson P, et al. Hepatitis C-role of perinatal transmission. Aust N Z J Obstet Gynaecol. 1998;38(4):424-7. PMID: 9890224. Excluded for poor quality.

Gentile I, Borgia G. Randomised controlled trial: ledipasvir/sofosbuvir administration achieves very high rate of viral clearance in patients with HCV genotype 1 infection without cirrhosis, regardless of ribavirin co-administration or length of treatment. BMJ Evid Based Med. 2014;19(6):223-4. Excluded for ineligible study design for Key Question.

George J, Burnevich E, Sheen IS, et al. Elbasvir/grazoprevir in Asia-Pacific/Russian participants with chronic hepatitis C virus genotype 1, 4, or 6 infection. Hepatol Commun. 2018;2(5):595-606. doi: 10.1002/hep4.1177. PMID: 29761174. Excluded for ineligible study design for Key Question.

Gerber L, Estep M, Stepanova M, et al. Effects of viral eradication with ledipasvir and sofosbuvir, with or without ribavirin, on measures of fatigue in patients with chronic hepatitis C virus infection. Clin Gastroenterol Hepatol. 2016;14(1):156-64.e3. doi: 10.1016/j.cgh.2015.07.035. PMID: 26241510. Excluded for ineligible study design for Key Question.

Giordanino C, Sacco M, Ceretto S, et al. Durability of the response to peginterferon-alpha2b and ribavirin in patients with chronic hepatitis C: a cohort study in the routine clinical setting. Eur J Gastroenterol Hepatol. 2014;26(1):52-8. doi: 10.1097/MEG.0b013e328362dc99. PMID: 23719564. Excluded for ineligible outcome.

Gopalakrishnan S, Khatri A, Mensing S, et al. Exposure-response relationship for ombitasvir and paritaprevir/ritonavir in hepatitis C virus subgenotype 1b-infected Japanese patients in the phase 3 randomized GIFT-I study. Adv Ther. 2016;33(4):670-83. doi: 10.1007/s12325-016-0320-y. PMID: 27084721. Excluded for ineligible study design for Key Question.

Granovsky MO, Minkoff HL, Tess BH, et al. Hepatitis C virus infection in the mothers and infants cohort study. Pediatrics. 1998;102(2 Pt 1):355-9. PMID: 9685438. Excluded for insufficient statistical analysis.

Grebely J, Feld JJ, Wyles D, et al. Sofosbuvir-based direct-acting antiviral therapies for HCV in people receiving opioid substitution therapy: an analysis of phase 3 studies. Open Forum Infect Dis. 2018;5(2):ofy001. doi: 10.1093/ofid/ofy001. PMID: 29450210. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Grebely J, Mauss S, Brown A, et al. Efficacy and safety of ledipasvir/sofosbuvir with and without ribavirin in patients with chronic HCV genotype 1 infection receiving opioid substitution therapy: analysis of phase 3 ION trials. Clin Infect Dis. 2016;63(11):1405-11. PMID: 27553375. Excluded for ineligible study design for Key Question.

Grebely J, Puoti M, Wedemeyer H, et al. Efficacy and safety of ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin in patients with chronic hepatitis C virus genotype 1 infection receiving opioid substitution therapy: a post hoc analysis of 12 clinical trials. Open Forum Infect Dis. 2018;5(11):ofy248. doi: 10.1093/ofid/ofy248. PMID: 30430131. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Greig SL. Sofosbuvir/velpatasvir: a review in chronic hepatitis C. Drugs. 2016;76(16):1567-78. doi: 10.1007/s40265-016-0648-2. PMID: 27730529. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Gunn RA, Murray PJ, Brennan CH, et al. Evaluation of screening criteria to identify persons with hepatitis C virus infection among sexually transmitted disease clinic clients: results from the San Diego Viral Hepatitis Integration Project. Sex Transm Dis. 2003;30(4):340-4. PMID: 12671556. Excluded for poor quality.

Gupta N, Mbituyumuremyi A, Kabahizi J, et al. Treatment of chronic hepatitis C virus infection in Rwanda with ledipasvir-sofosbuvir (SHARED): a single-arm trial. Lancet Gastroenterol Hepatol. 2019;4(2):119-26. doi: 10.1016/S2468-1253(18)30382-0. PMID: 30552056. Excluded for ineligible population.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Hadziyannis SJ, Sette H, Jr., Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med. 2004;140(5):346-55. PMID: 14996676. Excluded for outdated medication.

Hagiwara S, Nishida N, Watanabe T, et al. Outcome of asunaprevir/daclatasvir combination therapy for chronic liver disease type C. Dig Dis. 2016;34(6):620-6. doi: 10.1159/000448822. PMID: 27750228. Excluded for ineligible intervention.

Hagiwara S, Nishida N, Watanabe T, et al. Outcome of combination therapy with sofosbuvir and ledipasvir for chronic type C liver disease. Oncology. 2017;92 Suppl 1:3-9. doi: 10.1159/000451010. PMID: 27974712. Excluded for ineligible population.

Hajarizadeh B, Cunningham EB, Reid H, et al. Direct-acting antiviral treatment for hepatitis C among people who use or inject drugs: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2018;3(11):754-67. PMID: 30245064. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Harada N, Hiramatsu N, Oze T, et al. Risk factors for hepatocellular carcinoma in hepatitis C patients with normal alanine aminotransferase treated with pegylated interferon and ribavirin. J Viral Hepat. 2014;21(5):357-65. doi: 10.1111/jvh.12151. PMID: 24716638. Excluded for ineligible population.

Harada N, Hiramatsu N, Oze T, et al. Incidence of hepatocellular carcinoma in HCV-infected patients with normal alanine aminotransferase levels categorized by Japanese treatment guidelines. J Gastroenterol. 2013;48(4):535-43. doi: 10.1007/s00535-012-0657-1. PMID: 22976932. Excluded for ineligible population.

Hasegawa E, Kobayashi M, Kawamura Y, et al. Efficacy and anticarcinogenic activity of interferon for hepatitis C virus-related compensated cirrhosis in patients with genotype 1b low viral load or genotype 2. Hepatol Res. 2007;37(10):793-800. doi: 10.1111/j.1872-034X.2007.00140.x. PMID: 17593231. Excluded for ineligible population.

Hassanein T, Cooksley G, Sulkowski M, et al. The impact of peginterferon alfa-2a plus ribavirin combination therapy on health-related quality of life in chronic hepatitis C. J Hepatol. 2004;40(4):675-81. doi: 10.1016/j.jhep.2003.12.014. PMID: 15030985. Excluded for ineligible intervention.

Hayashi N, Seto C, Kato M, et al. Once-daily simeprevir (TMC435) with peginterferon/ribavirin for treatment-naive hepatitis C genotype 1-infected patients in Japan: the DRAGON study. J Gastroenterol. 2014;49(1):138-47. doi: 10.1007/s00535-013-0875-1. PMID: 24005956. Excluded for ineligible intervention.

Heidrich B, Wiegand SB, Buggisch P, et al. Treatment of naive patients with chronic hepatitis C genotypes 2 and 3 with pegylated interferon alpha and ribavirin in a real world setting: relevance for the new era of DAA. PLoS One. 2014;9(10):e108751. doi: 10.1371/journal.pone.0108751. PMID: 25302676. Excluded for ineligible intervention.

Helbling B, Jochum W, Stamenic I, et al. HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. J Viral Hepat. 2006;13(11):762-9. doi: 10.1111/j.1365-2893.2006.00753.x. PMID: 17052276. Excluded for outdated medication.

Hetta HF, Mekky MA, Khalil NK, et al. Extra-hepatic infection of hepatitis C virus in the colon tissue and its relationship with hepatitis C virus pathogenesis. J Med Microbiol. 2016;65(8):703-12. doi: 10.1099/jmm.0.000272. PMID: 27166142. Excluded for ineligible outcome.

Hezode C, Colombo M, Bourliere M, et al. Elbasvir/grazoprevir for patients with hepatitis C virus infection and inherited blood disorders: A phase III study. Hepatology. 2017;66(3):736-45. doi: 10.1002/hep.29139. PMID: 28256747. Excluded for ineligible population.

Hezode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med. 2009;360(18):1839-50. doi: 10.1056/NEJMoa0807650. PMID: 19403903. Excluded for outdated medication.

Hezode C, Lebray P, De Ledinghen V, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, for hepatitis C virus genotype 3 in a French early access programme. Liver Int. 2017 (pagination)doi: 10.1111/liv.13383. PMID: 28177199. Excluded for ineligible study design for Key Question.

Hill A, Khwairakpam G, Wang J, et al. High sustained virological response rates using imported generic direct acting antiviral treatment for hepatitis C. J Virus Erad. 2017;3(4):200-3. PMID: 29057082. Excluded for ineligible study design for Key Question.

Hirakawa M, Ikeda K, Arase Y, et al. Hepatocarcinogenesis following HCV RNA eradication by interferon in chronic hepatitis patients. Intern Med. 2008;47(19):1637-43. PMID: 18827409. Excluded for ineligible comparator.

Hosry J, Mahale P, Turturro F, et al. Antiviral therapy improves overall survival in hepatitis C virus-infected patients who develop diffuse large B-cell lymphoma. Int J Cancer. 2016;139(11):2519-28. doi: 10.1002/ijc.30372. PMID: 27501007. Excluded for ineligible intervention.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Hsu CS, Huang CJ, Kao JH, et al. Interferon-based therapy decreases risks of hepatocellular carcinoma and complications of cirrhosis in chronic hepatitis C patients. PLoS One. 2013;8(7):e70458. doi: 10.1371/journal.pone.0070458. PMID: 23894660. Excluded for ineligible population.

Hsu YC, Ho HJ, Huang YT, et al. Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. Gut. 2015;64(3):495-503. doi: 10.1136/gutjnl-2014-308163. PMID: 25398770. Excluded for ineligible comparator.

Hsu YC, Ho HJ, Wu MS, et al. Postoperative peg-interferon plus ribavirin is associated with reduced recurrence of hepatitis C virus-related hepatocellular carcinoma. Hepatology. 2013;58(1):150-7. doi: 10.1002/hep.26300. PMID: 23389758. Excluded for ineligible population.

Hsu YC, Lin JT, Ho HJ, et al. Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients. Hepatology. 2014;59(4):1293-302. doi: 10.1002/hep.26892. PMID: 24122848. Excluded for ineligible intervention.

Hsu YH, Hung PH, Muo CH, et al. Interferon-based treatment of hepatitis C virus infection reduces all-cause mortality in patients with end-stage renal disease: an 8-year nationwide cohort study in Taiwan. Medicine. 2015;94(47):e2113. doi: 10.1097/MD.0000000000002113. PMID: 26632730. Excluded for ineligible population.

Hu C, Yuan G, Liu J, et al. Sofosbuvir-based therapies for patients with hepatitis C virus infection: real-world experience in China. Can J Gastroenterol Hepatol. 2018;2018:3908767. doi: 10.1155/2018/3908767. PMID: 30538973. Excluded for ineligible study design for Key Question.

Hu CC, Lin CL, Kuo YL, et al. Efficacy and safety of ribavirin plus pegylated interferon alfa in geriatric patients with chronic hepatitis C. Aliment Pharmacol Ther. 2013;37(1):81-90. doi: 10.1111/apt.12112. PMID: 23121150. Excluded for ineligible intervention.

Huang JF, Yeh ML, Yu ML, et al. The tertiary prevention of hepatocellular carcinoma in chronic hepatitis C patients. J Gastroenterol Hepatol. 2015;30(12):1768-74. doi: 10.1111/jgh.13012. PMID: 26094738. Excluded for ineligible population.

Huang QT, Hang LL, Zhong M, et al. Maternal HCV infection is associated with intrauterine fetal growth disturbance: a meta-analysis of observational studies. Medicine. 2016;95(35):e4777. doi: 10.1097/MD.0000000000004777. PMID: 27583932. Excluded for ineligible intervention.

Huang QT, Huang Q, Zhong M, et al. Chronic hepatitis C virus infection is associated with increased risk of preterm birth: a meta-analysis of observational studies. J Viral Hepat. 2015;22(12):1033-42. doi: 10.1111/jvh.12430. PMID: 26081198. Excluded for ineligible intervention.

Hum J, Jou JH, Green PK, et al. Improvement in glycemic control of type 2 diabetes after successful treatment of hepatitis C virus. Diabetes Care. 2017;40(9):1173-80. doi: 10.2337/dc17-0485. PMID: 28659309. Excluded for ineligible study design for Key Question.

Hung CH, Lee CM, Lu SN, et al. Long-term effect of interferon alpha-2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. J Viral Hepat. 2006;13(6):409-14. doi: 10.1111/j.1365-2893.2005.00707.x. PMID: 16842444. Excluded for ineligible population.

Hung CH, Lee CM, Wang JH, et al. Impact of diabetes mellitus on incidence of hepatocellular carcinoma in chronic hepatitis C patients treated with interferon-based antiviral therapy. Int J Cancer. 2011;128(10):2344-52. doi: 10.1002/ijc.25585. PMID: 20669224. Excluded for ineligible population.

Hussar DA, Kavelak HL. Ledipasvir/sofosbuvir; ombitasvir/paritaprevir/ritonavir/dasabuvir sodium monohydrate; and peramivir. J Am Pharm Assoc. 2015;55(2):216, 9-20, 22. doi: 10.1331/JAPhA.2015.15512. PMID: 25749267. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Hussar DA, Snell CW. Boceprevir, telaprevir, and rilpivirine hydrochloride. J Am Pharm Assoc. 2012;52(1):120-6. doi: 10.1331/JAPhA.2012.12506. PMID: 22257626. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Ide K, Sato I, Imai T, et al. Comparison of the safety profiles of pegylated interferon alpha-2a and alpha-2b administered in combination with ribavirin for chronic hepatitis C infection: a real-world retrospective cohort study. Biol Pharm Bull. 2016;39(12):2060-5. doi: 10.1248/bpb.b16-00617. PMID: 27645378. Excluded for ineligible intervention.

Indolfi G, Serranti D, Resti M. Direct-acting antivirals for children and adolescents with chronic hepatitis C. Lancet Child Adolesc Health. 2018;2(4):298-304. doi: 10.1016/s2352-4642(18)30037-3. PMID: 30169301. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Ioannou GN, Beste LA, Chang MF, et al. Effectiveness of sofosbuvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir and dasabuvir regimens for treatment of patients with hepatitis C in the veterans affairs national health care system. Gastroenterology. 2016;151(3):457-71.e5. doi: 10.1053/j.gastro.2016.05.049. PMID: 27267053. Excluded for ineligible outcome.

Ioannou GN, Beste LA, Green PK. Similar effectiveness of boceprevir and telaprevir treatment regimens for hepatitis C virus infection on the basis of a nationwide study of veterans. Clin Gastroenterol Hepatol. 2014;12(8):1371-80. doi: 10.1016/j.cgh.2013.12.011. PMID: 24361415. Excluded for ineligible intervention.

Ishikawa T, Higuchi K, Kubota T, et al. Combination PEG-IFN a-2b/ribavirin therapy following treatment of hepatitis C virus-associated hepatocellular carcinoma is capable of improving hepatic functional reserve and survival. Hepatogastroenterology. 2012;59(114):529-32. doi: 10.5754/hge10867. PMID: 22024226. Excluded for ineligible population.

Islam N, Krajden M, Shoveller J, et al. Incidence, risk factors, and prevention of hepatitis C reinfection: a population-based cohort study. Lancet Gastroenterol Hepatol. 2017;2(3):200-10. doi: 10.1016/s2468-1253(16)30182-0. PMID: 28404135. Excluded for ineligible intervention.

Ismail WA, Wadea FM. The outcome of combined treatment with ombitasvir-paritaprevir-ritonavir, sofosbuvir with or without ribavirin as salvage therapy for Egyptian HCV experienced patients: a single center study. Drug Discov Ther. 2018;12(6):368-73. doi: 10.5582/ddt.2018.01080. PMID: 30674772. Excluded for ineligible population.

Iwasaki Y, Araki Y, Taniguchi H, et al. Randomized trial of peginterferon alpha-2b plus low and escalating dose of ribavirin in patients with chronic hepatitis C with high viral load genotype 1. J Med Virol. 2015;87(4):625-33. doi: 10.1002/jmv.24097. PMID: 25611729. Excluded for ineligible intervention.

Iwasaki Y, Okamoto R, Ishii Y, et al. Randomized trial of low-dose peginterferon alpha-2b plus low and escalating doses of ribavirin in older patients with chronic hepatitis C with high viral load genotype 1. J Med Virol. 2015;87(12):2082-9. doi: 10.1002/jmv.24276. PMID: 26010427. Excluded for ineligible intervention.

Izumi N, Asahina Y, Kurosaki M, et al. Inhibition of hepatocellular carcinoma by PegIFNalpha-2a in patients with chronic hepatitis C: a nationwide multicenter cooperative study. J Gastroenterol. 2013;48(3):382-90. doi: 10.1007/s00535-012-0641-9. PMID: 22875473. Excluded for ineligible comparator.

Jacobson IM, Brown RS, Jr., Freilich B, et al. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. Hepatology. 2007;46(4):971-81. doi: 10.1002/hep.21932. PMID: 17894303. Excluded for outdated medication.

Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013;368(20):1867-77. doi: 10.1056/NEJMoa1214854. PMID: 23607593. Excluded for ineligible intervention.

Jacobson IM, Lawitz E, Gane EJ, et al. Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials. Gastroenterology. 2017;153(1):113-22. doi: 10.1053/j.gastro.2017.03.047. PMID: 28390869. Excluded for ineligible intervention.

Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011;364(25):2405-16. doi: 10.1056/NEJMoa1012912. PMID: 21696307. Excluded for inadequate duration.

Jakobsen JC, Nielsen EE, Feinberg J, et al. Direct-acting antivirals for chronic hepatitis C. Cochrane Database Syst Rev. 2017;6:CD012143. doi: 10.1002/14651858.CD012143.pub3. PMID: 28585310. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Jensen CM, Holle LM. Ledipasvir-sofosbuvir: a once-daily oral treatment option for chronic hepatitis C virus genotype 1 infection. Pharmacotherapy. 2016;36(5):562-74. doi: 10.1002/phar.1748. PMID: 27027412. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Jensen DM, Asselah T, Dieterich D, et al. Faldaprevir, pegylated interferon, and ribavirin for treatment-naive HCV genotype-1: pooled analysis of two phase 3 trials. Ann Hepatol. 2016;15(3):333-49. doi: 10.5604/16652681.1198803. PMID: 27049487. Excluded for ineligible intervention.

Jhaveri M, Procaccini N, Kowdley KV. Update on hepatitis C treatment: systematic review of clinical trials. Minerva Gastroenterol Dietol. 2017;63(1):62-73. doi: 10.23736/S1121-421X.16.02345-X. PMID: 27768010. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Jhaveri R, Hashem M, El-Kamary SS, et al. Hepatitis C virus (HCV) vertical transmission in 12-month-old infants born to HCV-infected women and assessment of maternal risk factors. Open Forum Infect Dis. 2015;2(2):ofv089. doi: 10.1093/ofid/ofv089. PMID: 26180831. Excluded for insufficient statistical analysis.

Kaishima T, Akita T, Ohisa M, et al. Cost-effectiveness analyses of anti-hepatitis C virus treatments using quality of life scoring among patients with chronic liver disease in Hiroshima prefecture, Japan. Hepatol Res. 2018;48(7):509-20. doi: 10.1111/hepr.13053. PMID: 29316059. Excluded for ineligible intervention.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Kalafateli M, Buzzetti E, Thorburn D, et al. Pharmacological interventions for acute hepatitis C infection. Cochrane Database Syst Rev. 2017 (4)doi: 10.1002/14651858.CD011644.pub2. PMID: 28285495. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Kallman J, O'Neil MM, Larive B, et al. Fatigue and health-related quality of life (HRQL) in chronic hepatitis C virus infection. Dig Dis Sci. 2007;52(10):2531-9. doi: 10.1007/s10620-006-9708-x. PMID: 17406828. Excluded for ineligible study design for Key Question.

Kamal SM, Ahmed A, Mahmoud S, et al. Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis. Liver Int. 2011;31(3):401-11. doi: 10.1111/j.1478-3231.2010.02435.x. PMID: 21281434. Excluded for ineligible intervention.

Kaneko R, Nakazaki N, Omori R, et al. Efficacy of direct-acting antiviral treatment for chronic hepatitis C: a single hospital experience. World J Hepatol. 2018;10(1):88-94. doi: 10.4254/wjh.v10.i1.88. PMID: 29399282. Excluded for ineligible study design for Key Question.

Kanogawa N, Ogasawara S, Chiba T, et al. Sustained virologic response achieved after curative treatment of hepatitis C virus-related hepatocellular carcinoma as an independent prognostic factor. J Gastroenterol Hepatol. 2015;30(7):1197-204. doi: 10.1111/jgh.12925. PMID: 25682720. Excluded for ineligible intervention.

Kashiwagi K, Kubo N, Nakashima H, et al. A prospective comparison of the effect of interferon-alpha and interferon-beta treatment in patients with chronic hepatitis C on the incidence of hepatocellular carcinoma development. J Infect Chemother. 2003;9(4):333-40. doi: 10.1007/s10156-003-0271-5. PMID: 14691655. Excluded for insufficient statistical analysis.

Kattakuzhy S, Gross C, Emmanuel B, et al. Expansion of treatment for hepatitis C virus infection by task shifting to community-based nonspecialist providers: a nonrandomized clinical trial. Ann Intern Med. 2017;167(5):311-8. doi: 10.7326/M17-0118. PMID: 28785771. Excluded for ineligible population.

Kattakuzhy S, Wilson E, Sidharthan S, et al. Moderate sustained virologic response rates with 6-week combination directly acting anti-hepatitis C virus therapy in patients with advanced liver disease. Clin Infect Dis. 2016;62(4):440-7. doi: 10.1093/cid/civ897. PMID: 26503379. Excluded for ineligible intervention.

Kawakubo M, Eguchi Y, Okada M, et al. Chronic hepatitis C treatment with daclatasvir plus asunaprevir does not lead to a decreased quality of life. Intern Med. 2018;57(14):1959-66. doi: 10.2169/internalmedicine.0091-17. PMID: 29526929. Excluded for ineligible intervention.

Kawamura Y, Arase Y, Ikeda K, et al. Diabetes enhances hepatocarcinogenesis in noncirrhotic, interferon-treated hepatitis C patients. Am J Med. 2010;123(10):951-6.e1. doi: 10.1016/j.amjmed.2010.05.013. PMID: 20920698. Excluded for ineligible comparator.

Kawaoka T, Kawakami Y, Tsuji K, et al. Dose comparison study of pegylated interferon-alpha-2b plus ribavirin in naive Japanese patients with hepatitis C virus genotype 2: a randomized clinical trial. J Gastroenterol Hepatol. 2009;24(3):366-71. doi: 10.1111/j.1440-1746.2008.05650.x. PMID: 19032459. Excluded for outdated medication.

Keating GM. Ombitasvir/paritaprevir/ritonavir: a review in chronic HCV genotype 4 infection. Drugs. 2016;76(12):1203-11. doi: 10.1007/s40265-016-0612-1. PMID: 27401997. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Khan AQ, Awan A, Shahbuddin S, et al. Peginterferon alfa 2a/ribavirin versus peginterferon alfa 2b/ribavirin combination therapy in chronic hepatitis C genotype 3. Gastroenterology. 2007;132(4):A200-A. Excluded for outdated medication.

Khatri A, Menon RM, Marbury TC, et al. Pharmacokinetics and safety of co-administered paritaprevir plus ritonavir, ombitasvir, and dasabuvir in hepatic impairment. J Hepatol. 2015;63(4):805-12. doi: 10.1016/j.jhep.2015.05.029. PMID: 26070406. Excluded for ineligible outcome.

Khatri A, Mensing S, Podsadecki T, et al. Exposure-efficacy analyses of ombitasvir, paritaprevir/ritonavir with dasabuvir +/- ribavirin in HCV genotype 1-infected patients. Clin Drug Investig. 2016;36(8):625-35. doi: 10.1007/s40261-016-0407-x. PMID: 27153823. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Khokhar N, Niazi TK, Qureshi MO. Hepatocellular carcinoma after sustained viral response to interferon and ribavirin therapy in cirrhosis secondary to chronic hepatitis C. J Coll Physicians Surg Pak. 2013;23(10):699-702. doi: 10.2013/JCPSP.699702. PMID: 24112253. Excluded for ineligible comparator.

Kimer N, Dahl EK, Gluud LL, et al. Antiviral therapy for prevention of hepatocellular carcinoma in chronic hepatitis C: systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2012;2(5):e001313. doi: 10.1136/bmjopen-2012-001313. PMID: 23089208. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Klibanov OM, Gale SE, Santevecchi B. Ombitasvir/paritaprevir/ritonavir and dasabuvir tablets for hepatitis C virus genotype 1 infection. Ann Pharmacother. 2015;49(5):566-81. doi: 10.1177/1060028015570729. PMID: 25680759. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Kobayashi M, Suzuki F, Fujiyama S, et al. Sustained virologic response by direct antiviral agents reduces the incidence of hepatocellular carcinoma in patients with HCV infection. J Med Virol. 2017;89(3):476-83. doi: 10.1002/jmv.24663. PMID: 27531586. Excluded for ineligible population.

Koff RS. Review article: the efficacy and safety of sofosbuvir, a novel, oral nucleotide NS5B polymerase inhibitor, in the treatment of chronic hepatitis C virus infection. Aliment Pharmacol Ther. 2014;39(5):478-87. doi: 10.1111/apt.12601. PMID: 24387618. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Koh C, Heller T, Haynes-Williams V, et al. Long-term outcome of chronic hepatitis C after sustained virological response to interferon-based therapy. Aliment Pharmacol Ther. 2013;37(9):887-94. doi: 10.1111/apt.12273. PMID: 23461575. Excluded for ineligible outcome.

Kohli A, Kapoor R, Sims Z, et al. Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study. Lancet Infect Dis. 2015;15(9):1049-54. doi: 10.1016/S1473-3099(15)00157-7. PMID: 26187031. Excluded for ineligible population.

Kohli A, Kattakuzhy S, Sidharthan S, et al. Four-week direct-acting antiviral regimens in noncirrhotic patients with hepatitis C virus genotype 1 infection: An open-label, nonrandomized trial. Ann Intern Med. 2015;163(12):899-907. doi: 10.7326/M15-0642. PMID: 26595450. Excluded for ineligible intervention.

Kohli A, Osinusi A, Sims Z, et al. Virological response after 6 week triple-drug regimens for hepatitis C: a proof-of-concept phase 2A cohort study. Lancet. 2015;385(9973):1107-13. doi: 10.1016/S0140-6736(14)61228-9. PMID: 25591505. Excluded for ineligible study design for Key Question.

Komatsu TE, Boyd S, Sherwat A, et al. Regulatory analysis of effects of hepatitis C virus NS5A polymorphisms on efficacy of elbasvir and grazoprevir. Gastroenterology. 2017;152(3):586-97. doi: 10.1053/j.gastro.2016.10.017. PMID: 27773808. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Kowdley KV, Nelson DR, Lalezari JP, et al. On-treatment HCV RNA as a predictor of sustained virological response in HCV genotype 3-infected patients treated with daclatasvir and sofosbuvir. Liver Int. 2016;36(11):1611-8. doi: 10.1111/liv.13165. PMID: 27188960. Excluded for ineligible population.

Krans EE, Zickmund SL, Rustgi VK, et al. Screening and evaluation of hepatitis C virus infection in pregnant women on opioid maintenance therapy: a retrospective cohort study. Subst Abus. 2016;37(1):88-95. doi: 10.1080/08897077.2015.1118720. PMID: 26569631. Excluded for ineligible outcome.

Krawitt EL, Gordon SR, Grace ND, et al. A study of low dose peginterferon alpha-2b with ribavirin for the initial treatment of chronic hepatitis C. Am J Gastroenterol. 2006;101(6):1268-73. doi: 10.1111/j.1572-0241.2006.00614.x. PMID: 16771948. Excluded for outdated medication.

Krishnan P, Tripathi R, Schnell G, et al. Resistance analysis of baseline and treatment-emergent variants in hepatitis C virus genotype 1 in the AVIATOR study with paritaprevir-ritonavir, ombitasvir, and dasabuvir. Antimicrob Agents Chemother. 2015;59(9):5445-54. PMID: 26100711. Excluded for ineligible outcome.

Kronfli N, Bhatnagar SR, Hull MW, et al. Trends in cause-specific mortality in HIV-hepatitis C co-infection following hepatitis C treatment scale-up. AIDS. 2019 doi: 10.1097/qad.0000000000002156. PMID: 30649045. Excluded for ineligible population.

Kumada H, Toyota J, Okanoue T, et al. Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan. J Hepatol. 2012;56(1):78-84. doi: 10.1016/j.jhep.2011.07.016. PMID: 21827730. Excluded for outdated medication.

Kunimoto H, Ikeda K, Sorin Y, et al. Long-term outcomes of hepatitis-C-infected patients achieving a sustained virological response and undergoing raadical treatment for hepatocellular carcinoma. Oncology. 2016;90(3):167-75. doi: 10.1159/000443891. PMID: 26901157. Excluded for ineligible population.

Kwo P, Gane EJ, Peng CY, et al. Effectiveness of elbasvir and grazoprevir combination, with or without ribavirin, for treatment-experienced patients with chronic hepatitis C Infection. Gastroenterology. 2017;152(1):164-75.e4. doi: 10.1053/j.gastro.2016.09.045. PMID: 27720838. Excluded for ineligible population.

Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet. 2010;376(9742):705-16. doi: 10.1016/s0140-6736(10)60934-8. PMID: 20692693. Excluded for outdated medication.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Kwo PY, Poordad F, Asatryan A, et al. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. J Hepatol. 2017;67(2):263-71. PMID: 28412293. Excluded for ineligible study design for Key Question.

La Torre A, Biadaioli R, Capobianco T, et al. Vertical transmission of HCV. Acta Obstet Gynecol Scand. 1998;77(9):889-92. PMID: 9808375. Excluded for poor quality.

Lagasca AM, Kan VL. Hepatitis C treatment at a veterans affairs medical center after the availability of direct-acting agents: things are looking up. Clin Infect Dis. 2015;61(8):1347-9. doi: 10.1093/cid/civ573. PMID: 26187023. Excluded for ineligible outcome.

Lagging M, Langeland N, Pedersen C, et al. Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. Hepatology. 2008;47(6):1837-45. doi: 10.1002/hep.22253. PMID: 18454508. Excluded for outdated medication.

Lam JT, Jacob S. Boceprevir: a recently approved protease inhibitor for hepatitis C virus infection. Am J Health Syst Pharm. 2012;69(24):2135-9. doi: 10.2146/ajhp110500. PMID: 23230035. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Lanini S, Mammone A, Puro V, et al. Triple therapy for hepatitis C improves viral response but also increases the risk of severe infections and anaemia: a frequentist meta-analysis approach. New Microbiol. 2014;37(3):263-76. PMID: 25180842. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Lavitas P, Tesell M, Hydery T, et al. Overview of comprehensive hepatitis C virus medication management in a state medicaid program. J Manag Care Spec Pharm. 2016;22(10):1161-6. doi: 10.18553/jmcp.2016.22.10.1161. PMID: 27668564. Excluded for ineligible outcome.

Lawitz E, Gane E, Pearlman B, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015;385(9973):1075-86. doi: 10.1016/S0140-6736(14)61795-5. PMID: 25467591. Excluded for ineligible population.

Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013;368(20):1878-87. doi: 10.1056/NEJMoa1214853. PMID: 23607594. Excluded for ineligible intervention.

Lawitz E, Poordad F, Gutierrez JA, et al. Short-duration treatment with elbasvir/grazoprevir and sofosbuvir for hepatitis C: a randomized trial. Hepatology. 2017;65(2):439-50. doi: 10.1002/hep.28877. PMID: 27770561. Excluded for ineligible intervention.

Lawitz E, Poordad F, Kowdley KV, et al. A phase 2a trial of 12-week interferon-free therapy with two direct-acting antivirals (ABT-450/r, ABT-072) and ribavirin in IL28B C/C patients with chronic hepatitis C genotype 1. J Hepatol. 2013;59(1):18-23. doi: 10.1016/j.jhep.2013.02.009. PMID: 23439262. Excluded for ineligible intervention.

Lawitz E, Poordad F, Wells J, et al. Sofosbuvir-velpatasvir-voxilaprevir with or without ribavirin in direct-acting antiviral-experienced patients with genotype 1 hepatitis C virus. Hepatology. 2017;65(6):1803-9. doi: 10.1002/hep.29130. PMID: 28220512. Excluded for ineligible intervention.

Lawitz E, Reau N, Hinestrosa F, et al. Efficacy of sofosbuvir, velpatasvir, and GS-9857 in patients with genotype 1 hepatitis C virus infection in an open-label, phase 2 trial. Gastroenterology. 2016;151(5):893-901.e1. doi: 10.1053/j.gastro.2016.07.039. PMID: 27486034. Excluded for ineligible intervention.

Lawitz E, Sullivan G, Rodriguez-Torres M, et al. Exploratory trial of ombitasvir and ABT-450/r with or without ribavirin for HCV genotype 1, 2, and 3 infection. J Infect. 2015;70(2):197-205. doi: 10.1016/j.jinf.2014.09.008. PMID: 25246359. Excluded for ineligible intervention.

Lee SS, Jeong SH, Jang ES, et al. Prospective cohort study on the outcomes of hepatitis C virus-related cirrhosis in South Korea. J Gastroenterol Hepatol. 2015;30(8):1281-7. doi: 10.1111/jgh.12950. PMID: 25778783. Excluded for ineligible population.

Lee SS, Roberts SK, Berak H, et al. Safety of peginterferon alfa-2a plus ribavirin in a large multinational cohort of chronic hepatitis C patients. Liver Int. 2012;32(8):1270-7. doi: 10.1111/j.1478-3231.2012.02819.x. PMID: 22621707. Excluded for ineligible intervention.

Lens S, Calleja JL, Campillo A, et al. Aplastic anemia and severe pancytopenia during treatment with peg-interferon, ribavirin and telaprevir for chronic hepatitis C. World J Gastroenterol. 2015;21(17):5421-6. doi: 10.3748/wjg.v21.i17.5421. PMID: 25954117. Excluded for ineligible population.

Lens S, Torres F, Puigvehi M, et al. Predicting the development of liver cirrhosis by simple modelling in patients with chronic hepatitis C. Aliment Pharmacol Ther. 2016;43(3):364-74. doi: 10.1111/apt.13472. PMID: 26582599. Excluded for ineligible study design for Key Question.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Leventer-Roberts M, Hammerman A, Brufman I, et al. Effectiveness of dasabuvir/ombitasvir/paritaprevir/ritonavir for hepatitis C virus in clinical practice: a population-based observational study. PLoS One. 2017;12(7):e0176858. doi: 10.1371/journal.pone.0176858. PMID: 28686590. Excluded for ineligible intervention.

Li J, Gordon SC, Rupp LB, et al. Sustained virological response to hepatitis C treatment decreases the incidence of complications associated with type 2 diabetes. Aliment Pharmacol Ther. 2019;49(5):599-608. doi: 10.1111/apt.15102. PMID: 30650468. Excluded for ineligible population.

Lin CW, Menon R, Liu W, et al. Exposure-safety response relationship for ombitasvir, paritaprevir/ritonavir, dasabuvir, and ribavirin in patients with chronic hepatitis C virus genotype 1 infection: analysis of data from five phase II and six phase III studies. Clin Drug Investig. 2017 doi: 10.1007/s40261-017-0520-5. PMID: 28378135. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Lin HH, Kao JH, Hsu HY, et al. Absence of infection in breast-fed infants born to hepatitis C virus-infected mothers. J Pediatr. 1995;126(4):589-91. PMID: 7535353. Excluded for poor quality.

Linas BP, Hu H, Barter DM, et al. Hepatitis C screening trends in a large integrated health system. Am J Med. 2014;127(5):398-405. doi: 10.1016/j.amjmed.2014.01.012. PMID: 24486288. Excluded for ineligible outcome.

Litwin AH, Smith BD, Drainoni ML, et al. Primary care-based interventions are associated with increases in hepatitis C virus testing for patients at risk. Dig Liver Dis. 2012;44(6):497-503. doi: 10.1016/j.dld.2011.12.014. PMID: 22342471. Excluded for ineligible outcome.

Liu CH, Huang YJ, Yang SS, et al. Generic sofosbuvir-based interferon-free direct acting antiviral agents for patients with chronic hepatitis C virus infection: a real-world multicenter observational study. Scientific Reports. 2018;8(1):13699. doi: 10.1038/s41598-018-32060-7. PMID: 30209349. Excluded for ineligible study design for Key Question.

Liu CH, Liu CJ, Su TH, et al. Real-world effectiveness and safety of sofosbuvir and ledipasvir with or without ribavirin for patients with hepatitis C virus genotype 1 infection in Taiwan. PLoS One. 2018;13(12):e0209299. doi: 10.1371/journal.pone.0209299. PMID: 30576344. Excluded for ineligible study design for Key Question.

Liu CH, Su TH, Liu CJ, et al. Sofosbuvir-based direct acting antiviral therapies for patients with hepatitis C virus genotype 2 infection. J Gastroenterol Hepatol. 2019;29:29. doi: 10.1111/jgh.14615. PMID: 30693965. Excluded for ineligible study design for Key Question.

Liu CJ, Chuang WL, Sheen IS, et al. Efficacy of ledipasvir and sofosbuvir treatment of HCV infection in patients coinfected with HBV. Gastroenterology. 2018;154(4):989-97. doi: 10.1053/j.gastro.2017.11.011. PMID: 29174546. Excluded for ineligible outcome.

Liu Y, Wang Z, Tobe RG, et al. Cost effectiveness of daclatasvir plus asunaprevir therapy for Chinese patients with chronic hepatitis C virus genotype 1b. Clin Drug Investig. 2018;38(5):427-37. doi: 10.1007/s40261-018-0621-9. PMID: 29417464. Excluded for ineligible intervention.

Lok AS, Everhart JE, Wright EC, et al. Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. Gastroenterology. 2011;140(3):840-9; quiz e12. doi: 10.1053/j.gastro.2010.11.050. PMID: 21129375. Excluded for ineligible intervention.

Louie V, Latt NL, Gharibian D, et al. Real-world experiences with a direct-acting antiviral agent for patients with hepatitis C virus infection. Perm J. 2017;21doi: 10.7812/TPP/16-096. PMID: 28368787. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Loustaud-Ratti V, Maynard M, Thevenon S, et al. Efficiency and safety of an early dose adjustment of ribavirin in patients infected with hepatitis c underexposed to the drug and treated with peginterferon ribavirin. Ther Drug Monit. 2016;38(6):684-92. doi: 10.1097/FTD.0000000000000332. PMID: 27559840. Excluded for ineligible intervention.

Lu M, Li J, Zhang T, et al. Serum biomarkers indicate long-term reduction in liver fibrosis in patients with sustained virological response to treatment for HCV infection. Clin Gastroenterol Hepatol. 2016;14(7):1044-55.e3. doi: 10.1016/j.cgh.2016.01.009. PMID: 26804385. Excluded for ineligible outcome.

Lucejko M, Parfieniuk-Kowerda A, Flisiak R. Ombitasvir/paritaprevir/ritonavir plus dasabuvir combination in the treatment of chronic HCV infection. Expert Opin Pharmacother. 2016;17(8):1153-64. doi: 10.1080/14656566.2016.1176143. PMID: 27064432. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Lyons MS, Kunnathur VA, Rouster SD, et al. Prevalence of diagnosed and undiagnosed hepatitis C in a Midwestern urban emergency department. Clin Infect Dis. 2016;62(9):1066-71. doi: 10.1093/cid/ciw073. PMID: 26908799. Excluded for ineligible outcome.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Maan R, Al Marzooqi SH, Klair JS, et al. The frequency of acute kidney injury in patients with chronic hepatitis C virus infection treated with sofosbuvir-based regimens. Aliment Pharmacol Ther. 2017 (pagination)doi: 10.1111/apt.14117. PMID: 28470850. Excluded for ineligible intervention.

Maan R, van der Meer AJ, Hansen BE, et al. Risk of infections during interferon-based treatment in patients with chronic hepatitis C virus infection and advanced hepatic fibrosis. J Gastroenterol Hepatol. 2015;30(6):1057-64. doi: 10.1111/jgh.12929. PMID: 25682797. Excluded for ineligible intervention.

Mach TH, Ciesla A, Warunek W, et al. Efficacy of pegylated interferon alfa-2a or alfa-2b in combination with ribavirin in the treatment of chronic hepatitis caused by hepatitis C virus genotype 1b. Pol Arch Med Wewn. 2011;121(12):434-9. PMID: 22157768. Excluded for outdated medication.

Macias J, Rivero A, Cifuentes C, et al. Sustained virological response to pegylated interferon plus ribavirin leads to normalization of liver stiffness in hepatitis C virus-infected patients. Enferm Infecc Microbiol Clin. 2013;31(7):424-9. doi: 10.1016/j.eimc.2012.12.004. PMID: 23453582. Excluded for ineligible population.

Magni C, Niero F, Argenteri B, et al. Antiviral activity and tolerability between pegylated interferon Alpha-2a and Alpha-2b in naÏve patients with chronic hepatitis C: results of a prospective monocentric randomized trial: 883. Hepatology. 2009;50:720A. Excluded for outdated medication.

Mangia A, Santoro R, Minerva N, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N Engl J Med. 2005;352(25):2609-17. doi: 10.1056/NEJMoa042608. PMID: 15972867. Excluded for outdated medication.

Manns M, Zeuzem S, Sood A, et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol. 2011;55(3):554-63. doi: 10.1016/j.jhep.2010.12.024. PMID: 21237227. Excluded for outdated medication.

Manns MP, Fried MW, Zeuzem S, et al. Simeprevir with peginterferon/ribavirin for treatment of chronic hepatitis C virus genotype 1 infection: pooled safety analysis from phase IIb and III studies. J Viral Hepat. 2015;22(4):366-75. doi: 10.1111/jvh.12346. PMID: 25363449. Excluded for ineligible outcome.

Manns MP, McCone J, Jr., Davis MN, et al. Overall safety profile of boceprevir plus peginterferon alfa-2b and ribavirin in patients with chronic hepatitis C genotype 1: a combined analysis of 3 phase 2/3 clinical trials. Liver Int. 2014;34(5):707-19. doi: 10.1111/liv.12300. PMID: 24118703. Excluded for ineligible intervention.

Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001;358(9286):958-65. PMID: 11583749. Excluded for outdated medication.

Marcellin P, Forns X, Goeser T, et al. Telaprevir is effective given every 8 or 12 hours with ribavirin and peginterferon alfa-2a or -2b to patients with chronic hepatitis C. Gastroenterology. 2011;140(2):459-68.e1; quiz e14. doi: 10.1053/j.gastro.2010.10.046. PMID: 21034744. Excluded for outdated medication.

Marcus JL, Hurley LB, Chamberland S, et al. No difference in effectiveness of 8 vs 12 weeks of ledipasvir and sofosbuvir for treatment of hepatitis C in black patients. Clin Gastroenterol Hepatol. 2018;16(6):927-35. doi: 10.1016/j.cgh.2018.03.003. PMID: 29535057. Excluded for ineligible study design for Key Question.

Martinello M, Bhagani S, Gane E, et al. Shortened therapy of eight weeks with paritaprevir/ritonavir/ombitasvir and dasabuvir is highly effective in people with recent HCV genotype 1 infection. J Viral Hepat. 2018;25(10):1180-8. doi: 10.1111/jvh.12917. PMID: 29660224. Excluded for ineligible intervention.

Martinez SM, Foucher J, Combis JM, et al. Longitudinal liver stiffness assessment in patients with chronic hepatitis C undergoing antiviral therapy. PLoS One. 2012;7(10):e47715. doi: 10.1371/journal.pone.0047715. PMID: 23082200. Excluded for ineligible outcome.

Martinez-Macias RF, Cordero-Perez P, Juarez-Rodriguez OA, et al. Interferon-based therapy delays but metabolic comorbidity accelerates progression of chronic hepatitis C. Ann Hepatol. 2015;14(1):36-45. PMID: 25536640. Excluded for poor quality.

Masip M, Tuneu L, Pages N, et al. Prevalence and detection of neuropsychiatric adverse effects during hepatitis C treatment. Int J Clin Pharm. 2015;37(6):1143-51. doi: 10.1007/s11096-015-0177-1. PMID: 26267215. Excluded for ineligible intervention.

Matsumoto N, Ikeda H, Shigefuku R, et al. Hemoglobin decrease with iron deficiency induced by daclatasvir plus asunaprevir combination therapy for chronic hepatitis C virus genotype 1b. PLoS One. 2016;11(3):e0151238. doi: 10.1371/journal.pone.0151238. PMID: 26990758. Excluded for ineligible intervention.

Mauss S, Klinker H. Drug-drug interactions in the treatment of HCV among people who inject drugs. Clin Infect Dis. 2013;57 Suppl 2:S125-8. doi: 10.1093/cid/cit299. PMID: 23884060. Excluded for ineligible intervention.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Mazzarelli C, Considine A, Childs K, et al. Efficacy and tolerability of direct-acting antivirals for hepatitis C in older adults. J Am Geriatr Soc. 2018;66(7):1339-45. doi: 10.1111/jgs.15392. PMID: 29799112. Excluded for ineligible study design for Key Question.

McCombs J, Matsuda T, Tonnu-Mihara I, et al. The risk of long-term morbidity and mortality in patients with chronic hepatitis C: results from an analysis of data from a Department of Veterans Affairs clinical registry. JAMA Intern Med. 2014;174(2):204-12. doi: 10.1001/jamainternmed.2013.12505. PMID: 24193887. Excluded for ineligible population.

McConachie SM, Wilhelm SM, Kale-Pradhan PB. New direct-acting antivirals in hepatitis C therapy: a review of sofosbuvir, ledipasvir, daclatasvir, simeprevir, paritaprevir, ombitasvir and dasabuvir. Expert Rev Clin Pharmacol. 2016;9(2):287-302. doi: 10.1586/17512433.2016.1129272. PMID: 26651915. Excluded for ineligible study design for Key Question.

McCormack PL. Daclatasvir: a review of its use in adult patients with chronic hepatitis C virus infection. Drugs. 2015;75(5):515-24. doi: 10.1007/s40265-015-0362-5. PMID: 25721433. Excluded for ineligible study design for Key Question.

McDonald SA, Innes HA, Hayes PC, et al. What is the impact of a country-wide scale-up in antiviral therapy on the characteristics and sustained viral response rates of patients treated for hepatitis C? J Hepatol. 2015;62(2):262-8. doi: 10.1016/j.jhep.2014.08.046. PMID: 25195556. Excluded for ineligible intervention.

McEwan P, Ward T, Yuan Y, et al. The impact of timing and prioritization on the cost-effectiveness of birth cohort testing and treatment for hepatitis C virus in the United States. Hepatology. 2013;58(1):54-64. doi: 10.1002/hep.26304. PMID: 23389841. Excluded for ineligible study design for Key Question.

McGinn T, O'Connor-Moore N, Alfandre D, et al. Validation of a hepatitis C screening tool in primary care. Arch Intern Med. 2008;168(18):2009-13. doi: 10.1001/archinte.168.18.2009. PMID: 18852403. Excluded for poor quality.

McHutchison J, Manns M, Harvey J, et al. Adherence to therapy enhances sustained response in chronic hepatitis C patients receiving PEG-interferon alfa-2b plus ribavirin. J Hepatol. 2001;34:2-3. Excluded for ineligible intervention.

McHutchison J, Sulkowski M. Scientific rationale and study design of the individualized dosing efficacy vs flat dosing to assess optimal pegylated interferon therapy (IDEAL) trial: determining optimal dosing in patients with genotype 1 chronic hepatitis C. J Viral Hepat. 2008;15(7):475-81. doi: 10.1111/j.1365-2893.2008.00973.x. PMID: 18363672. Excluded for outdated medication.

McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med. 2009;360(18):1827-38. doi: 10.1056/NEJMoa0806104. PMID: 19403902. Excluded for outdated medication.

McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med. 2009;361(6):580-93. doi: 10.1056/NEJMoa0808010. PMID: 19625712. Excluded for inadequate duration.

McIntyre PG, Tosh K, McGuire W. Caesarean section versus vaginal delivery for preventing mother to infant hepatitis C virus transmission. Cochrane Database Syst Rev. 2010 (6) PMID: 17054264. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

McMenamin MB, Jackson AD, Lambert J, et al. Obstetric management of hepatitis C-positive mothers: analysis of vertical transmission in 559 mother-infant pairs. Am J Obstet Gynecol. 2008;199(3):315.e1-5. doi: 10.1016/j.ajog.2008.05.021. PMID: 18771997. Excluded for insufficient statistical analysis.

McPhee F, Suzuki Y, Toyota J, 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. 2015;32(7):637-49. doi: 10.1007/s12325-015-0221-5. PMID: 26155891. Excluded for ineligible intervention.

Mecenate F, Pellicelli AM, Barbaro G, et al. Short versus standard treatment with pegylated interferon alfa-2A plus ribavirin in patients with hepatitis C virus genotype 2 or 3: the cleo trial. BMC Gastroenterol. 2010;10:21. doi: 10.1186/1471-230x-10-21. PMID: 20170514. Excluded for outdated medication.

Merchant RC, Baird JR, Liu T, et al. Brief intervention to increase emergency department uptake of combined rapid human immunodeficiency virus and hepatitis C screening among a drug misusing population. Acad Emerg Med. 2014;21(7):752-67. doi: 10.1111/acem.12419. PMID: 25125271. Excluded for ineligible outcome.

Messori A, Badiani B, Trippoli S. Achieving sustained virological response in hepatitis C reduces the long-term risk of hepatocellular carcinoma: an updated meta-analysis employing relative and absolute outcome measures. Clin Drug Investig. 2015;35(12):843-50. doi: 10.1007/s40261-015-0338-y. PMID: 26446006. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Messori A, Fadda V, Maratea D, et al. Pegylated interferon-alpha2a versus pegylated interferon-alpha2b in hepatitis C: reappraisal of effectiveness on the basis of trial sequential analysis. Eur J Gastroenterol Hepatol. 2014;26(2):246-8. doi: 10.1097/MEG.0b013e3283657e20. PMID: 24366456. Excluded for ineligible intervention.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Mettikanont P, Bunchorntavakul C, Reddy KR. Systematic review: epidemiology and response to direct-acting antiviral therapy in genotype 6 chronic hepatic C virus (HCV). Aliment Pharmacol Ther. 2019;27:27. doi: 10.1111/apt.15100. PMID: 30687952. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Meyer-Wyss B, Rich P, Egger H, et al. Comparison of two PEG-interferon alpha-2b doses (1.0 or 1.5 microg/kg) combined with ribavirin in interferon-naive patients with chronic hepatitis C and up to moderate fibrosis. J Viral Hepat. 2006;13(7):457-65. doi: 10.1111/j.1365-2893.2005.00709.x. PMID: 16792539. Excluded for outdated medication.

Michielsen P, Ho E, Francque S. Does antiviral therapy reduce the risk of hepatocellular carcinoma in patients with chronic hepatitis C? Minerva Gastroenterol Dietol. 2012;58(1):65-79. PMID: 22419005. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Midgard H, Bjoro B, Maeland A, et al. Hepatitis C reinfection after sustained virological response. J Hepatol. 2016;64(5):1020-6. doi: 10.1016/j.jhep.2016.01.001. PMID: 26780289. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Mihaila RG. Hepatitis C virus - associated B cell non-Hodgkin's lymphoma. World J Gastroenterol. 2016;22(27):6214-23. doi: 10.3748/wjg.v22.i27.6214. PMID: 27468211. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Miller ER, McNally S, Wallace J, et al. The ongoing impacts of hepatitis C-a systematic narrative review of the literature. BMC Public Health. 2012;12:672. doi: 10.1186/1471-2458-12-672. PMID: 22900973. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Miller MH, Dillon JF. Early diagnosis improves outcomes in hepatitis C. Practitioner. 2015;259(1787):25-7, 3. PMID: 26753270. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Mimidis K, Papadopoulos VP, Elefsiniotis I, et al. Hepatitis C virus survival curve analysis in naive patients treated with peginterferon alpha-2b plus ribavirin. A randomized controlled trial for induction with high doses of peginterferon and predictability of sustained viral response from early virologic data. J Gastrointestin Liver Dis. 2006;15(3):213-9. PMID: 17013444. Excluded for outdated medication.

Minaei AA, Kowdley KV. ABT-450/ ritonavir and ABT-267 in combination with ABT-333 for the treatment of hepatitis C virus. Expert Opin Pharmacother. 2015;16(6):929-37. doi: 10.1517/14656566.2015.1024653. PMID: 25800085. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Minola E, Maccabruni A, Pacati I, et al. Amniocentesis as a possible risk factor for mother-to-infant transmission of hepatitis C virus. Hepatology. 2001;33(5):1341-2. doi: 10.1053/jhep.2001.0103305le02. PMID: 11343269. Excluded for ineligible study design for Key Question.

Mir F, Kahveci AS, Ibdah JA, et al. Sofosbuvir/velpatasvir regimen promises an effective pan-genotypic hepatitis C virus cure. Drug Des Devel Ther. 2017;11:497-502. doi: 10.2147/DDDT.S130945. PMID: 28260862. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Miyase S, Haraoka K, Ouchida Y, et al. Randomized trial of peginterferon alpha-2a plus ribavirin versus peginterferon alpha-2b plus ribavirin for chronic hepatitis C in Japanese patients. J Gastroenterol. 2012;47(9):1014-21. doi: 10.1007/s00535-012-0560-9. PMID: 22382633. Excluded for outdated medication.

Miyazaki R, Miyagi K. Effect and safety of daclatasvir-asunaprevir combination therapy for chronic hepatitis C virus genotype 1b -infected patients on hemodialysis. Therap Apher Dial. 2016;20(5):462-7. doi: 10.1111/1744-9987.12407. PMID: 27098678. Excluded for ineligible intervention.

Mizokami M, Yokosuka O, Takehara T, 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;15(6):645-53. doi: 10.1016/S1473-3099(15)70099-X. PMID: 25863559. Excluded for ineligible population.

Money D, Boucoiran I, Wagner E, et al. Obstetrical and neonatal outcomes among women infected with hepatitis C and their infants. J Obstet Gynaecol Can. 2014;36(9):785-94. PMID: 25222357. Excluded for ineligible outcome.

Monteith C, Ni Ainle F, Cooley S, et al. Hepatitis C virus-associated thrombocytopenia in pregnancy: impact upon multidisciplinary care provision. J Perinat Med. 2014;42(1):135-8. doi: 10.1515/jpm-2013-0080. PMID: 24006316. Excluded for ineligible outcome.

Moreno-Planas JM, Larrubia-Marfil JR, Sanchez-Ruano JJ, et al. Influence of baseline MELD score in the efficacy of treatment of hepatitis C with simeprevir and sofosbuvir. Enferm Infecc Microbiol Clin. 2018;36(5):277-83. doi: 10.1016/j.eimc.2017.05.001. PMID: 28641865. Excluded for ineligible population.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Morgan RL, Baack B, Smith BD, et al. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med. 2013;158(5_Part_1):329-37. doi: 10.7326/0003-4819-158-5-201303050-00005. PMID: 23460056. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Morgan TR, Ghany MG, Kim H-Y, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology. 2010;52(3):833-44. PMID: 20564351. Excluded for ineligible population.

Morio K, Imamura M, Kawakami Y, et al. Real-world efficacy and safety of daclatasvir and asunaprevir therapy for hepatitis C virus-infected cirrhosis patients. J Gastroenterol Hepatol. 2017;32(3):645-50. doi: 10.1111/jgh.13511. PMID: 27513614. Excluded for ineligible intervention.

Morio R, Imamura M, Kawakami Y, et al. Safety and efficacy of dual therapy with daclatasvir and asunaprevir for older patients with chronic hepatitis C. J Gastroenterol. 2017;52(4):504-11. doi: 10.1007/s00535-016-1255-4. PMID: 27631593. Excluded for ineligible intervention.

Moriya T, Sasaki F, Mizui M, et al. Transmission of hepatitis C virus from mothers to infants: its frequency and risk factors revisited. Biomed Pharmacother. 1995;49(2):59-64. PMID: 7605903. Excluded for poor quality.

Mourad A, Deuffic-Burban S, Ganne-Carrie N, et al. Hepatocellular carcinoma screening in patients with compensated hepatitis C virus (HCV)-related cirrhosis aware of their HCV status improves survival: a modeling approach. Hepatology. 2014;59(4):1471-81. doi: 10.1002/hep.26944. PMID: 24677195. Excluded for ineligible intervention.

Muir AJ, Poordad F, Lalezari J, et al. Daclatasvir in combination with asunaprevir and beclabuvir for hepatitis C virus genotype 1 infection with compensated cirrhosis. JAMA. 2015;313(17):1736-44. doi: 10.1001/jama.2015.3868. PMID: 25942724. Excluded for ineligible intervention.

Mulligan K, Sullivan J, Yoon L, et al. Evaluating HCV screening, linkage to care, and treatment across insurers. Am J Manag Care. 2018;24(8):e257-e64. PMID: 30130026. Excluded for ineligible outcome.

Mullins C, Gibson W, Klibanov OM. Harvoni (ledipasvir and sofosbuvir) for hepatitis C. Nurse Pract. 2015;40(11):22-6. doi: 10.1097/01.NPR.0000472253.59198.1c. PMID: 26474199. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Murfin M. New medications for treatment of chronic hepatitis C. JAAPA. 2015;28(7):57-9. doi: 10.1097/01.JAA.0000466592.48713.85. PMID: 26107799. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Myers RP, Regimbeau C, Thevenot T, et al. Interferon for acute hepatitis C. Cochrane Database Syst Rev. 2009 (1). Excluded for ineligible intervention.

Nafisi S, Roy S, Gish R, et al. Defining the possibilities: is short duration treatment of chronic hepatitis C genotype 1 with sofosbuvir-containing regimens likely to be as effective as current regimens? Expert Rev Anti Infect Ther. 2016;14(1):41-56. doi: 10.1586/14787210.2016.1114883. PMID: 26654939. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Nagaoki Y, Imamura M, Aikata H, et al. The risks of hepatocellular carcinoma development after HCV eradication are similar between patients treated with peg-interferon plus ribavirin and direct-acting antiviral therapy. PLoS One. 2017;12(8):e0182710. doi: 10.1371/journal.pone.0182710. PMID: 28797106. Excluded for ineligible comparator.

Nagaty A, Abd El-Wahab EW. Real-life results of sofosbuvir based therapy in chronic hepatitis C -naive and -experienced patients in Egypt. PLoS One. 2017;12(10):e0184654. doi: 10.1371/journal.pone.0184654. PMID: 28981513. Excluded for ineligible study design for Key Question.

Nahon P, Bourcier V, Layese R, et al. Eradication of hepatitis C virus infection in patients with cirrhosis reduces risk of liver and non-liver complications. Gastroenterology. 2017;152(1):142-56.e2. doi: 10.1053/j.gastro.2016.09.009. PMID: 27641509. Excluded for ineligible population.

Nakamura Y, Imamura M, Kawakami Y, et al. Efficacy and safety of daclatasvir plus asunaprevir therapy for chronic hepatitis C patients with renal dysfunction. J Med Virol. 2017;89(4):665-71. doi: 10.1002/jmv.24679. PMID: 27602542. Excluded for ineligible intervention.

Nam HC, Lee HL, Yang H, et al. Efficacy and safety of daclatasvir and asunaprevir for hepatitis C virus genotype 1b infection. Clin Mol Hepatol. 2016;22(2):259-66. doi: 10.3350/cmh.2016.0020. PMID: 27377910. Excluded for ineligible intervention.

Neary MP, Cort S, Bayliss MS, et al. Sustained virologic response is associated with improved health-related quality of life in relapsed chronic hepatitis C patients. Semin Liver Dis. 1999;19 Suppl 1:77-85. PMID: 10349695. Excluded for ineligible intervention.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Negro F, Forton D, Craxi A, et al. Extrahepatic morbidity and mortality of chronic hepatitis C. Gastroenterology. 2015;149(6):1345-60. doi: 10.1053/j.gastro.2015.08.035. PMID: 26319013. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Nettles RE, Gao M, Bifano M, et al. Multiple ascending dose study of BMS-790052, a nonstructural protein 5A replication complex inhibitor, in patients infected with hepatitis C virus genotype 1. Hepatology. 2011;54(6):1956-65. doi: 10.1002/hep.24609. PMID: 21837752. Excluded for ineligible intervention.

Ng V, Saab S. Effects of a sustained virologic response on outcomes of patients with chronic hepatitis C. Clin Gastroenterol Hepatol. 2011;9(11):923-30. doi: 10.1016/j.cgh.2011.05.028. PMID: 21699815. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Nguyen J, Barritt ASt, Jhaveri R. Cost effectiveness of early treatment with direct-acting antiviral therapy in adolescent patients with hepatitis C virus infection. J Pediatr. 2019;207:90-6. doi: 10.1016/j.jpeds.2018.12.012. PMID: 30738661. Excluded for ineligible outcome.

Nguyen K, Van Nguyen T, Shen D, et al. Prevalence and presentation of hepatitis B and C virus (HBV and HCV) infection in Vietnamese Americans via serial community serologic testing. J Immigr Minor Health. 2015;17(1):13-20. doi: 10.1007/s10903-013-9975-5. PMID: 24474437. Excluded for ineligible study design for Key Question.

Nguyen LH, Nguyen MH. Systematic review: Asian patients with chronic hepatitis C infection. Aliment Pharmacol Ther. 2013;37(10):921-36. doi: 10.1111/apt.12300. PMID: 23557103. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Nguyen MT, Herrine SK, Laine CA, et al. Description of a new hepatitis C risk assessment tool. Arch Intern Med. 2005;165(17):2013-8. doi: 10.1001/archinte.165.17.2013. PMID: 16186472. Excluded for poor quality.

Nishida N, Kono M, Minami T, et al. Safety, tolerability, and efficacy of sofosbuvir plus ribavirin in elderly patients infected with hepatitis C virus genotype 2. Dig Dis. 2016;34(6):632-9. doi: 10.1159/000448824. PMID: 27750230. Excluded for ineligible study design for Key Question.

Nishiguchi S, Shiomi S, Nakatani S, et al. Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis. Lancet. 2001;357(9251):196-7. doi: 10.1016/s0140-6736(00)03595-9. PMID: 11213099. Excluded for ineligible population.

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Oeda S, Iwane S, Takasaki M, et al. Optimal follow-up of patients with viral hepatitis improves the detection of early-stage hepatocellular carcinoma and the prognosis of survival. Intern Med. 2016;55(19):2749-58. doi: 10.2169/internalmedicine.55.6730. PMID: 27725532. Excluded for ineligible intervention.

Ogawa E, Furusyo N, Kajiwara E, et al. Comparative safety study on severe anemia by simeprevir versus telaprevir-based triple therapy for chronic hepatitis C. J Gastroenterol Hepatol. 2015;30(8):1309-16. doi: 10.1111/jgh.12945. PMID: 25777545. Excluded for ineligible outcome.

Ohashi K, Ishikawa T, Suzuki M, et al. Health-related quality of life on the clinical course of patients with chronic hepatitis C receiving daclatasvir/asunaprevir therapy: a prospective observational study comparing younger (<70) and elderly (>=70) patients. Exp Ther Med. 2018;15(1):970-6. doi: 10.3892/etm.2017.5488. PMID: 29399105. Excluded for ineligible population.

Ohmer S, Honegger J. New prospects for the treatment and prevention of hepatitis C in children. Curr Opin Pediatr. 2016;28(1):93-100. doi: 10.1097/MOP.0000000000000313. PMID: 26709684. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Ojha RP, MacDonald BR, Chu TC, et al. Comparative effectiveness of 8- and 12-week ledipasvir/sofosbuvir regimens for HCV infection. Antivir Ther. 2018;23(7):585-92. doi: 10.3851/IMP3249. PMID: 29969099. Excluded for ineligible study design for Key Question.

Okamoto M, Nagata I, Murakami J, et al. Prospective reevaluation of risk factors in mother-to-child transmission of hepatitis C virus: high virus load, vaginal delivery, and negative anti-NS4 antibody. J Infect Dis. 2000;182(5):1511-4. doi: 10.1086/315883. PMID: 11023474. Excluded for poor quality.

Okanoue T, Itoh Y, Minami M, et al. Interferon therapy lowers the rate of progression to hepatocellular carcinoma in chronic hepatitis C but not significantly in an advanced stage: a retrospective study in 1148 patients. Viral Hepatitis Therapy Study Group. J Hepatol. 1999;30(4):653-9. PMID: 10207807. Excluded for poor quality.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

O'Leary JG, Fontana RJ, Brown K, et al. Efficacy and safety of simeprevir and sofosbuvir with and without ribavirin in subjects with recurrent genotype 1 hepatitis C postorthotopic liver transplant: the randomized GALAXY study. Transpl Int. 2017;30(2):196-208. PMID: 27896858. Excluded for ineligible intervention.

Omata M, Yoshida H, Shiratori Y. Prevention of hepatocellular carcinoma and its recurrence in chronic hepatitis C patients by interferon therapy. Clin Gastroenterol Hepatol. 2005;3(10 Suppl 2):S141-3. PMID: 16234063. Excluded for ineligible study design for Key Question.

Onofrey S, Aneja J, Haney GA, et al. Underascertainment of acute hepatitis C virus infections in the U.S. surveillance system: a case series and chart review. Ann Intern Med. 2015;163(4):254-61. doi: 10.7326/M14-2939. PMID: 26121304. Excluded for ineligible intervention.

Osinusi A, Townsend K, Kohli A, et al. Virologic response following combined ledipasvir and sofosbuvir administration in patients with HCV genotype 1 and HIV co-infection. JAMA. 2015;313(12):1232-9. doi: 10.1001/jama.2015.1373. PMID: 25706232. Excluded for ineligible population.

Ozono Y, Nagata K, Hasuike S, et al. Efficacy and safety of sofosbuvir and ledipasvir in Japanese patients aged 75 years or over with hepatitis C genotype 1. World J Hepatol. 2017;9(36):1340-5. doi: 10.4254/wjh.v9.i36.1340. PMID: 29359017. Excluded for ineligible study design for Key Question.

Paccagnini S, Principi N, Massironi E, et al. Perinatal transmission and manifestation of hepatitis C virus infection in a high risk population. Pediatr Infect Dis J. 1995;14(3):195-9. PMID: 7761184. Excluded for ineligible population.

Parisi MR, Soldini L, Vidoni G, et al. Point-of-care testing for HCV infection: recent advances and implications for alternative screening. New Microbiol. 2014;37(4):449-57. PMID: 25387283. Excluded for ineligible study design for Key Question.

Paydas S. Hepatitis C virus and lymphoma. Crit Rev Oncol Hematol. 2015;93(3):246-56. doi: 10.1016/j.critrevonc.2014.10.008. PMID: 25457774. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Pearlman BL, Ehleben C, Perrys M. The combination of simeprevir and sofosbuvir is more effective than that of peginterferon, ribavirin, and sofosbuvir for patients with hepatitis C-related child's class A cirrhosis. Gastroenterology. 2015;148(4):762-70.e2; quiz e11-2. doi: 10.1053/j.gastro.2014.12.027. PMID: 25557952. Excluded for ineligible population.

Pembrey L, European Paediatric Hepatitis C Virus Network. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. European Paediatric Hepatitis C Virus Network. BJOG. 2001;108(4):371-7. PMID: 11305543. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Perello C, Carrion JA, Ruiz-Antoran B, et al. Effectiveness and safety of ombitasvir, paritaprevir, ritonavir +/- dasabuvir +/- ribavirin: an early access programme for Spanish patients with genotype 1/4 chronic hepatitis C virus infection. J Viral Hepat. 2017;24(3):226-37. PMID: 27976491. Excluded for ineligible study design for Key Question.

Petersen T, Townsend K, Gordon LA, et al. High adherence to all-oral directly acting antiviral HCV therapy among an inner-city patient population in a phase 2a study. Hepatol Int. 2016;10(2):310-9. doi: 10.1007/s12072-015-9680-7. PMID: 26612014. Excluded for ineligible intervention.

Pillai AA, Maheshwari R, Vora R, et al. Treatment of HCV infection in liver transplant recipients with ledipasvir and sofosbuvir without ribavirin. Aliment Pharmacol Ther. 2017;45(11):1427-32. doi: 10.1111/apt.14059. PMID: 28382751. Excluded for ineligible population.

Pillai AA, Wedd J, Norvell JP, et al. Simeprevir and sofosbuvir (SMV-SOF) for 12 weeks for the treatment of chronic hepatitis C genotype 1 infection: a real world (Transplant) hepatology practice experience. Am J Gastroenterol. 2016;111(2):250-60. doi: 10.1038/ajg.2015.422. PMID: 26832650. Excluded for ineligible intervention.

Pinzani M. Liver fibrosis in the post-HCV era. Semin Liver Dis. 2015;35(2):157-65. doi: 10.1055/s-0035-1550056. PMID: 25974901. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Pipan C, Amici S, Astori G, et al. Vertical transmission of hepatitis C virus in low-risk pregnant women. Eur J Clin Microbiol Infect Dis. 1996;15(2):116-20. PMID: 8801082. Excluded for poor quality.

Pockros PJ, Jensen D, Tsai N, et al. JUMP-C: a randomized trial of mericitabine plus pegylated interferon alpha-2a/ribavirin for 24 weeks in treatment-naive HCV genotype 1/4 patients. Hepatology. 2013;58(2):514-23. doi: 10.1002/hep.26275. PMID: 23359491. Excluded for ineligible intervention.

Pol S, Bourliere M, Lucier S, et al. Safety and efficacy of daclatasvir-sofosbuvir in HCV genotype 1-mono-infected patients. J Hepatol. 2017;66(1):39-47. PMID: 27622858. Excluded for ineligible study design for Key Question.

Pol S, Ghalib RH, Rustgi VK, et al. Daclatasvir for previously untreated chronic hepatitis C genotype-1 infection: a randomised, parallel-group, double-blind, placebo-controlled, dose-finding, phase 2a trial. Lancet Infect Dis. 2012;12(9):671-7. doi: 10.1016/S1473-3099(12)70138-X. PMID: 22714001. Excluded for ineligible intervention.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Polepally AR, Badri PS, Eckert D, et al. Effects of mild and moderate renal impairment on ombitasvir, paritaprevir, ritonavir, dasabuvir, and ribavirin pharmacokinetics in patients with chronic HCV infection. Eur J Drug Metab Pharmacokinet. 2017;42(2):333-9. doi: 10.1007/s13318-016-0341-6. PMID: 27165046. Excluded for ineligible intervention.

Pontali E, Fiore V, Ialungo AM, et al. Treatment with direct-acting antivirals in a multicenter cohort of HCV-infected inmates in Italy. Int J Drug Policy. 2018;59:50-3. doi: 10.1016/j.drugpo.2018.06.017. PMID: 29986272. Excluded for ineligible population.

Poordad F, Agarwal K, Younes Z, et al. Low relapse rate leads to high concordance of sustained virologic response (SVR) at 12 weeks with SVR at 24 weeks after treatment with ABT-450/ritonavir, ombitasvir, and dasabuvir plus ribavirin in subjects with chronic hepatitis C virus genotype 1 infection in the AVIATOR study. Clin Infect Dis. 2015;60(4):608-10. doi: 10.1093/cid/ciu865. PMID: 25365973. Excluded for ineligible population.

Poordad F, McCone J, Jr., Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011;364(13):1195-206. doi: 10.1056/NEJMoa1010494. PMID: 21449783. Excluded for inadequate duration.

Poordad F, Sievert W, Mollison L, et al. Fixed-dose combination therapy with daclatasvir, asunaprevir, and beclabuvir for noncirrhotic patients with HCV genotype 1 infection. JAMA. 2015;313(17):1728-35. doi: 10.1001/jama.2015.3860. PMID: 25942723. Excluded for ineligible intervention.

Porter JC, Lusk HM, Katz AR. Prevalence of HCV infection among clients in community-based health settings in Hawaii, 2002-2010: assessing risk factors. Am J Public Health. 2014;104(8):1534-9. doi: 10.2105/AJPH.2013.301282. PMID: 24028267. Excluded for ineligible study design for Key Question.

Porto AF, Tormey L, Lim JK. Management of chronic hepatitis C infection in children. Curr Opin Pediatr. 2012;24(1):113-20. doi: 10.1097/MOP.0b013e32834eb73f. PMID: 22157364. Excluded for ineligible population.

Pothineni NV, Delongchamp R, Vallurupalli S, et al. Impact of hepatitis C seropositivity on the risk of coronary heart disease events. Am J Cardiol. 2014;114(12):1841-5. doi: 10.1016/j.amjcard.2014.09.020. PMID: 25438910. Excluded for ineligible intervention.

Poullot E, Bouscary D, Guyader D, et al. Large granular lymphocyte leukemia associated with hepatitis C virus infection and B cell lymphoma: improvement after antiviral therapy. Leuk Lymphoma. 2013;54(8):1797-9. doi: 10.3109/10428194.2012.752486. PMID: 23176408. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Poynard T, Moussalli J, Munteanu M, et al. Slow regression of liver fibrosis presumed by repeated biomarkers after virological cure in patients with chronic hepatitis C. J Hepatol. 2013;59(4):675-83. doi: 10.1016/j.jhep.2013.05.015. PMID: 23712051. Excluded for ineligible population.

Pradat P, Tillmann HL, Sauleda S, et al. Long-term follow-up of the hepatitis C HENCORE cohort: response to therapy and occurrence of liver-related complications. J Viral Hepat. 2007;14(8):556-63. doi: 10.1111/j.1365-2893.2006.00829.x. PMID: 17650289. Excluded for ineligible outcome.

Prasad MR, Honegger JR. Hepatitis C virus in pregnancy. Am J Perinatol. 2013;30(2):149-59. doi: 10.1055/s-0033-1334459. PMID: 23389935. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Prasad N, Patel MR, Pandey A, et al. Direct-acting antiviral agents in hepatitis C virus-infected renal allograft recipients: treatment and outcome experience from single center. Indian J Nephrol. 2018;28(3):220-5. doi: 10.4103/ijn.IJN_190_17. PMID: 29962673. Excluded for ineligible population.

Puigvehi M, De Cuenca B, Viu A, et al. Eight weeks of paritaprevir/r/ombitasvir + dasabuvir in HCV genotype 1b with mild-moderate fibrosis: results from a real-world cohort. Liver Int. 2019;39(1):90-7. doi: 10.1111/liv.13950. PMID: 30160363. Excluded for ineligible intervention.

Punzalan CS, Barry C, Zacharias I, et al. Sofosbuvir plus simeprevir treatment of recurrent genotype 1 hepatitis C after liver transplant. Clin Transplant. 2015;29(12):1105-11. doi: 10.1111/ctr.12634. PMID: 26358816. Excluded for ineligible population.

Qu Y, Guo Y, Li T, et al. Efficacy and safety of sofosbuvir-based interferon-free therapies for hepatitis C in liver transplant recipients. J Gastroenterol Hepatol. 2017;32(4):740-8. doi: 10.1111/jgh.13614. PMID: 27749979. Excluded for ineligible population.

Rabie R, Mumtaz K, Renner EL. Efficacy of antiviral therapy for hepatitis C after liver transplantation with cyclosporine and tacrolimus: a systematic review and meta-analysis. Liver Transpl. 2013;19(1):36-48. doi: 10.1002/lt.23516. PMID: 22821730. Excluded for ineligible population.

Rasenack J, Zeuzem S, Feinman SV, et al. Peginterferon alpha-2a (40kD) [Pegasys] improves HR-QOL outcomes compared with unmodified interferon alpha-2a [Roferon-A]: in patients with chronic hepatitis C. Pharmacoeconomics. 2003;21(5):341-9. PMID: 12627987. Excluded for ineligible intervention.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Reddy KR, Bourliere M, Sulkowski M, et al. Ledipasvir and sofosbuvir in patients with genotype 1 hepatitis C virus infection and compensated cirrhosis: an integrated safety and efficacy analysis. Hepatology. 2015;62(1):79-86. doi: 10.1002/hep.27826. PMID: 25846144. Excluded for ineligible population.

Reddy KR, Lim JK, Kuo A, et al. All-oral direct-acting antiviral therapy in HCV-advanced liver disease is effective in real-world practice: observations through HCV-TARGET database. Aliment Pharmacol Ther. 2017;45(1):115-26. doi: 10.1111/apt.13823. PMID: 27790729. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Reddy KR, Zeuzem S, Zoulim F, et al. Simeprevir versus telaprevir with peginterferon and ribavirin in previous null or partial responders with chronic hepatitis C virus genotype 1 infection (ATTAIN): a randomised, double-blind, non-inferiority phase 3 trial. Lancet Infect Dis. 2015;15(1):27-35. doi: 10.1016/S1473-3099(14)71002-3. PMID: 25482330. Excluded for ineligible intervention.

Reid CT, De Gascun C, Hall W, et al. Is universal screening for hepatitis C infection prior to commencing antitumour necrosis factor-alpha therapy necessary? Br J Dermatol. 2013;169(6):1319-21. doi: 10.1111/bjd.12598. PMID: 24032395. Excluded for ineligible study design for Key Question.

Rein DB, Smith BD, Wittenborn JS, et al. The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. Ann Intern Med. 2012;156(4):263-70. doi: 10.7326/0003-4819-156-4-201202210-00378. PMID: 22056542. Excluded for ineligible intervention.

Rein DB, Wittenborn JS, Smith BD, et al. The cost-effectiveness, health benefits, and financial costs of new antiviral treatments for hepatitis C virus. Clin Infect Dis. 2015;61(2):157-68. doi: 10.1093/cid/civ220. PMID: 25778747. Excluded for ineligible study design for Key Question.

Renard S, Borentain P, Salaun E, et al. Severe pulmonary arterial hypertension in patients treated for hepatitis C with sofosbuvir. Chest. 2016;149(3):e69-73. doi: 10.1016/j.chest.2015.09.018. PMID: 26965976. Excluded for ineligible study design for Key Question.

Resti M, Azzari C, Mannelli F, et al. Mother to child transmission of hepatitis C virus: prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. Tuscany Study Group on hepatitis C virus infection. BMJ. 1998;317(7156):437-41. PMID: 9703524. Excluded for poor quality.

Roberts EA, Yeung L. Maternal-infant transmission of hepatitis C virus infection. Hepatology. 2002;36(5 Suppl 1):S106-13. doi: 10.1053/jhep.2002.36792. PMID: 12407583. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Rodger AJ, Jolley D, Thompson SC, et al. The impact of diagnosis of hepatitis C virus on quality of life. Hepatology. 1999;30(5):1299-301. PMID: 10534353. Excluded for poor quality.

Rodriguez-Torres M, Lawitz E, Yangco B, et al. Daclatasvir and peginterferon/ribavirin for black/African-American and Latino patients with HCV infection. Ann Hepatol. 2016;15(6):834-45. doi: 10.5604/16652681.1222098. PMID: 27740516. Excluded for ineligible intervention.

Rosen I, Kori M, Eshach Adiv O, et al. Pegylated interferon alfa and ribavirin for children with chronic hepatitis C. World J Gastroenterol. 2013;19(7):1098-103. doi: 10.3748/wjg.v19.i7.1098. PMID: 23467199. Excluded for ineligible intervention.

Rosenberg WM, Tanwar S, Trembling P. Complexities of HCV management in the new era of direct-acting antiviral agents. QJM. 2014;107(1):17-9. doi: 10.1093/qjmed/hct181. PMID: 24065837. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Rossi C, Butt ZA, Wong S, et al. Hepatitis C virus reinfection after successful treatment with direct-acting antiviral therapy in a large population-based cohort. J Hepatol. 2018;69(5):1007-14. doi: 10.1016/j.jhep.2018.07.025. PMID: 30142429. Excluded for ineligible outcome.

Rostaing L, Alric L, Kamar N. Use of direct-acting agents for hepatitis C virus-positive kidney transplant candidates and kidney transplant recipients. Transpl Int. 2016;29(12):1257-65. doi: 10.1111/tri.12870. PMID: 27717014. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Ruggeri M, Rolli FR, Kondili LA, et al. Cost-effectiveness analysis of daclatasvir/sofosbuvir for the treatment of the HCV patients failed after the first line with second generation of DAAs in Italy. Expert Rev Pharmacoecon Outcomes Res. 2018:1-12. doi: 10.1080/14737167.2019.1537784. PMID: 30351994. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. Gastroenterology. 2010;138(1):108-15. doi: 10.1053/j.gastro.2009.08.071. PMID: 19766645. Excluded for outdated medication.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Saab S, Greenberg A, Li E, et al. Sofosbuvir and simeprevir is effective for recurrent hepatitis C in liver transplant recipients. Liver Int. 2015;35(11):2442-7. doi: 10.1111/liv.12856. PMID: 25913321. Excluded for ineligible population.

Saab S, Mehta D, Hudgens S, et al. Effect of ombitasvir/paritaprevir/ritonavir + dasabuvir regimen on health-related quality of life for patients with hepatitis C. Liver Int. 2018;38(8):1377-94. doi: 10.1111/liv.13690. PMID: 29314597. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Saab S, Park SH, Mizokami M, et al. Safety and efficacy of ledipasvir/sofosbuvir for the treatment of genotype 1 hepatitis C in subjects aged 65 years or older. Hepatology. 2016;63(4):1112-9. doi: 10.1002/hep.28425. PMID: 26704693. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Sadler MD, Lee SS. Revolution in hepatitis C antiviral therapy. Br Med Bull. 2015;113(1):31-44. doi: 10.1093/bmb/ldv004. PMID: 25680808. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Salemi JL, Whiteman VE, August EM, et al. Maternal hepatitis B and hepatitis C infection and neonatal neurological outcomes. J Viral Hepat. 2014;21(11):e144-53. doi: 10.1111/jvh.12250. PMID: 24666386. Excluded for ineligible intervention.

Sanchez Antolin G, Testillano M, Pascasio JM, et al. Efficacy and safety of therapy with simeprevir and sofosbuvir in liver transplant recipients infected by hepatitis C virus genotype 4: cohort Spanish society of liver transplantation cohort. Transplant Proc. 2016;48(9):3013-6. doi: 10.1016/j.transproceed.2016.08.034. PMID: 27932134. Excluded for ineligible population.

Sarpel D, Baichoo E, Dieterich DT. Chronic hepatitis B and C infection in the United States: a review of current guidelines, disease burden and cost effectiveness of screening. Expert Rev Anti Infect Ther. 2016;14(5):511-21. doi: 10.1586/14787210.2016.1174066. PMID: 27043049. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Sarrazin C, Dvory-Sobol H, Svarovskaia ES, et al. Prevalence of resistance-associated substitutions in HCV NS5A, NS5B, or NS3 and outcomes of treatment with ledipasvir and sofosbuvir. Gastroenterology. 2016;151(3):501-12.e1. doi: 10.1053/j.gastro.2016.06.002. PMID: 27296509. Excluded for ineligible study design for Key Question.

Sarrazin C, Isakov V, Svarovskaia ES, et al. Late relapse versus hepatitis C virus reinfection in patients with sustained virologic response after sofosbuvir-based therapies. Clin Infect Dis. 2017;64(1):44-52. doi: 10.1093/cid/ciw676. PMID: 27737953. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Saxena V, Khungar V, Verna EC, et al. Safety and efficacy of current direct-acting antiviral regimens in kidney and liver transplant recipients with hepatitis C: results from the HCV-TARGET study. Hepatology. 2017;66(4):1090-101. doi: 10.1002/hep.29258. PMID: 28504842. Excluded for ineligible population.

Saxena V, Nyberg L, Pauly M, et al. Safety and efficacy of simeprevir/sofosbuvir in hepatitis C-infected patients with compensated and decompensated cirrhosis. Hepatology. 2015;62(3):715-25. doi: 10.1002/hep.27922. PMID: 26033798. Excluded for ineligible population.

Scalioni LP, Cruz HM, de Paula VS, et al. Performance of rapid hepatitis C virus antibody assays among high- and low-risk populations. J Clin Virol. 2014;60(3):200-5. doi: 10.1016/j.jcv.2014.04.001. PMID: 24794796. Excluded for ineligible country.

Scavone C, Sportiello L, Rafaniello C, et al. New era in treatment options of chronic hepatitis C: focus on safety of new direct-acting antivirals (DAAs). Expert Opin Drug Saf. 2016;15(sup2):85-100. doi: 10.1080/14740338.2016.1221396. PMID: 27875916. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Schechter-Perkins EM, Miller NS, Hall J, et al. Implementation and preliminary results of an emergency department nontargeted, opt-out hepatitis C virus screening program. Acad Emerg Med. 2018;31:31. doi: 10.1111/acem.13484. PMID: 29851238. Excluded for ineligible study design for Key Question.

Schreiber J, McNally J, Chodavarapu K, et al. Treatment of a patient with genotype 7 hepatitis C virus infection with sofosbuvir and velpatasvir. Hepatology. 2016;64(3):983-5. PMID: 27177605. Excluded for ineligible study design for Key Question.

Schutz A, Moser S, Schwanke C, et al. Directly observed therapy of chronic hepatitis C with ledipasvir/sofosbuvir in people who inject drugs at risk of nonadherence to direct-acting antivirals. J Viral Hepat. 2018;25(7):870-3. doi: 10.1111/jvh.12857. PMID: 29316001. Excluded for ineligible study design for Key Question.

Scott GD, Rieger KE. New-onset cutaneous lichen planus following therapy for hepatitis C with ledipasvir-sofosbuvir. J Cutan Pathol. 2016;43(4):408-9. doi: 10.1111/cup.12656. PMID: 26816004. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Scott N, McBryde E, Vickerman P, et al. The role of a hepatitis C virus vaccine: modelling the benefits alongside direct-acting antiviral treatments. BMC Med. 2015;13:198. doi: 10.1186/s12916-015-0440-2. PMID: 26289050. Excluded for ineligible study design for Key Question.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Seaberg EC, Witt MD, Jacobson LP, et al. Differences in hepatitis C virus prevalence and clearance by mode of acquisition among men who have sex with men. J Viral Hepat. 2014;21(10):696-705. doi: 10.1111/jvh.12198. PMID: 25280229. Excluded for ineligible intervention.

Sears DM, Cohen DC, Ackerman K, et al. Birth cohort screening for chronic hepatitis during colonoscopy appointments. Am J Gastroenterol. 2013;108(6):981-9. doi: 10.1038/ajg.2013.50. PMID: 23511461. Excluded for ineligible study design for Key Question.

Serfaty L. Follow-up of patients with chronic hepatitis C and a sustained viral response. Liver Int. 2016;36 Suppl 1:67-71. doi: 10.1111/liv.13016. PMID: 26725900. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Shebl FM, El-Kamary SS, Shardell M, et al. Estimating incidence rates with misclassified disease status: a likelihood-based approach, with application to hepatitis C virus. Int J Infect Dis. 2012;16(7):e527-31. doi: 10.1016/j.ijid.2012.02.017. PMID: 22543295. Excluded for ineligible study design for Key Question.

Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med. 2011;365(11):1014-24. doi: 10.1056/NEJMoa1014463. PMID: 21916639. Excluded for outdated medication.

Shiffman ML. Universal screening for chronic hepatitis C virus. Liver Int. 2016;36 Suppl 1:62-6. doi: 10.1111/liv.13012. PMID: 26725899. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Shiffman ML, Rustgi V, Bennett M, et al. Safety and efficacy of ombitasvir/paritaprevir/ritonavir plus dasabuvir with or without ribavirin in HCV-infected patients taking concomitant acid-reducing agents. Am J Gastroenterol. 2016;111(6):845-51. doi: 10.1038/ajg.2016.108. PMID: 27045929. Excluded for ineligible intervention.

Shiffman ML, Sterling RK, Contos M, et al. Long term changes in liver histology following treatment of chronic hepatitis C virus. Ann Hepatol. 2014;13(4):340-9. PMID: 24927604. Excluded for ineligible outcome.

Shiffman ML, Suter F, Bacon BR, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med. 2007;357(2):124-34. doi: 10.1056/NEJMoa066403. PMID: 17625124. Excluded for outdated medication.

Shiha G, Esmat G, Hassany M, et al. Ledipasvir/sofosbuvir with or without ribavirin for 8 or 12 weeks for the treatment of HCV genotype 4 infection: results from a randomised phase III study in Egypt. Gut. 2018;17:17. doi: 10.1136/gutjnl-2017-315906. PMID: 29666174. Excluded for ineligible population.

Shiha G, Soliman R, ElBasiony M, et al. Sofosbuvir plus daclatasvir with or without ribavirin for treatment of chronic HCV genotype 4 patients: real-life experience. Hepatol Int. 2018;12(4):339-47. doi: 10.1007/s12072-018-9861-2. PMID: 29663115. Excluded for ineligible study design for Key Question.

Shindo M, Hamada K, Oda Y, et al. Long-term follow-up study of sustained biochemical responders with interferon therapy. Hepatology. 2001;33(5):1299-302. doi: 10.1053/jhep.2001.24100. PMID: 11343259. Excluded for poor quality.

Shindoh J, Hasegawa K, Matsuyama Y, et al. Low hepatitis C viral load predicts better long-term outcomes in patients undergoing resection of hepatocellular carcinoma irrespective of serologic eradication of hepatitis C virus. J Clin Oncol. 2013;31(6):766-73. doi: 10.1200/JCO.2012.44.3234. PMID: 23129744. Excluded for ineligible population.

Shiratori Y, Ito Y, Yokosuka O, et al. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. Ann Intern Med. 2005;142(2):105-14. PMID: 15657158. Excluded for ineligible population.

Shousha HI, Akl K, Ragheb S, et al. Generic sofosbuvir/ledipasvir for treatment of naive, non-cirrhotic, easy to treat patients with chronic hepatitis c genotype 4: 8 vs. 12 weeks of treatment. Hepat Mon. 2018;18(9). Excluded for ineligible intervention.

Simmons B, Saleem J, Heath K, et al. Long-term treatment outcomes of patients infected with hepatitis C virus: a systematic review and meta-analysis of the survival benefit of achieving a sustained virological response. Clin Infect Dis. 2015;61(5):730-40. doi: 10.1093/cid/civ396. PMID: 25987643. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Singal AG, Volk ML, Jensen D, et al. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol. 2010;8(3):280-8.e1. doi: 10.1016/j.cgh.2009.11.018. PMID: 19948249. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Siqueira FM, Ferreira VL, Borba HHL, et al. Quality of life of Brazilian chronic hepatitis C patients treated with interferon-free therapies. Rev Inst Med Trop Sao Paulo. 2018;60:e72. doi: 10.1590/S1678-9946201860072. PMID: 30462795. Excluded for ineligible population.

Slim J, Afridi MS. Managing adverse effects of interferon-alfa and ribavirin in combination therapy for HCV. Infect Dis Clin North Am. 2012;26(4):917-29. doi: 10.1016/j.idc.2012.08.006. PMID: 23083824. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Smith BD, Yartel AK. Comparison of hepatitis C virus testing strategies: birth cohort versus elevated alanine aminotransferase levels. Am J Prev Med. 2014;47(3):233-41. doi: 10.1016/j.amepre.2014.05.011. PMID: 25145616. Excluded for ineligible comparator.

Smith BD, Yartel AK, Krauskopf K, et al. Hepatitis C virus antibody positivity and predictors among previously undiagnosed adult primary care outpatients: cross-sectional analysis of a multisite retrospective cohort study. Clin Infect Dis. 2015;60(8):1145-52. doi: 10.1093/cid/civ002. PMID: 25595745. Excluded for ineligible outcome.

Smith MA, Lim A. Profile of paritaprevir/ritonavir/ombitasvir plus dasabuvir in the treatment of chronic hepatitis C virus genotype 1 infection. Drug Des Devel Ther. 2015;9:6083-94. doi: 10.2147/DDDT.S80226. PMID: 26622169. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Smith MA, Love BL, Mohammad RA. The changing landscape of adverse drug events associated with chronic hepatitis C virus therapy. Expert Opin Drug Saf. 2015;14(11):1649-52. doi: 10.1517/14740338.2015.1088002. PMID: 26365685. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Snow KJ, Richards AH, Kinner SA. Use of multiple data sources to estimate hepatitis C seroprevalence among prisoners: a retrospective cohort study. PLoS One. 2017;12(7):e0180646. doi: 10.1371/journal.pone.0180646. PMID: 28686715. Excluded for ineligible country.

Snow KJ, Young JT, Preen DB, et al. Incidence and correlates of hepatitis C virus infection in a large cohort of prisoners who have injected drugs. BMC Public Health. 2014;14:830. doi: 10.1186/1471-2458-14-830. PMID: 25113132. Excluded for ineligible country.

Soga K, Shibasaki K, Aoyagi Y. Effect of interferon on incidence of hepatocellular carcinoma in patients with chronic hepatitis C. Hepatogastroenterology. 2005;52(64):1154-8. PMID: 16001651. Excluded for poor quality.

Solis-Munoz P, Mingote-Adan C, Solis-Herruzo JA. Neurocognitive function and dysfunction after hepatitis C therapy. Hepatology. 2014;60(1):431. doi: 10.1002/hep.26919. PMID: 24178628. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Solund C, Andersen ES, Mossner B, et al. Outcome and adverse events in patients with chronic hepatitis C treated with direct-acting antivirals: a clinical randomized study. Eur J Gastroenterol Hepatol. 2018;30(10):1177-86. doi: 10.1097/MEG.0000000000001192. PMID: 29994874. Excluded for ineligible population.

Sommese L, Sabia C, Paolillo R, et al. Screening tests for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus in blood donors: evaluation of two chemiluminescent immunoassay systems. Scand J Infect Dis. 2014;46(9):660-4. doi: 10.3109/00365548.2014.926564. PMID: 25073538. Excluded for ineligible outcome.

Sood A, Midha V, Hissar S, et al. Comparison of low-dose pegylated interferon versus standard high-dose pegylated interferon in combination with ribavirin in patients with chronic hepatitis C with genotype 3: an Indian experience. J Gastroenterol Hepatol. 2008;23(2):203-7. doi: 10.1111/j.1440-1746.2007.05057.x. PMID: 17645472. Excluded for outdated medication.

Soriano V, Young B, Terrault N. Report from the International Conference on Viral Hepatitis (ICVH), San Francisco, March 2016. AIDS Rev. 2016;18(2):81-8. PMID: 27196355. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Sou FM, Wu CK, Chang KC, et al. Clinical characteristics and prognosis of HCC occurrence after antiviral therapy for HCV patients between sustained and non-sustained responders. J Formos Med Assoc. 2019;118(1 Pt 3):504-13. doi: 10.1016/j.jfma.2018.10.017. PMID: 30527565. Excluded for insufficient statistical analysis.

Southern WN, Drainoni ML, Smith BD, et al. Physician nonadherence with a hepatitis C screening program. Qual Manag Health Care. 2014;23(1):1-9. doi: 10.1097/QMH.0000000000000007. PMID: 24368717. Excluded for ineligible outcome.

Southern WN, Norton B, Steinman M, et al. A birth-cohort testing intervention identified hepatitis C virus infection among patients with few identified risks: a cross-sectional study. BMC Infect Dis. 2015;15:553. doi: 10.1186/s12879-015-1283-3. PMID: 26626449. Excluded for ineligible outcome.

Spelman T, Morris MD, Zang G, et al. A longitudinal study of hepatitis C virus testing and infection status notification on behaviour change in people who inject drugs. J Epidemiol Community Health. 2015;69(8):745-52. doi: 10.1136/jech-2014-205224. PMID: 25814695. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Spencer JD, Latt N, Beeby PJ, et al. Transmission of hepatitis C virus to infants of human immunodeficiency virus-negative intravenous drug-using mothers: rate of infection and assessment of risk factors for transmission. J Viral Hepat. 1997;4(6):395-409. PMID: 9430360. Excluded for poor quality.

Stasi C, Arena U, Zignego AL, et al. Longitudinal assessment of liver stiffness in patients undergoing antiviral treatment for hepatitis C. Dig Liver Dis. 2013;45(10):840-3. doi: 10.1016/j.dld.2013.03.023. PMID: 23660078. Excluded for ineligible outcome.

Stasi C, Piluso A, Arena U, et al. Evaluation of the prognostic value of liver stiffness in patients with hepatitis C virus treated with triple or dual antiviral therapy: a prospective pilot study. World J Gastroenterol. 2015;21(10):3013-9. doi: 10.3748/wjg.v21.i10.3013. PMID: 25780300. Excluded for ineligible outcome.

Stein MR, Soloway IJ, Jefferson KS, et al. Concurrent group treatment for hepatitis C: implementation and outcomes in a methadone maintenance treatment program. J Subst Abuse Treat. 2012;43(4):424-32. doi: 10.1016/j.jsat.2012.08.007. PMID: 23036920. Excluded for ineligible intervention.

Steininger C, Kundi M, Jatzko G, et al. Increased risk of mother-to-infant transmission of hepatitis C virus by intrapartum infantile exposure to maternal blood. J Infect Dis. 2003;187(3):345-51. doi: 10.1086/367704. PMID: 12552417. Excluded for insufficient statistical analysis.

Stepanova M, Nader F, Cure S, et al. Patients' preferences and health utility assessment with SF-6D and EQ-5D in patients with chronic hepatitis C treated with sofosbuvir regimens. Aliment Pharmacol Ther. 2014;40(6):676-85. doi: 10.1111/apt.12880. PMID: 25040192. Excluded for ineligible intervention.

Stewart RA, MacDonald BR, Chu TC, et al. Ledipasvir/sofosbuvir effectively treats hepatitis C virus infections in an underserved population. Dig Dis Sci. 2018;63(12):3233-40. doi: 10.1007/s10620-018-5205-2. PMID: 30014226. Excluded for ineligible study design for Key Question.

Stockman LJ, Greer J, Holzmacher R, et al. Performance of risk-based and birth-cohort strategies for identifying hepatitis C virus infection among people entering prison, Wisconsin, 2014. Public Health Rep. 2016;131(4):544-51. doi: 10.1177/0033354916662212. PMID: 27453598. Excluded for ineligible population.

Stockman LJ, Guilfoye SM, Benoit AL, et al. Rapid hepatitis C testing among persons at increased risk for infection-Wisconsin, 2012-2013. MMWR. 2014;63(14):309-11. PMID: 24717818. Excluded for ineligible outcome.

Su F, Green PK, Berry K, et al. The association between race/ethnicity and the effectiveness of direct antiviral agents for hepatitis C virus infection. Hepatology. 2017;65(2):426-38. doi: 10.1002/hep.28901. PMID: 27775854. Excluded for ineligible comparator.

Suda G, Kudo M, Nagasaka A, et al. Efficacy and safety of daclatasvir and asunaprevir combination therapy in chronic hemodialysis patients with chronic hepatitis C. J Gastroenterol. 2016;51(7):733-40. doi: 10.1007/s00535-016-1162-8. PMID: 26768604. Excluded for ineligible intervention.

Suraweera D, Weeratunga AN, Saab S. Spotlight on grazoprevir-elbasvir once-daily combination and its potential in the treatment of hepatitis C. Drug Des Devel Ther. 2016;10:2119-27. doi: 10.2147/DDDT.S90537. PMID: 27418810. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Suryaprasad AG, White JZ, Xu F, et al. Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006-2012. Clin Infect Dis. 2014;59(10):1411-9. doi: 10.1093/cid/ciu643. PMID: 25114031. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Suwanthawornkul T, Anothaisintawee T, Sobhonslidsuk A, et al. Efficacy of second generation direct-acting antiviral agents for treatment naive hepatitis C genotype 1: a systematic review and network meta-analysis. PLoS One. 2015;10(12):e0145953. doi: 10.1371/journal.pone.0145953. PMID: 26720298. Excluded for ineligible intervention.

Syriopoulou V, Nikolopoulou G, Daikos GL, et al. Mother to child transmission of hepatitis C virus: rate of infection and risk factors. Scand J Infect Dis. 2005;37(5):350-3. doi: 10.1080/00365540510032105. PMID: 16051571. Excluded for poor quality.

Tada T, Kumada T, Toyoda H, et al. Viral eradication reduces all-cause mortality, including non-liver-related disease, in patients with progressive hepatitis C virus-related fibrosis. J Gastroenterol Hepatol. 2017;32(3):687-94. doi: 10.1111/jgh.13589. PMID: 27577675. Excluded for ineligible study design for Key Question.

Tajiri H, Miyoshi Y, Funada S, et al. Prospective study of mother-to-infant transmission of hepatitis C virus. Pediatr Infect Dis J. 2001;20(1):10-4. PMID: 11176560. Excluded for poor quality.

Takahashi H, Mizuta T, Eguchi Y, et al. Post-challenge hyperglycemia is a significant risk factor for the development of hepatocellular carcinoma in patients with chronic hepatitis C. J Gastroenterol. 2011;46(6):790-8. doi: 10.1007/s00535-011-0381-2. PMID: 21331763. Excluded for ineligible comparator.

Takeda K, Noguchi R, Namisaki T, et al. Efficacy and tolerability of interferon-free regimen for patients with genotype-1 HCV infection. Exp Ther Med. 2018;16(3):2743-50. doi: 10.3892/etm.2018.6481. PMID: 30210615. Excluded for ineligible study design for Key Question.

Takeuchi LC, Pham TK, Katz AR. Hepatitis C virus antibody prevalence, demographics and associated factors among persons screened at Hawai'i community-based health settings, 2010-2013. Hawaii J Med Public Health. 2015;74(1):9-15. PMID: 25628977. Excluded for ineligible study design for Key Question.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Taki S, Tamai H, Ida Y, et al. The real-world safety and efficacy of daclatasvir and asunaprevir for elderly patients. Gut Liver. 2018;12(1):86-93. doi: 10.5009/gnl17048. PMID: 28798288. Excluded for ineligible intervention.

Tam E, Luetkemeyer AF, Mantry PS, et al. Ledipasvir/sofosbuvir for treatment of hepatitis C virus in sofosbuvir-experienced, NS5A treatment-naive patients: findings from two randomized trials. Liver Int. 2018;38(6):1010-21. doi: 10.1111/liv.13616. PMID: 29091342. Excluded for ineligible population.

Tamai H, Shingaki N, Ida Y, et al. Real-world safety and efficacy of sofosbuvir and ledipasvir for elderly patients. Jgh Open. 2018;2(6):300-6. doi: 10.1002/jgh3.12088. PMID: 30619941. Excluded for ineligible population.

Tame M, Buonfiglioli F, Del Gaudio M, et al. Long-term leukocyte natural alpha-interferon and ribavirin treatment in hepatitis C virus recurrence after liver transplantation. World J Gastroenterol. 2013;19(32):5278-85. doi: 10.3748/wjg.v19.i32.5278. PMID: 23983430. Excluded for ineligible population.

Tanaka T, Selzner N, Therapondos G, et al. Virological response for recurrent hepatitis C improves long-term survival in liver transplant recipients. Transpl Int. 2013;26(1):42-9. doi: 10.1111/j.1432-2277.2012.01571.x. PMID: 23137287. Excluded for ineligible population.

Tanase AM, Dumitrascu T, Dima S, et al. Influence of hepatitis viruses on clinicopathological profiles and long-term outcome in patients undergoing surgery for hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int. 2014;13(2):162-72. PMID: 24686543. Excluded for ineligible population.

Tang L, Kamat M, Shukla A, et al. Comparative antiviral efficacy of generic sofosbuvir versus brand name sofosbuvir with ribavirin for the treatment of hepatitis C. Interdiscip Perspect Infect Dis. 2018;2018:9124604. doi: 10.1155/2018/9124604. PMID: 30364048. Excluded for ineligible intervention.

Tanzi M, Bellelli E, Benaglia G, et al. The prevalence of HCV infection in a cohort of pregnant women, the related risk factors and the possibility of vertical transmission. Eur J Epidemiol. 1997;13(5):517-21. PMID: 9258562. Excluded for poor quality.

Taylor BS, Hanson JT, Veerapaneni P, et al. Hospital-based hepatitis C screening of baby boomers in a majority Hispanic south Texas cohort: successes and barriers to implementation. Public Health Rep. 2016;131 Suppl 2:74-83. doi: 10.1177/00333549161310S212. PMID: 27168665. Excluded for ineligible outcome.

Teriaky A, Reau N. Evaluation of hepatitis C patients in the direct-acting antiviral era. Clin Liver Dis. 2015;19(4):591-604, v. doi: 10.1016/j.cld.2015.06.001. PMID: 26466649. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Terrault NA, Zeuzem S, Di Bisceglie AM, et al. Effectiveness of ledipasvir-sofosbuvir combination in patients with hepatitis C virus infection and factors associated with sustained virologic response. Gastroenterology. 2016;151(6):1131-40.e5. doi: 10.1053/j.gastro.2016.08.004. PMID: 27565882. Excluded for ineligible study design for Key Question.

Thomas SL, Newell ML, Peckham CS, et al. A review of hepatitis C virus (HCV) vertical transmission: risks of transmission to infants born to mothers with and without HCV viraemia or human immunodeficiency virus infection. Int J Epidemiol. 1998;27(1):108-17. PMID: 9563703. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Thu Thuy PT, Bunchorntavakul C, Tan Dat H, et al. Sofosbuvir-ledipasvir with or without ribavirin for chronic hepatitis C genotype-1 and 6: real-world experience in Vietnam. Antivir Ther. 2018;23(5):415-23. doi: 10.3851/IMP3217. PMID: 29303482. Excluded for ineligible population.

Tong MJ, Chang PW, Huynh TT, et al. Adverse events associated with ribavirin in sofosbuvir-based therapies for patients with chronic hepatitis C: a community practice experience. J Dig Dis. 2016;17(2):113-21. doi: 10.1111/1751-2980.12313. PMID: 26749171. Excluded for ineligible intervention.

Tong MJ, el-Farra NS, Reikes AR, et al. Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med. 1995;332(22):1463-6. doi: 10.1056/nejm199506013322202. PMID: 7739682. Excluded for ineligible intervention.

Torres DM, Harrison SA. Killing two birds with one stone: screening for chronic hepatitis C at the time of colonoscopy in the baby boomer cohort. Am J Gastroenterol. 2013;108(6):990-2. doi: 10.1038/ajg.2013.54. PMID: 23735918. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Torres HA, Mahale P, Blechacz B, et al. Effect of hepatitis C virus infection in patients with cancer: addressing a neglected population. J Natl Compr Canc Netw. 2015;13(1):41-50. PMID: 25583768. Excluded for ineligible population.

Tovo PA, Palomba E, Ferraris G, et al. Increased risk of maternal-infant hepatitis C virus transmission for women coinfected with human immunodeficiency virus type 1. Italian Study Group for HCV infection in children. Clin Infect Dis. 1997;25(5):1121-4. PMID: 9402369. Excluded for insufficient statistical analysis.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Toyoda H, Atsukawa M, Takaguchi K, et al. Real-world virological efficacy and safety of elbasvir and grazoprevir in patients with chronic hepatitis C virus genotype 1 infection in Japan. J Gastroenterol. 2018;08:08. doi: 10.1007/s00535-018-1473-z. PMID: 29740665. Excluded for ineligible study design for Key Question.

Toyoda H, Kumada T, Tada T, et al. Risk factors of hepatocellular carcinoma development in non-cirrhotic patients with sustained virologic response for chronic hepatitis C virus infection. J Gastroenterol Hepatol. 2015;30(7):1183-9. doi: 10.1111/jgh.12915. PMID: 25678094. Excluded for ineligible comparator.

Toyoda H, Kumada T, Tada T, et al. Safety and efficacy of dual direct-acting antiviral therapy (daclatasvir and asunaprevir) for chronic hepatitis C virus genotype 1 infection in patients on hemodialysis. J Gastroenterol. 2016;51(7):741-7. doi: 10.1007/s00535-016-1174-4. PMID: 26872889. Excluded for ineligible intervention.

Traynor K. Sofosbuvir approved for chronic hepatitis C infection. Am J Health Syst Pharm. 2014;71(2):90. doi: 10.2146/news140006. PMID: 24375596. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Trepka MJ, Zhang G, Leguen F, et al. Benefits and adverse effects of hepatitis C screening: early results of a screening program. J Public Health Manag Pract. 2007;13(3):263-9. doi: 10.1097/01.PHH.0000267684.23529.2c. PMID: 17435493. Excluded for poor quality.

Truchi R, Gelsi E, Cherikh F, et al. Hepatitis C virus cure as motivation for alcohol withdrawal? Hepatology. 2013;57(4):1678. doi: 10.1002/hep.25659. PMID: 22334280. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Tsuji K, Kurosaki M, Itakura J, et al. Real-world efficacy and safety of ledipasvir and sofosbuvir in patients with hepatitis C virus genotype 1 infection: a nationwide multicenter study by the Japanese Red Cross Liver Study Group. J Gastroenterol. 2018;53(10):1142-50. doi: 10.1007/s00535-018-1455-1. PMID: 29626296. Excluded for ineligible study design for Key Question.

Tsujita E, Yamashita Y, Takeishi K, et al. Second hepatectomy for recurrent hepatocellular carcinoma achieved sustained virological response to interferon therapy for hepatitis C. Hepatogastroenterology. 2013;60(128):2048-54. doi: 10.5754/hge13382. PMID: 24088310. Excluded for ineligible population.

Turer E, Rockey DC, Singal AG. A potential novel use for direct antiviral therapy. Hepatology. 2013;57(1):414-5. doi: 10.1002/hep.26145. PMID: 23172611. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Turner BJ, Taylor BS, Hanson J, et al. High priority for hepatitis C screening in safety net hospitals: results from a prospective cohort of 4582 hospitalized baby boomers. Hepatology. 2015;62(5):1388-95. doi: 10.1002/hep.28018. PMID: 26250753. Excluded for ineligible population.

Uojima H, Kobayashi S, Hidaka H, et al. Efficacy and tolerability of ombitasvir/paritaprevir/ritonavir in HCV genotype 1-infected elderly Japanese patients. Ann Hepatol. 2018;18(1):109-15. doi: 10.5604/01.3001.0012.7868. PMID: 30596630. Excluded for ineligible population.

Vafiadis I, Trilianos P, Vlachogiannakos J, et al. Efficacy and safety of interferon-based therapy in the treatment of adult thalassemic patients with chronic hepatitis C: a 12 years audit. Ann Hepatol. 2013;12(4):364-70. PMID: 23813130. Excluded for ineligible outcome.

Valla DC, Chevallier M, Marcellin P, et al. Treatment of hepatitis C virus-related cirrhosis: a randomized, controlled trial of interferon alfa-2b versus no treatment. Hepatology. 1999;29(6):1870-5. doi: 10.1002/hep.510290616. PMID: 10347132. Excluded for ineligible population.

van der Meer AJ. Achieving sustained virological response: what's the impact on further hepatitis C virus-related disease? Expert Rev Gastroenterol Hepatol. 2015;9(5):559-66. doi: 10.1586/17474124.2015.1001366. PMID: 25579804. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;308(24):2584-93. doi: 10.1001/jama.2012.144878. PMID: 23268517. Excluded for ineligible population.

Vashakidze E, Imnadze T. Combined antiviral treatment of hepatitis C virus infection with pegylated interferon (Peg-Ifn) a-2a (Pegferon) and ribavirin (Copegus) in inmates. Georgian Med. 2017 (264):86-90. PMID: 28480857. Excluded for ineligible intervention.

Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med. 2007;147(10):677-84. PMID: 18025443. Excluded for ineligible population.

Vermehren J, Peiffer KH, Welsch C, et al. The efficacy and safety of direct acting antiviral treatment and clinical significance of drug-drug interactions in elderly patients with chronic hepatitis C virus infection. Aliment Pharmacol Ther. 2016;44(8):856-65. doi: 10.1111/apt.13769. PMID: 27549000. Excluded for ineligible study design for Key Question.

Vermehren J, Schlosser B, Domke D, et al. High prevalence of anti-HCV antibodies in two metropolitan emergency departments in Germany: a prospective screening analysis of 28,809 patients. PLoS One. 2012;7(7):e41206. doi: 10.1371/journal.pone.0041206. PMID: 22848445. Excluded for ineligible study design for Key Question.

Vierling JM, Zeuzem S, Poordad F, et al. Safety and efficacy of boceprevir/peginterferon/ribavirin for HCV G1 compensated cirrhotics: meta-analysis of 5 trials. J Hepatol. 2014;61(2):200-9. doi: 10.1016/j.jhep.2014.03.022. PMID: 24747798. Excluded for ineligible population.

Virabhak S, Yasui K, Yamazaki K, et al. Cost-effectiveness of direct-acting antiviral regimen ombitasvir/paritaprevir/ritonavir in treatment-naive and treatment-experienced patients infected with chronic hepatitis C virus genotype 1b in Japan. J Med Econ. 2016;19(12):1144-56. doi: 10.1080/13696998.2016.1206908. PMID: 27348464. Excluded for ineligible study design for Key Question.

Virlogeux V, Choupeaux L, Pradat P, et al. Sofosbuvir plus daclatasvir with or without ribavirin for chronic hepatitis C infection: impact of drug concentration on viral load decay. Dig Liver Dis. 2016;48(11):1351-6. doi: 10.1016/j.dld.2016.07.014. PMID: 27498075. Excluded for ineligible study design for Key Question.

Voelker R. Birth cohort screening may help find hepatitis C cases. JAMA. 2012;307(12):1242. doi: 10.1001/jama.2012.337. PMID: 22453559. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

von Felden J, Vermehren J, Ingiliz P, et al. High efficacy of sofosbuvir/velpatasvir and impact of baseline resistance-associated substitutions in hepatitis C genotype 3 infection. Aliment Pharmacol Ther. 2018;47(9):1288-95. doi: 10.1111/apt.14592. PMID: 29536554. Excluded for ineligible population.

von Wagner M, Huber M, Berg T, et al. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. Gastroenterology. 2005;129(2):522-7. doi: 10.1016/j.gastro.2005.05.008. PMID: 16083709. Excluded for outdated medication.

Vukovic VR, Baskic D, Mijailovic Z, et al. Association between risk factors, basal viral load, virus genotype and the degree of liver fibrosis with the response to the therapy in patients with chronic hepatitis C virus infection. Vojnosanit Pregl. 2015;72(6):505-9. PMID: 26226722. Excluded for ineligible outcome.

Vuppalanchi R, Kwo PY. The cost-effectiveness of birth cohort screening for hepatitis C antibody in US primary care settings. Gastroenterology. 2013;144(2):457-9. doi: 10.1053/j.gastro.2012.12.013. PMID: 23260498. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Walker DR, Pedrosa MC, Manthena SR, et al. Early view of the effectiveness of new direct-acting antiviral (DAA) regimens in patients with hepatitis C virus (HCV). Adv Ther. 2015;32(11):1117-27. doi: 10.1007/s12325-015-0258-5. PMID: 26538232. Excluded for ineligible population.

Walsh CE, Workowski K, Terrault NA, et al. Ledipasvir-sofosbuvir and sofosbuvir plus ribavirin in patients with chronic hepatitis C and bleeding disorders. Haemophilia. 2017;23(2):198-206. doi: 10.1111/hae.13178. PMID: 28124511. Excluded for ineligible population.

Wang C, Sun JH, O'Boyle DR, 2nd, et al. Persistence of resistant variants in hepatitis C virus-infected patients treated with the NS5A replication complex inhibitor daclatasvir. Antimicrob Agents Chemother. 2013;57(5):2054-65. doi: 10.1128/AAC.02494-12. PMID: 23403428. Excluded for ineligible intervention.

Wang X, Liu F, Wei F, et al. Efficacy and safety of pegylated interferon plus ribavirin therapy for chronic hepatitis C genotype 6: a meta-analysis. PLoS One. 2014;9(6):e100128. doi: 10.1371/journal.pone.0100128. PMID: 24963667. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Ware JE, Jr., Bayliss MS, Mannocchia M, et al. Health-related quality of life in chronic hepatitis C: impact of disease and treatment response. The Interventional Therapy Group. Hepatology. 1999;30(2):550-5. doi: 10.1002/hep.510300203. PMID: 10421667. Excluded for ineligible outcome.

Waruingi W, Mhanna MJ, Kumar D, et al. Hepatitis C virus universal screening versus risk based selective screening during pregnancy. J Neonatal Perinatal Med. 2015;8(4):371-8. doi: 10.3233/NPM-15915024. PMID: 26836823. Excluded for poor quality.

Wedemeyer H, Dore GJ, Ward JW. Estimates on HCV disease burden worldwide - filling the gaps. J Viral Hepat. 2015;22 Suppl 1:1-5. doi: 10.1111/jvh.12371. PMID: 25560838. Excluded for ineligible outcome.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Wedemeyer H, Jensen D, Herring R, Jr., et al. PROPEL: a randomized trial of mericitabine plus peginterferon alpha-2a/ribavirin therapy in treatment-naive HCV genotype 1/4 patients. Hepatology. 2013;58(2):524-37. doi: 10.1002/hep.26274. PMID: 23348636. Excluded for ineligible intervention.

Wehmeyer MH, Ingiliz P, Christensen S, et al. Real-world effectiveness of sofosbuvir-based treatment regimens for chronic hepatitis C genotype 3 infection: results from the multicenter German hepatitis C cohort (GECCO-03). J Med Virol. 2018;90(2):304-12. doi: 10.1002/jmv.24903. PMID: 28710853. Excluded for ineligible population.

Wehmeyer MH, Jordan S, Luth S, et al. Efficacy and safety of sofosbuvir-based triple therapy in hepatitis C genotype 4 infection. Dig Liver Dis. 2015;47(9):811-4. doi: 10.1016/j.dld.2015.05.018. PMID: 26091766. Excluded for ineligible outcome.

Wei L, Wang FS, Zhang MX, et al. Daclatasvir plus asunaprevir in treatment-naive patients with hepatitis C virus genotype 1b infection. World J Gastroenterol. 2018;24(12):1361-72. doi: 10.3748/wjg.v24.i12.1361. PMID: 29599611. Excluded for ineligible intervention.

Weiler N, Zeuzem S, Welker MW. Concise review: Interferon-free treatment of hepatitis C virus-associated cirrhosis and liver graft infection. World J Gastroenterol. 2016;22(41):9044-56. doi: 10.3748/wjg.v22.i41.9044. PMID: 27895394. Excluded for ineligible population.

Welker MW, Luhne S, Lange CM, et al. Lactic acidosis in patients with hepatitis C virus cirrhosis and combined ribavirin/sofosbuvir treatment. J Hepatol. 2016;64(4):790-9. doi: 10.1016/j.jhep.2015.11.034. PMID: 26658684. Excluded for ineligible population.

Welzel TM, Petersen J, Herzer K, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. Gut. 2016;65(11):1861-70. doi: 10.1136/gutjnl-2016-312444. PMID: 27605539. Excluded for ineligible study design for Key Question.

Werner CR, Schwarz JM, Egetemeyr DP, et al. Second-generation direct-acting-antiviral hepatitis C virus treatment: efficacy, safety, and predictors of SVR12. World J Gastroenterol. 2016;22(35):8050-9. doi: 10.3748/wjg.v22.i35.8050. PMID: 27672299. Excluded for ineligible population.

White DA, Anderson ES, Pfeil SK, et al. Hepatitis C virus screening and emergency department length of stay. PLoS One. 2016;11(10):e0164831. doi: 10.1371/journal.pone.0164831. PMID: 27760176. Excluded for ineligible study design for Key Question.

White DA, Anderson ES, Pfeil SK, et al. Results of a rapid hepatitis C virus screening and diagnostic testing program in an urban emergency department. Ann Emerg Med. 2016;67(1):119-28. doi: 10.1016/j.annemergmed.2015.06.023. PMID: 26253712. Excluded for ineligible outcome.

Wilder JM, Jeffers LJ, Ravendhran N, et al. Safety and efficacy of ledipasvir-sofosbuvir in black patients with hepatitis C virus infection: a retrospective analysis of phase 3 data. Hepatology. 2016;63(2):437-44. doi: 10.1002/hep.28334. PMID: 26547499. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Winckler FC, Braz AMM, Silva VND, et al. Influence of the inflammatory response on treatment of hepatitis C with triple therapy. Rev Soc Bras Med Trop. 2018;51(6):731-6. doi: 10.1590/0037-8682-0137-2018. PMID: 30517525. Excluded for ineligible population.4

Wisloff T, White R, Dalgard O, et al. Feasibility of reaching world health organization targets for hepatitis C and the cost-effectiveness of alternative strategies. J Viral Hepat. 2018;25(9):1066-77. doi: 10.1111/jvh.12904. PMID: 29624813. Excluded for ineligible intervention.

Wong VW, Wong GL, Chim AM, et al. Targeted hepatitis C screening among ex-injection drug users in the community. J Gastroenterol Hepatol. 2014;29(1):116-20. doi: 10.1111/jgh.12355. PMID: 24033786. Excluded for ineligible country.

Woodrell C, Weiss J, Branch A, et al. Primary care-based hepatitis C treatment outcomes with first-generation direct-acting agents. J Addict Med. 2015;9(5):405-10. doi: 10.1097/ADM.0000000000000147. PMID: 26291545. Excluded for ineligible intervention.

Wu CJ, Roytman MM, Hong LK, et al. Real-world experience with sofosbuvir-based regimens for chronic hepatitis C, including patients with factors previously associated with inferior treatment response. Hawaii J Med Public Health. 2015;74(9 Suppl 2):3-7. PMID: 26793407. Excluded for ineligible intervention.

Wu CK, Chang KC, Hung CH, et al. Dynamic alpha-fetoprotein, platelets and AST-to-platelet ratio index predict hepatocellular carcinoma in chronic hepatitis C patients with sustained virological response after antiviral therapy. J Antimicrob Chemother. 2016;71(7):1943-7. doi: 10.1093/jac/dkw097. PMID: 27073265. Excluded for ineligible intervention.

Wu CK, Chang KC, Tseng PL, et al. Comparison of therapeutic response and clinical outcome between HCV patients with normal and abnormal alanine transaminase levels. PLoS One. 2016;11(3):e0142378. doi: 10.1371/journal.pone.0142378. PMID: 26968010. Excluded for ineligible study design for Key Question.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Wyles D, Brau N, Kottilil S, et al. Sofosbuvir and velpatasvir for the treatment of hepatitis C virus in patients coinfected with human immunodeficiency virus type 1: an open-label, phase 3 study. Clin Infect Dis. 2017;65(1):6-12. doi: 10.1093/cid/cix260. PMID: 28369210. Excluded for ineligible population.

Wyles DL, Rodriguez-Torres M, Lawitz E, et al. All-oral combination of ledipasvir, vedroprevir, tegobuvir, and ribavirin in treatment-naive patients with genotype 1 HCV infection. Hepatology. 2014;60(1):56-64. doi: 10.1002/hep.27053. PMID: 24501005. Excluded for ineligible intervention.

Xu F, Leidner AJ, Tong X, et al. Estimating the number of patients infected with chronic HCV in the United States who meet highest or high-priority treatment criteria. Am J Public Health. 2015;105(7):1285-9. doi: 10.2105/AJPH.2015.302652. PMID: 25973816. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Yakoot M, Abdo AM, Yousry A, et al. Very rapid virologic response and early HCV response kinetics, as quick measures to compare efficacy and guide a personalized response-guided therapy. Drug Des Devel Ther. 2016;10:2659-67. doi: 10.2147/DDDT.S111496. PMID: 27601883. Excluded for ineligible intervention.

Yamashita N, Ohho A, Yamasaki A, et al. Hepatocarcinogenesis in chronic hepatitis C patients achieving a sustained virological response to interferon: significance of lifelong periodic cancer screening for improving outcomes. J Gastroenterol. 2014;49(11):1504-13. doi: 10.1007/s00535-013-0921-z. PMID: 24317936. Excluded for poor quality.

Yang CHT, Goel A, Ahmed A. Clinical utility of ledipasvir/sofosbuvir in the treatment of adolescents and children with hepatitis C. Adolesc Helath Med Ther. 2018;9:103-10. doi: 10.2147/AHMT.S147896. PMID: 30104913. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Yang D, Liang HJ, Li D, et al. The efficacy and safety of telaprevir-based regimens for treating chronic hepatitis C virus genotype 1 infection: a meta-analysis of randomized trials. Intern Med. 2013;52(6):653-60. PMID: 23503406. Excluded for ineligible intervention.

Yang S, Britt RB, Hashem MG, et al. Outcomes of pharmacy-led hepatitis C direct-acting antiviral utilization management at a veterans affairs medical center. J Manag Care Spec Pharm. 2017;23(3):364-9. doi: 10.18553/jmcp.2017.23.3.364. PMID: 28230455. Excluded for ineligible intervention.

Yang YH, Chen WC, Tsan YT, et al. Statin use and the risk of cirrhosis development in patients with hepatitis C virus infection. J Hepatol. 2015;63(5):1111-7. doi: 10.1016/j.jhep.2015.07.006. PMID: 26196278. Excluded for ineligible intervention.

Yang YM, Choi EJ. Efficacy and safety outcomes of sofosbuvir-based treatment regimens for hepatitis C virus-infected patients with or without cirrhosis from phase III clinical trials. Ther Clin Risk Manag. 2017;13:477-97. doi: 10.2147/tcrm.S134818. PMID: 28442915. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Yano M, Kumada H, Kage M, et al. The long-term pathological evolution of chronic hepatitis C. Hepatology. 1996;23(6):1334-40. doi: 10.1002/hep.510230607. PMID: 8675148. Excluded for ineligible outcome.

Yao Y, Yue M, Wang J, et al. Grazoprevir and elbasvir in patients with genotype 1 hepatitis C virus infection: a comprehensive efficacy and safety analysis. Can J Gastroenterol Hepatol. 2017;2017:8186275. doi: 10.1155/2017/8186275. PMID: 28164081. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Yenice N, Mehtap O, Gumrah M, et al. The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients. Turk J Gastroenterol. 2006;17(2):94-8. PMID: 16830289. Excluded for outdated medication.

Yoshida EM, Sulkowski MS, Gane EJ, et al. Concordance of sustained virological response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus. Hepatology. 2015;61(1):41-5. doi: 10.1002/hep.27366. PMID: 25314116. Excluded for ineligible intervention.

Young J, Weis N, Hofer H, et al. The effectiveness of daclatasvir based therapy in European patients with chronic hepatitis C and advanced liver disease. BMC Infect Dis. 2017;17(1):45. doi: 10.1186/s12879-016-2106-x. PMID: 28061762. Excluded for ineligible population.

Younossi Z, Blissett D, Blissett R, et al. In an era of highly effective treatment, hepatitis C screening of the United States general population should be considered. Liver Int. 2018;38(2):258-65. doi: 10.1111/liv.13519. PMID: 28719013. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Younossi Z, Henry L. Systematic review: patient-reported outcomes in chronic hepatitis C-the impact of liver disease and new treatment regimens. Aliment Pharmacol Ther. 2015;41(6):497-520. doi: 10.1111/apt.13090. PMID: 25616122. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Younossi ZM. The efficacy of new antiviral regimens for hepatitis C infection: Evidence from a systematic review. Hepatology. 2018;67(3):1160-2. doi: 10.1002/hep.29580. PMID: 29023922. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Younossi ZM, LaLuna LL, Santoro JJ, et al. Implementation of baby boomer hepatitis C screening and linking to care in gastroenterology practices: a multi-center pilot study. BMC Gastroenterol. 2016;16:45. doi: 10.1186/s12876-016-0438-z. PMID: 27044402. Excluded for ineligible study design for Key Question.

Younossi ZM, Stepanova M, Chan HL, et al. Patient-reported outcomes in Asian patients with chronic hepatitis C treated with ledipasvir and sofosbuvir. Medicine. 2016;95(9):e2702. doi: 10.1097/MD.0000000000002702. PMID: 26945356. Excluded for ineligible population.

Younossi ZM, Stepanova M, Esteban R, et al. Superiority of interferon-free regimens for chronic hepatitis C: the effect on health-related quality of life and qork productivity. Medicine. 2017;96(7):e5914. doi: 10.1097/MD.0000000000005914. PMID: 28207507. Excluded for ineligible intervention.

Younossi ZM, Stepanova M, Feld J, et al. Sofosbuvir/velpatasvir improves patient-reported outcomes in HCV patients: results from ASTRAL-1 placebo-controlled trial. J Hepatol. 2016;65(1):33-9. doi: 10.1016/j.jhep.2016.02.042. PMID: 26956698. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Younossi ZM, Stepanova M, Henry L, et al. Sofosbuvir and ledipasvir are associated with high sustained virologic response and improvement of health-related quality of life in East Asian patients with hepatitis C virus infection. J Viral Hepat. 2018;25(12):1429-37. doi: 10.1111/jvh.12965. PMID: 29974665. Excluded for ineligible population.

Younossi ZM, Stepanova M, Marcellin P, et al. Treatment with ledipasvir and sofosbuvir improves patient-reported outcomes: results from the ION-1, -2, and -3 clinical trials. Hepatology. 2015;61(6):1798-808. doi: 10.1002/hep.27724. PMID: 25627448. Excluded for not a study: letter, editorial, non-systematic review article, no original data.

Younossi ZM, Stepanova M, Nader F, et al. Patient-reported outcomes of elderly adults with chronic hepatitis C treated with interferon- and ribavirin-free regimens. J Am Geriatr Soc. 2016;64(2):386-93. doi: 10.1111/jgs.13928. PMID: 26825683. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Younossi ZM, Stepanova M, Nader F, et al. Patient-reported outcomes in chronic hepatitis C patients with cirrhosis treated with sofosbuvir-containing regimens. Hepatology. 2014;59(6):2161-9. doi: 10.1002/hep.27161. PMID: 24710669. Excluded for ineligible population.

Younossi ZM, Stepanova M, Nader F, et al. The patient's journey with chronic hepatitis C from interferon plus ribavirin to interferon- and ribavirin-free regimens: a study of health-related quality of life. Aliment Pharmacol Ther. 2015;42(3):286-95. doi: 10.1111/apt.13269. PMID: 26059536. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Younossi ZM, Stepanova M, Omata M, et al. Quality of life of Japanese patients with chronic hepatitis C treated with ledipasvir and sofosbuvir. Medicine. 2016;95(33):e4243. doi: 10.1097/MD.0000000000004243. PMID: 27537553. Excluded for ineligible population.

Younossi ZM, Stepanova M, Pol S, et al. The impact of ledipasvir/sofosbuvir on patient-reported outcomes in cirrhotic patients with chronic hepatitis C: the SIRIUS study. Liver Int. 2016;36(1):42-8. doi: 10.1111/liv.12886. PMID: 26059860. Excluded for ineligible population.

Younossi ZM, Tanaka A, Eguchi Y, et al. Treatment of hepatitis C virus leads to economic gains related to reduction in cases of hepatocellular carcinoma and decompensated cirrhosis in Japan. J Viral Hepat. 2018;25(8):945-51. doi: 10.1111/jvh.12886. PMID: 29478258. Excluded for ineligible intervention.

Youssef NF, El Kassas M, Farag A, et al. Health-related quality of life in patients with chronic hepatitis C receiving sofosbuvir-based treatment, with and without interferon: a prospective observational study in Egypt. BMC Gastroenterol. 2017;17(1):18. doi: 10.1186/s12876-017-0581-1. PMID: 28109264. Excluded for ineligible intervention.

Yu ML, Dai CY, Huang JF, et al. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. Gut. 2007;56(4):553-9. doi: 10.1136/gut.2006.102558. PMID: 16956917. Excluded for outdated medication.

Zamor PJ, Vierling J, Ghalib R, et al. Elbasvir/grazoprevir in black adults with hepatitis C virus infection: a pooled analysis of phase 2/3 clinical trials. Am J Gastroenterol. 2018;113(6):863-71. doi: 10.1038/s41395-018-0053-4. PMID: 29695828. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Zanetti AR, Tanzi E, Newell ML. Mother-to-infant transmission of hepatitis C virus. J Hepatol. 1999;31 Suppl 1:96-100. PMID: 10622569. Excluded for poor quality.

Zanetti AR, Tanzi E, Romano L, et al. A prospective study on mother-to-infant transmission of hepatitis C virus. Intervirology. 1998;41(4-5):208-12. doi: 10.1159/000024938. PMID: 10213898. Excluded for poor quality.

Zanini B, Benini F, Pigozzi MG, et al. Addicts with chronic hepatitis C: difficult to reach, manage or treat? World J Gastroenterol. 2013;19(44):8011-9. doi: 10.3748/wjg.v19.i44.8011. PMID: 24307794. Excluded for ineligible intervention.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

Zeuzem S, Berg T, Gane E, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. Gastroenterology. 2014;146(2):430-41.e6. doi: 10.1053/j.gastro.2013.10.058. PMID: 24184810. Excluded for ineligible population.

Zeuzem S, Diago M, Gane E, et al. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. Gastroenterology. 2004;127(6):1724-32. PMID: 15578510. Excluded for outdated medication.

Zeuzem S, Hezode C, Bronowicki JP, et al. Daclatasvir plus simeprevir with or without ribavirin for the treatment of chronic hepatitis C virus genotype 1 infection. J Hepatol. 2016;64(2):292-300. doi: 10.1016/j.jhep.2015.09.024. PMID: 26453968. Excluded for ineligible intervention.

Zeuzem S, Serfaty L, Vierling J, et al. The safety and efficacy of elbasvir and grazoprevir in participants with hepatitis C virus genotype 1b infection. J Gastroenterol. 2018;53(5):679-88. doi: 10.1007/s00535-018-1429-3. PMID: 29344726. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Zuniga IA, Chen JJ, Lane DS, et al. Analysis of a hepatitis C screening programme for US veterans. Epidemiol Infect. 2006;134(2):249-57. doi: 10.1017/s095026880500498x. PMID: 16490127. Excluded for poor quality.

Zuure F, Davidovich U, Kok G, et al. Evaluation of a risk assessment questionnaire to assist hepatitis C screening in the general population. Euro Surveill. 2010;15(15):19539. PMID: 20429995. Excluded for poor quality.

Zuure FR, Urbanus AT, Langendam MW, et al. Outcomes of hepatitis C screening programs targeted at risk groups hidden in the general population: a systematic review. BMC Public Health. 2014;14:66. doi: 10.1186/1471-2458-14-66. PMID: 24450797. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
  - For RCTs: Adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - For cohort studies: Consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to treat analysis for RCTs

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.
Fair: Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is used for RCTs.
Poor: Studies are graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Systematic Reviews

Criteria:

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance (especially important for systematic reviews)

Definition of ratings based on above criteria:

Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.
Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.
Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (greater than 100) of broad-spectrum patients with and without disease.
Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.
Poor: Has a fatal flaw, such as: uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients.

Source: U.S. Preventive Services Task Force Procedure Manual. Accessed at https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes

Appendix B Table 1. Key Question 5: Evidence Table of Interventions to Prevent Mother-to-Infant Transmission of HCV Infection – Study Characteristics

Author year Country Study Name *Quality*	Study Type	Definition of mother-to-infant transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IVDU
Ceci 2001[108] Italy *Fair*	Prospective cohort study	Presence of anti-HCV antibodies beyond 18 months or HCV-positive on two separate tests	HCV maternal risk factors (exposure to blood products and IVDU), HCV viral load, HCV genotype, gestational age, mode of delivery, birth weight	24 months	HCV-positive, HIV-negative women	HIV-positive	2447/ 78/ 78/ 78	Maternal age (n=78) Median (range): 30 (21 to 42) *Characteristics of HCV-RNA positive mothers (n=60) HCV risk factors Absent: 25 (42%) Blood transfusion: 14 (23%) IVDU: 20 (33%) Blood transfusion and IVDU: 1 (2%) Mode of delivery Vaginal: 43 (72%) Cesarean: 17 (28%) Gestational age <36 weeks: 9 (15%) ≥36 weeks: 51 (85%) Birth weight <2500g: 14 (23%) ≥2500g: 46 (77%) HCV risk factors Absent: 25 (42%) Blood transfusion: 14 (23%) IVDU: 20 (33%) Blood transfusion and IVDU: 1 (2%) Mode of delivery Vaginal: 43 (72%) Cesarean: 17 (28%) Gestational age <36 weeks: 9 (15%) ≥36 weeks: 51 (85%) Birth weight <2500g: 14 (23%) ≥2500g: 46 (77%)	Maternal HCV-RNA status (n=78) Positive: 60 (77%) Negative: 18 (23%) *Characteristics of HCV-RNA positive mothers (n=60) genotype 1a: 9 (15%) 1b: 25 (42%) 2a: 20 (33%) 3: 6 (10%) Viral load <0.2X106: 9 (15%) >0.2X106: 51 (85%)

Appendix B Table 1. Key Question 5: Evidence Table of Interventions to Prevent Mother-to-Infant Transmission of HCV Infection – Study Characteristics

Author year Country Study Name *Quality*	Study Type	Definition of mother-to-infant transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IVDU
European Pediatric Hep C Virus Network 2005 (Tovo)[106] Italy, Spain, Germany, Ireland, U.K., Norway, Sweden *Good*	Multicenter prospective cohort study	Children considered infected if they had ≥2 positive HCV RNA PCR test results and/or were anti-HCV antibody positive after 18 months. Children considered uninfected if they had <2 positive HCV RNA PCR test results and ≤2 negative HCV RNA PCR rest results and/or were anti-HCV antibody negative after 18 months.	Account for differences between centers in the HCV RNA PCR assays used to determine infection, allow for center-associated unobserved differences in background characteristics, authors incorporated a random effect in multivariable models at the center level	Children received clinical examination at birth, 6 weeks, and 3, 6, 9, 12, 18, and 24 months; and thereafter every 6 months if infected or every year if uninfected	HCV infected mothers and their singleton infants or first-born infants from multiple pregnancies with confirmed HCV infection status.	Second-born twins and second- and third-born triplets were excluded. Mother-infant pairs with infants of indeterminate infection status were excluded.	1787/ 1479/ 1479 /1220 (1034 HIV-)	Maternal age (n=1205) Mean (SD): 31.7 (5.17) Median (range): 32 (17.1 to 45.1) Mode of delivery (n=1455) Vaginal: 764 (52.5%) Emergency cesarean section: 160 (11%) Elective cesarean: 480 (33%) Cesarean section (unspecified): 51 (3.5%) Infant feeding type (n=1357) Breast-fed: 452 (32.7%) Formula fed: 930 (67.3%) Sex of child (n=1470) Male: 802 (54.6%) Female: 668 (45.4%) Gestational age (n=1382) ≤34 weeks: 97 (7%) 35 to 36 weeks: 122 (8.8%) ≥37 weeks: 1163 (84.2%)	Maternal HIV infection (n=1391) Yes: 208 (15%) No: 1183 (85%) Child HIV infection (n=1435) Yes: 10 (0.7%) No: 1397 (97.4%) Indeterminate: 28 (1.9%) Maternal IVDU (n=1162) History: 448 (38.6%) No history: 714 (61.4%)
Gibb 2000[105] Ireland, U.K. *Fair*	Prospective cohort study	Positive result for HCV antibody within 90 days of birth	Adjusted for HIV status, breastfeeding, and mode of delivery	24 months	Mother known to be HCV infected during pregnancy or if child had positive result for HCV antibody within 90 days of birth	U.K. children born before 1996	499/ 441/ 441/ 441	Maternal age (n=441) Mean (SD): 27 (6) Race (n=441) White: 413 (94%) Non-white: 28 (6%) Breastfeeding (n=414) Yes: 59 (14%) No: 355 (86%) Mode of delivery (n=424) Vaginal: 339 (80%) Emergency cesarean: 54 (13%) Elective cesarean: 31 (7%)	Maternal HIV infection (n=441) Yes: 22 (5%) No: 328 (74%) Unknown: 91 (21%) Maternal IVDU (n=441) History: 343 (78%) No history: 98 (22%)

Appendix B Table 1. Key Question 5: Evidence Table of Interventions to Prevent Mother-to-Infant Transmission of HCV Infection – Study Characteristics

Author year Country Study Name *Quality*	Study Type	Definition of mother-to-infant transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IVDU
Mast 2005[104] U.S. (Houston & Honolulu) *Good*	Prospective cohort study	Infant serum collected at birth and 8 well-child visits. Testing included detection of antibody to HCV, detection of HCV RNA (qualitative and quantitative), and genotyping.	Variables with p<.1 from the univariate analysis and maternal demographic characteristics included in multivariate analysis	Infants born to HCV+ mothers followed from birth to ≥12 months, HCV-infected infants followed annually until age 5	Women presenting for prenatal care (and in Houston, those who did not receive prenatal care who presented for delivery at 2 county hospitals) were offered testing. Women with positive anti-HCV test results were invited to enroll (those with indeterminate status were invited to enroll until HCV status was confirmed).	Mothers with serum testing as RIBA indeterminate and HCV RNA negative were excluded from the analysis.	75,909/ 567/ 332/ 242 women & 244 infants	Age (n=242) <20: 7 (2.9%) 20 to 29: 103 (42.6%) 30 to 39: 120 (49.6%) ≥40: 12 (4.9%) Race (n=242) White: 79 (32.6%) Black: 77 (31.8%) Hispanic: 49 (20.3%)	Mother HCV RNA+ (n=242) At enrollment or delivery: 194 (79.5%) Both: 179 (77.2%) Delivery: 5 (2.2%) Enrollment: 4 (1.7%) Maternal HIV infection (n=242): Yes: 11 (4.5%) HIV and HCV RNA+ (n=242) 7 (2.9%) Maternal IVDU (n=242) 126 (52.3%) Geometric mean HCV RNA level at delivery (n=194) HIV-: 2.38*106 Maternal HCV genotype (n=116) 1a: 76 (66%) 1b: 16 (14%) 2b: 10 (9%) 3a: 13 (11%) 4a: 1 (.01%)
Resti 2002[107] Italy *Good*	Prospective cohort	HCV RNA-positive at any testing or persistence of anti-HCV beyond age 2 years	Maternal HCV RNA status, maternal HIV-1 status, maternal IVDU, type of feeding, mode of delivery	24 months	Anti-HCV positive women attending 24 study sites between April 1993 through December 1996	Twin pairs & siblings	NR/ 1493/ 1493/ 1372	n=1372 mother-infant pairs Maternal age: NR Type of delivery: Cesarean: 377 (27.5%) Vaginal: 924 (67.3%) Missing: 71 (5.2%) Type of infant feeding: Breast: 360 (26.2%) Formula: 921 (67.1%) Missing: 91 (6.7%) Birth weight, g:	Maternal HCV viremia: Positive: 897 (65.4%) Negative: 387 (28.2%) Missing: 88 (6.4%) Maternal HIV-1 status: Positive: 194 (14.1%) Negative: 1178 (85.9%) Missing: 0

Appendix B Table 1. Key Question 5: Evidence Table of Interventions to Prevent Mother-to-Infant Transmission of HCV Infection – Study Characteristics

Author year Country Study Name *Quality*	Study Type	Definition of mother-to-infant transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IVDU
								<2500: 145 (10.6%) >2500: 1042 (83.2%) Missing: 185 (6.2%) Gestational age, weeks: <36: 107 (7.8%) >36: 1127 (82.1%) Missing: 138 (10.1%)	Maternal IVDU: Yes: 461 (33.6%) No: 911 (66.4%) Missing: 0

Abbreviations: HCV = hepatitis C virus; IVDU = injection drug use; NR = not reported; PCR = polymerase chain reaction; RIBA = recombinant-immunoblot-assay; RNA = ribonucleic acid; SD = standard deviation; U.K. = United Kingdom; U.S. = United States.

Appendix B Table 2. Key Question 5: Evidence Table of Interventions to Prevent Mother-to-Infant Transmission of HCV Infection – Study Outcomes

Author year Country Study Name *Quality*	Overall transmission	Transmission by labor management: IUPC	Transmission by labor management: Fetal monitoring	Transmission by labor management: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding
Ceci 2001[108] Italy *Fair*	Overall transmission (n=78) 2 consecutive positive tests: 8 (10%) 24 month followup: 2 (3%) not adjusted	NR	NR	NR	No association (data NR)	NR
European Pediatric Hep C Virus Network 2005 (Tovo)[106] Italy, Spain, Germany, Ireland, U.K., Norway, Sweden *Good*	91/1479 6.2% (95% CI, 5.0% to 7.5%)	NR	NR	NR	Elective cesarean vs. emergency cesarean or vaginal delivery (n=1220) OR 1.66 (95% CI, 1.00 to 2.74) unadjusted, p=0.05 OR 1.46 (95% CI, 0.86 to 2.48) adjusted, p=0.16 HIV- mothers elective vs. emergency cesarean or vaginal delivery (n=1034) 1.57 (95% CI, 0.88 to 2.83) unadjusted, p=0.13 1.59 (95% CI, 0.88 to 2.86) adjusted, p=0.13 Adjusted for: sex, mode of delivery, prematurity, and infant feeding type	Breast vs. formula (n=1220) OR 0.74 (95% CI, 0.42 to 1.31) unadjusted, p=0.30 OR .88 (95% CI, 0.48 to 1.61) adjusted, p=0.68 HIV- mothers breast vs. formula (n=1034) OR 0.88 (95% CI, 0.48 to 1.61) unadjusted, p=0.68 OR 0.92 (95% CI, 0.50 to 1.70) adjusted, p=0.60

Appendix B Table 2. Key Question 5: Evidence Table of Interventions to Prevent Mother-to-Infant Transmission of HCV Infection – Study Outcomes

Author year Country Study Name *Quality*	Overall transmission	Transmission by labor management: IUPC	Transmission by labor management: Fetal monitoring	Transmission by labor management: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding
Gibb 2000[105] Ireland, U.K. *Fair*	Overall (n=441) 6.7% (95% CI, 4.1 to 10.2) unadjusted	NR	NR	NR	Elective cesarean vs. emergency cesarean vs. vaginal (n=424) 0% (95% CI, 0 to 7.4) vs. 5.9% (95% CI, 1.0 to 17.8) vs. 7.7% (4.5 to 11.9) OR elective cesarean 0 (95% CI, 0 to 0.86) vs. OR emergency cesarean 0.84 (95% CI, 0.12 to 3.63) Adjusted for HIV status and breastfeeding Elective cesarean vs. vaginal/emergency cesarean (n=424) 0% (85% CI, 0 to 7.4) vs. 7.4% (95% CI, 4.5 to 11.3) OR 0 (95% CI, 0 to 0.87) Adjusted for: HIV status and breastfeeding	Breast vs. formula (n=414) 7.7% (95% CI, 2.2 to 17.8) vs. 6.7% (95% CI, 3.7 to 10.6) OR 1.52 (95% CI, 0.35 to 5.12) Adjusted for: HIV status and mode of delivery
Mast 2005[104] U.S. (Houston & Honolulu) *Good*	9/244 (3.7%)	NR	Results are for HCV RNA+/HIV- mothers (n=188) Internal vs. external 3/16 (18.8%) vs. 4/165 (2.4%), RR 7.7 (1.9-31.6), p=0.02 Internal fetal monitoring AOR, 6.7 (95% CI, 1.1 to 35.9)	Results are for HCV RNA+/HIV- mothers (n=189) Rupture of membranes before onset of laboryes vs. no 4/45 (8.9%) vs. 3/137 (2.2%), RR 4.1 (95% CI, 0.9 to 17.5), p=0.06 Duration of membrane rupture <1 vs. 1-5 vs. 6-12 vs. ≥130/53 vs. 1/59 (1.7%) vs. 4/40 (10%) vs. 2/30 (6.7%), p=0.02 Membrane rupture >6 hours OR, 9.3 (95% CI, 1.5 to 179.7) Adjusted	Results are for HCV RNA+/HIV- mothers (n=188) Elective cesarean vs. emergency cesarean vs. vaginal delivery 0/12 (0%) vs. 1/18 (5.5%) vs. 6/151 (4%), elective cesarean RR undefined, emergency cesarean RR 1.4 (95% CI, 0.2 to 1.1), p=0.55 Elective cesarean vs. emergency cesarean/vaginal 0/12 vs. 7/169 (4%), RR 0.87 (95% CI, 0.05 to 14)	Results are for HCV RNA+/HIV- mothers (n=189) Breast vs. formula 2/62 (3.2%) vs. 5/120 (4.2%), RR 0.8 (95% CI, 0.2 to 3.9), p=1.0

Appendix B Table 2. Key Question 5: Evidence Table of Interventions to Prevent Mother-to-Infant Transmission of HCV Infection – Study Outcomes

Author year Country Study Name *Quality*	Overall transmission	Transmission by labor management: IUPC	Transmission by labor management: Fetal monitoring	Transmission by labor management: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding
Resti 2002[107] Italy *Good*	98/1372 (7.1%, 95% CI, 2.2 to 7.2%)	NR	NR	NR	Cesarean vs. vaginal (n=1301): 22/377 (5.8%) vs. 73/924 (7.9%); Calculated OR (95% CI): OR 0.85 (0.71 to 1.09) Calculated AOR (95% CI): 0.83 (0.65 to 1.08) Per study for cesarean vs. vaginal (ref); OR (95% CI): 1.17 (0.92 to 1.41); p=0.19; AOR for vaginal (95% CI): 1.20 (0.93 to 1.55); p=0.15 Note: Appears to have reversed reference	Breast vs. formula (n=1281): 22/360 (6.1%) vs. 73/921 (7.9%); p=0.26; OR (95% CI): 0.86 (0.61 to 1.10); AOR for breast (95% CI): 0.95 (0.58 to 1.40)

Abbreviations: AOR = adjusted odds ratio; CI = confidence interval; HCV = hepatitis C virus; IUPC = Intra-uterine pressure catheter; NR = not reported; OR = odds ratio; RNA = ribonucleic acid; RR = relative risk; U.K. = United Kingdom; U.S. = United States.

Appendix B Table 3. Key Question 5: Evidence Table of Interventions to Prevent Mother-to-Infant Transmission of HCV Infection – Additional Study Outcomes

Author year Country Study Name *Quality*	Transmission by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)	Transmission by other risk factors (child)	Subgroup analyses	Adverse events	Funding source
Ceci 2001[108] Italy *Fair*	Transmission from women with no known risk of infection was significantly lower (RR=0.17%, 0.04-0.73%; p=0.0063)	By maternal blood transfusion (n=38) 2+ positive tests vs. 0 positive tests 3/8 (37.5%) vs. 2/30 (6.7%), p<0.05 By maternal viremia (n=38) 2+ positive tests vs. 0 positive tests 6.90 +/- 5.87 x 106 vs. 3.93 +/- 2.94 x 106	Note: Multivariate analysis found significant associations between HCV transmission and high maternal viral load, possession of HCV risk factors, and history of blood transfusion (p<0.05 for all, but no data shown); also states that no other variables were found to be significantly associated with HCV transmission	NR	NR	NR	NR

Appendix B Table 3. Key Question 5: Evidence Table of Interventions to Prevent Mother-to-Infant Transmission of HCV Infection – Additional Study Outcomes

Author year Country Study Name *Quality*	Transmission by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)	Transmission by other risk factors (child)	Subgroup analyses	Adverse events	Funding source
European Pediatric Hep C Virus Network 2005 (Tovo)[106] Italy, Spain, Germany, Ireland, U.K., Norway, Sweden *Good*	Mother HIV positive vs. negative (n=1220) OR 1.89 (95% CI, 1.05 to 3.40) unadjusted, p=0.03 OR 1.82 (95% CI, 0.94 to 3.52) adjusted, p=0.06	No additional risk factors analyzed	No additional risk factors analyzed	Female vs. male (n=1220) OR 2.12 (95% CI, 1.27 to 3.56) unadjusted, p=0.004 OR 2.07 (95% CI, 1.23 to 3.48) adjusted, p=0.006 Premature vs. term (n=1220) OR 0.54 (95% CI, 0.23 to 1.26) unadjusted, p=0.15 OR 0.45 (95% CI, 0.19 to 1.08) adjusted, p=0.07 HIV- mothers female vs. male (n=1034) OR 1.79 (95% CI, 1.00 to 3.22) unadjusted, p=0.05 OR 1.80 (95% CI, 1.00 to 3.24) adjusted, p=0.07 HIV- mothers premature vs. term (n=1034) OR 0.83 (95% CI, 0.32 to 2.13) unadjusted, p=0.69 OR 0.83 (95% CI, 0.32 to 2.15) adjusted, p=0.80	NR	NR	European Commission Regione Piemonte, Italy; U.K. Medical Research Council

Appendix B Table 3. Key Question 5: Evidence Table of Interventions to Prevent Mother-to-Infant Transmission of HCV Infection – Additional Study Outcomes

Author year Country Study Name *Quality*	Transmission by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)	Transmission by other risk factors (child)	Subgroup analyses	Adverse events	Funding source
Gibb 2000[105] Ireland, U.K. *Fair*	HIV positive vs. negative (n=441) 18.6% (95% CI, 5.8 to 38.6) vs. 6.4% (95% CI, 3.5 to 10.3) OR=3.8 (95% CI, 0.92 to 13.2) Adjusted for: breastfeeding and HIV status	No additional risk factors analyzed	No additional risk factors analyzed	NR	NR	NR	U.K. Department of Health
Mast 2005[104] U.S. (Houston & Honolulu) *Good*	Maternal HCV/RNA status at delivery positive vs. negative 9/190 (4.6%) vs. 0/54, RR undefined Remaining results are for HCV/RNA+ mothers (n=190) maternal HIV statuspositive vs. negative 2/8 (25%) vs. 7/182 (3.8%), RR 6.5 (95% CI, 1.6 to 26.4) Maternal HCV RNA level, genome copies/mL ≤106 vs. >106, <107 vs. ≥107 1/61 (1.6%) vs. 2/87 (2.3%) vs. 4/34 (11.8%), p=0.03 (results continued in next 2 columns)	Maternal age at delivery, years ≥30 vs. <305/100 (5) vs. 2/81 (2.5), RR 2.0 (95% CI, 0.4 to 10.2), p=0.46 Prior pregnancies >4 vs. ≤4 2/73 vs. 5/109, RR 0.6 (95% CI, 0.1 to 3.0) ALT level at delivery, U/L>35 vs. ≤353/45 (6.7) vs. 4/137, RR 2.3 (95% CI, 0.5 to 9.8) Duration of membrane rupture <1 vs. 1-5 vs. 6-12 vs. ≥13 0/53 (0) vs. 1/59 (1.7) vs. 4/40 (10) vs. 2/30 (6.7), (p=0.02) AOR for membrane rupture >6 hours, 9.3 (95% CI, 1.5 to 179.7) Duration of labor, hours ≤6 vs. 7-12 vs. ≥13 2/84 (2.4) vs. 4/48 (8.3) vs. 1/44 (2.3), (p=0.78)	Cigarette smoking during pregnancy Yes vs. No 1/99 (1) vs. 6/83 (7.23), RR 0.14 (95% CI, 0.02 to 1.1) Alcohol intake during pregnancy Yes vs. No 1/42 (2.4) vs. 6/140 (4.3), RR 0.6 (95% CI, 0.1 to 4.5) History of IVDU Yes vs. No 1/94 (1.1) vs. 6/88 (6.8), RR 0.2 (95% CI, 0.02 to 1.27) Amniotic fluid clear (ref) vs. meconium vs. bloody 2/129 (1.6) vs. 4/40 (10) vs. 1/10 (10), RR 6.5 (95% CI, 1.2 to 33.9) RR 6.5 (95% CI, 0.6 to 65.2)	Results for infants born to HCV/RNA+ mothers: (n=190) Sex Male vs. female 2/85 (2.3%) vs. 5/96 (5.2%), RR 0.45 (95% CI, 0.09 to 2.27), p=0.45 Gestational age <37 vs. ≥37 0/27 vs. 7/155 (4.5%), RR undefined, p=0.6 Birth weight <2500g vs. ≥2500g 1/22 (4.6%) vs. 6/160 (3.8%), RR 1.2 (95% CI, 0.2 to 9.6), p=1 Apgar score at 5 minutes ≤8 vs. >8 0/21 vs. 7/161 (4.4%), RR undefined, p=1	NR	NR	Centers for Disease Control

Appendix B Table 3. Key Question 5: Evidence Table of Interventions to Prevent Mother-to-Infant Transmission of HCV Infection – Additional Study Outcomes

Author year Country Study Name *Quality*	Transmission by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)	Transmission by other risk factors (child)	Subgroup analyses	Adverse events	Funding source
Resti 2002[107] Italy *Good*	Maternal HCV RNA status positive vs. negative (n=1284): 97/897 (10.8%) vs. 1/387 (0.3%); p=0.00001; OR (95% CI): 6.83 (5.85 to 7.81) Maternal HIV Status positive vs. negative (n=1372): 75/1178 (6.4%) vs. 23/194 (11.9%); p=0.007; OR (95% CI): 1.41 (1.16 to 1.66); AOR (95% CI): 1.13 (0.85 to 1.51); p=0.38 (results continued in next 2 columns)	Maternal IVDU Yes vs. No (n=1372): 53/461 (11.5%) vs. 45/911 (4.9%); p<0.001; OR (95% CI): 1.58 (1.37 to 1.78); AOR (95% CI): 1.53 (1.21 to 1.93); p=0.0003	No additional risk factors analyzed.	Infant birth weight <2500 g vs. >2500 g (n=1187): 8/145 (5.5%) vs. 78/1042 (7.5%); p=0.39; OR (95% CI): 1.17 (0.44 to 1.90) Gestational age <36 vs. >36 weeks (n=1149): 7/107 (6.5%) vs. 86/1127 (7.6%); p=0.68; OR (95% CI): 1.08 (0.69 to 1.47)	NR	NR	Italian Ministero della Ricerca Scientifica & Azienda Ospedaliera A. Meyer Research Department

Abbreviations: ALT = alanine aminotransferase; AOR = adjusted odds ratio; CI = confidence interval; HCV = hepatitis C virus; IVDU = injection drug use; NR = not reported; OR = odds ratio; RNA = ribonucleic acid; RR = relative risk; U.K. = United Kingdom; U.S. = United States.

Appendix B Table 4. Key Question 5: Quality Assessment of Studies of Interventions to Prevent Mother-to-Infant Transmission of HCV Infection

Author year	(1) Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	(2) Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	(3) Did the study maintain comparable groups through the study period?	(4) Did the study use accurate methods for ascertaining exposures and potential confounders?	(5) Were outcome assessors and/or data analysts blinded to the exposure being studied?	(6) Did the article report attrition?	(7) Is there important differential loss to followup or overall high loss to followup?	(8) Did the study perform appropriate statistical analyses on potential confounders?	(9) Were outcomes pre-specified and defined, and ascertained using accurate methods?	Overall Quality
Ceci 2001[108]	Yes	Unclear	Unclear	Yes	No	Yes	Unclear	Yes	Yes	Fair
European Paediatric Hepatitis C Virus Network 2005 (Tovo)[106]	Yes	Unclear	Unclear	Yes	Unclear	No	No	Yes	Yes	Good
Gibb 2000[105]	Unclear	Unclear	Unclear	Yes	No	No	No	Yes	Yes	Fair
Mast 2005[104]	Yes	Unclear	Unclear	Yes	No	Yes	No	Yes	Yes	Good
Resti 2002[107]	Yes	Unclear	Unclear	Yes	Unclear	Yes	No	Yes	Yes	Good

Appendix B Table 5. Key Question 6: Evidence Table of Observational Studies of Direct Acting Antiviral Therapy on Health Outcomes in Adults

Author year Country *Quality*	Type of study	Dates of enrollment	Treatment duration Followup	Inclusion criteria	Intervention(s)	N	Population	Outcomes	Funding source
Butt 2019[169] U.S. *Fair*	Retrospective cohort	NR	Treatment duration: NR Followup ≥5 years Group A: 3.7% Group B: 82% Group C: 43%	Adults with HCV infection included in the ERCHIVES database Excluded: HBV, HIV coinfection	A. DAA regimen (sofosbuvir + simeprevir, ledipasvir, or daclatasvir +/- ribavirin; paritaprevir + ritonavir + ombitasvir + dasabuvir +/- ribavirin; elbasvir + grazoprevir +/- ribavirin) (n=12,667) B. Pegylated IFN + ribavirin (n=4,436) C. Matched, untreated controls (n=17,103)	34,206	(A + B) vs. C Mean age 59 vs. 58 years 4% vs. 4% female 56% vs. 56% white; 24% vs. 24% black; 3% vs. 3% Hispanic; 17% vs. 17% other/unknown Fibrosis stage: <1.25: 23% vs. 33%; 1.26 to 3.25: 56% vs. 50%; >3.25: 21% vs. 17% Statin use: 22% vs. 26%	A vs. B vs. C CVD event (acute MI, unstable, angina, congestive heart failure, peripheral vascular disease, percutaneous transluminalcoronary angioplasty, CABG, stroke): 3.4% (435/12,667) vs. 18.1% (804/4,436) vs. 13.8% (2,361/17,103); A vs. C: aHR 0.57 (95% CI, 0.51 to 0.65); B vs. C: aHR 0.78 (95% CI, 0.71 to 0.85) Incidence rate/1,000 person-years of followup: 16.3 (95% CI, 14.7 to 18) vs. 23.5 (95% CI, 21.8 to 25.3) vs. 30.4 (95% CI, 29.2 to 31.7); A vs. C: p<0.001; B vs. C: p<0.001	Gilead

Appendix B Table 5. Key Question 6: Evidence Table of Observational Studies of Direct Acting Antiviral Therapy on Health Outcomes in Adults

Author year Country *Quality*	Type of study	Dates of enrollment	Treatment duration Followup	Inclusion criteria	Intervention(s)	N	Population	Outcomes	Funding source
Carrat 2019[168] France *Fair*	Prospective cohort	Aug 2012 to Dec 2015	Treatment duration: NR Followup: median 33.4 months (IQR 24.0 to 40.7 months)	Patients with chronic HCV infection recruited from 32 hepatology centers in France. Excluded: HBV, HIV coinfection, previous HCC diagnosis, history of decompensated cirrhosis, liver transplant recipient	A. DAA regimen (sofosbuvir + simeprevir +/- ribavirin; sofosbuvir + daclatasvir +/- ribavirin; sofosbuvir + ledipasvir +/- ribavirin; sofosbuvir + ribavirin; sofosbuvir + IFN alpha + ribavirin; sofosbuvir + velpatasvir +/- voxilaprevir; paritaprevir + ritonavir + ombitasvir +/- dasabuvir +/- ribavirin; elbasvir + grazoprevir +/- ribavirin) (n=4,521, *non-cirrhosis only*) B. Untreated patients (n=2,329, *non-cirrhosis only*)	6,850	*Total study population, including additional 3,045 patients with cirrhosis* A vs. B Mean age: 57 vs. 54 Female: 44% vs. 54% Race NR Fibrosis stage: F0, F1, or F2: 41% vs. 84% F3: 17% vs. 6% F4: 42% vs. 10% Genotype: GT1: 67% vs. 64%; GT2: 6% vs. 10%; GT3: 13% vs. 9%; GT4: 13% vs. 14%; GT5-7: 2% vs. 3%	A vs. B (noncirrhotics only) All-cause mortality: 0.8% (35/4,521) vs. 2.1% (48/2,329); aHR: 0.74 (95% CI, 0.43 to 1.28) Liver-related mortality: 0.1% (6/4,521) vs. 0.3% (6/2,329); unadjusted HR: 1.33 (95% CI, 0.46 to 3.84) HCC: 0.5% (21/4,521) vs. 0.6% (14/2,329); AHR: 1.02 (95% CI, 0.40 to 2.61) Decompensated cirrhosis: 0.2% (7/4,521) vs. 0.2% (4/2,329); unadjusted HR: 3.59 (95% CI, 0.66 to 19.5)	French National Agency for Aids and Viral Hepatitis Research; French National Agency of Research; French Ministry of Social Affairs and Health; Merck Sharp & Dohme; Janssen; AbbVie; Bristol-Myers Squibb; Roche

Appendix B Table 5. Key Question 6: Evidence Table of Observational Studies of Direct Acting Antiviral Therapy on Health Outcomes in Adults

Author year Country *Quality*	Type of study	Dates of enrollment	Treatment duration Followup	Inclusion criteria	Intervention(s)	N	Population	Outcomes	Funding source
Li 2018[170] U.S. *Fair*	Retrospective cohort	2002 to 2016	Treatment duration: ≥28 days Followup: 7.4 years (group A); 1.1 year (group B)	Adults with HCV infection included in the ERCHIVES database Excluded: HBV, HIV coinfection; HCC diagnosis	A. Pegylated IFN + ribavirin (n=3,534) B. DAA regimen (sofosbuvir + simeprevir +/- ribavirin; sofosbuvir + ledipasvir +/- ribavirin; sofosbuvir + daclatasvir +/- ribavirin; ombitasvir + paritaprevir + ritonavir + dasabuvir +/- ribavirin) (n=5,834) C. No antiviral treatment (n=8,468)	17,836	A vs. B vs. C Mean age 54 vs. 62 vs. 58 years 4% vs. 3% vs. 3% female 67% vs. 51% vs. 50% white; 17% vs. 31% vs. 35% black; 6% vs. 3% vs. 6% Hispanic; 11% vs. 15% vs. 9% other Fibrosis stage: <1.45: 46% vs. 37% vs. 49%; 1.45 to 3.50: 41% vs. 43% vs. 37%; >3.5: 13% vs. 20% vs. 15%	A vs. B vs. C HCC: 5.6% (196/3,534) vs. 0.9% (50/5,834) vs. 5.0% (436/8,468) Incidence rate/1,000 person-years/followup: -Total cohort: 7.48 (95% CI, 6.50 to 8.61) vs. 7.92 (95% CI, 6.00 to 10.45) vs. 10.90 (95% CI, 9.92 to 11.97); A vs. B: p=0.72; A vs. C: p<0.001	NR

Appendix B Table 5. Key Question 6: Evidence Table of Observational Studies of Direct Acting Antiviral Therapy on Health Outcomes in Adults

Author year Country *Quality*	Type of study	Dates of enrollment	Treatment duration Followup	Inclusion criteria	Intervention(s)	N	Population	Outcomes	Funding source
Younossi 2015[135] ION 1-3 Multinational (U.S., Europe) *Fair*	Retrospective cohort	October 2012 to June 2013	Treatment duration: 8 to 24 weeks Followup: 12 weeks post-treatment	Treatment-naïve or experienced with chronic HCV infection enrolled in ION-1, 2 or 3 trials	A. Sofosbuvir + ledipasvir (n=420) B. Sofosbuvir + ledipasvir + ribavirin (n=286)	706	*Population with no/mild fibrosis, NR by intervention group* Mean age 54 years 33% female 77% white 97% U.S.-based population Treatment-naïve: 71% Treatment-experienced: 29%	A vs. B Quality of life score, mean change from baseline SF-36 physical component score (scale 0 to 100): 1.70 (SD 5.85; p<0.05*) vs. 1.92 (SD 6.17; p<0.05*) SF-36 mental component score (scale 0 to 100): 2.51 (SD 7.95; p<0.05*) vs. 2.18 (SD 8.09; p<0.05) FACIT-F fatigue score (scale 0 to 52): 4.18 (SD 8.90; p<0.05) vs. 4.34 (SD 9.21; p<0.05) FACIT-F total score (scale 0 to 160): 10.27 (SD 19.57; p<0.05) vs. 10.75 (SD 20.02; p<0.05) CLDQ-HCV total score (scale 1 to 7): 0.61 (SD 0.88; p<0.05) vs. 0.50 (SD 0.85; p<0.05) WPAI:SHP work productivity impairment score (scale 0-1): -0.032 (SD 0.210; p<0.05) vs. -0.076 (SD 0.238; p<0.05) WPAI:SHP activity impairment score (scale 0-1): -0.082 (SD 0.240; p<0.05) vs. -0.093 (SD 0.230; p<0.05) SF-6D health utility score (0.2-1): 0.052 (SD 0.130; p<0.05) vs. 0.042 (SD 0.124; p<0.05)	Gilead

Appendix B Table 5. Key Question 6: Evidence Table of Observational Studies of Direct Acting Antiviral Therapy on Health Outcomes in Adults

Author year Country *Quality*	Type of study	Dates of enrollment	Treatment duration Followup	Inclusion criteria	Intervention(s)	N	Population	Outcomes	Funding source
Younossi 2017[136] ASTRAL 1-4 Multinational (U.S., Canada, Europe, Hong Kong) *Fair*	Retrospective cohort	July 2014 to December 2014	Treatment duration: 12 to 24 weeks Followup: 12 weeks post-treatment	Chronic HCV infection with no cirrhosis or compensated cirrhosis enrolled in ASTRAL-1, 2 or 3 trials (ASTRAL-4 enrolled only patients with decompensated cirrhosis)	A. Sofosbuvir + velpatasvir (n=813) B. Sofosbuvir +/- velpatasvir + ribavirin (n=299)	1,112	*Population with no cirrhosis, NR by intervention group* Mean age 52 years 41% female 84% white; 6% black; 8% Asian 42% U.S.-based population Treatment-naïve: 80% Treatment-experienced: 20%	A vs. B Mean improvement in patient-reported outcomes (composite SF-36, FACIT-F, CLDQ-HCV, WPAI:SHP; scale 0-100): 5.5 (SD NR; p>0.05*) vs. 6.1 (SD NR; p>0.05*)	Gilead

***** Within group difference from baseline

Abbreviations: aHR = adjusted hazard ratio; CABG = coronary artery bypass graft; CI = confidence interval; CLDQ-HCV = Chronic Liver Disease Questionnaire-Hepatitis C Version; CVD = cardiovascular disease; DAA = direct acting antiviral; ERCHIVES = Electronically Retrieved Cohort of HCV-Infected Veterans; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HR = hazard ratio; IFN = interferon; IQR = interquartile range; MI = myocardial infarction; NR = not reported; SD = standard deviation; SF-36 = Short Form 36; SF-6D = Short Form 6D; U.S. = United States; WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem. Study names are not acronyms.

Appendix B Table 6. Key Question 6: Quality Assessment of Observational Studies of Direct Acting Antiviral Therapy on Health Outcomes in Adults

Author year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to follow-up or overall high loss to follow-up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality rating
Butt 2019[169]	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Li 2018[170]	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Carrat 2019[168]	Yes	No	Yes	Unclear	Yes	Yes	No	Yes	Fair
Younossi 2017b[136]	Yes	NA	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Younossi 2015[135]	Yes	NA	Yes	Unclear	No	Yes	Unclear	Yes	Fair

Abbreviation: NA = not applicable.

Appendix B Table 7. Key Questions 6-8: Direct Acting Antiviral Therapy in Adolescents – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics** Age, Sex, Race/ethnicity, Fibrosis stage/ METAVIR score (mean/median if breakdown is NR), Genotype breakdown	**Loss to Followup**	**Definition of SVR**
Abdel Ghaffar 2019[201] Egypt *Fair*	Age 8 to 18 years Patients with cirrhosis excluded Genotype 4 Patients with HBV infection excluded	December 2016 to February 2018	40	Mean age 12 years (45% <12 years) 38% female Race NR Fibrosis stage F0: 35%; F1: 38%; F2 and F3: 15% Genotype 4: 100% (mixed 4 and 1a: 13%; mixed 4 and 1b: 15%) Treatment naïve: 100%	3% (1/40)	HCV RNA <LLOQ
Balistreri 2017[175] and Younossi 2018[172] Australia, U.K., U.S. *Fair*	Age 12 to <18 years Patients with cirrhosis permitted; liver biopsy not required Genotype 1 Patients with HBV infection excluded	November 2014 to October 2015	100	Mean age 15 years 63% female 90% white; 7% black; 2% Asian; 1% NR Fibrosis stage F0-F3: 42%; F4:1%; NR/unknown: 57% Genotype 1a: 81%; 1b: 19% Treatment naïve: 80% Treatment experienced 20% (prior treatment unclear; presumably IFN or pegylated IFN + ribavirin)	2% (2/100)	HCV RNA <15 IU/mL
El-Karaksy 2018[202] Egypt *Fair*	Age 12 to <18 years Fibrosis stage NR; fibrosis stage assessed by FibroScan Genotype 4 Patients with HBV infection excluded	NR	40	Mean age 14 years 35% female Race NR Fibrosis stage F0: 55%; F0 and F1: 13%; F1: 13%; F1 and F2: 5%; F3: 10%; F4: 5% (>100% due to rounding) Genotype 4: 100% Treatment-naïve: 75% Treatment-experienced: 25% (IFN +/- ribavirin)	0% (0/40)	Negative HCV RNA
Jonas 2019[171] DORA Multinational *Fair*	Age 12 to <18 years Patients with decompensated cirrhosis excluded; compensated cirrhosis allowed Genotype 1 to 6 Patients with HBV excluded	March 2017 to present (study is ongoing)	48	Median age 14 years 55% female 75% white; 9% black; 13% Asian; 4% mixed race Fibrosis stage F0-F1: 96%; F2: 2%; F3: 2% Genotype 1a: 51%; 1b: 28%; 2: 6%; 3: 9%; 4: 6%; no genotype 5 or 6 enrolled HIV coinfection: 4% Treatment-naïve: 77% Treatment-experienced: 23% (pegylated IFN + ribavirin)	2% (1/48; patient was not treated and excluded from analysis)	HCV RNA <15 IU/mL

Appendix B Table 7. Key Questions 6-8: Direct Acting Antiviral Therapy in Adolescents – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics** Age, Sex, Race/ethnicity, Fibrosis stage/ METAVIR score (mean/median if breakdown is NR), Genotype breakdown	**Loss to Followup**	**Definition of SVR**
Leung 2018[203] ZIRCON Multinational *Fair*	Age 12 to 17 years Patients with cirrhosis permitted, based on liver biopsy, FibroTest or FibroScan Genotype 1 or 4 Patients with HBV infection excluded	November 2015 to July 2016	38	Median age 15 years 66% female 76% white; 13% black; 8% Asian; 3% mixed race Fibrosis stage (30/38 patients): F0 and F1: 90%; F2: 3%; F3: 3%; F4: 3% Genotype 1a: 42%; 1b: 40%; 4: 18% Treatment naïve: 66% Treatment experienced: 34% (IFN +/- ribavirin)	0% (0/38)	HCV RNA <LLOQ
Wirth 2017[173] and Younossi 2018[174] Australia, Belgium, Germany, Italy, New Zealand, Russia, U.K., U.S. *Fair*	Age 12 to <18 years Patients with cirrhosis permitted; liver biopsy not required Genotype 2 or 3 Patients with HBV infection excluded	October 2014 to June 2016	52	Median age 15 years 40% female 90% white; 4% black; 2% Asian; 2% Hawaiian/Pacific Islander; 2% other Fibrosis stage NR; 40% no cirrhosis; 60% cirrhosis presence unknown Genotype 2: 25% Genotype 3: 75% Treatment-naive: 83% Treatment-experienced: 17% (prior treatment unclear; 6% prior nonresponder; 2% prior relapse; 1% IFN intolerant) PedsQL-4.0-SF-15 score (post-hoc analysis; n=50): 73.54 (SD 2.16)	2% (1/52)	HCV RNA <15 IU/mL
Yakoot 2018[176] Egypt *Good*	Age 12 to 17 years Fibrosis stage NR; FibroScan >12.5 kPa and/or APRI >2.0 excluded Genotype 4 Patients with HBV infection excluded	February 2017 to NR	30	Mean age 13 years 43% female Race NR Fibrosis stage F0: 17%; F1: 53%; F2: 27%; F3: 3% Genotype 4: 100% Treatment naïve: 73% Treatment experienced: 27% (prior treatment unclear)	3% (1/30)	HCV RNA <LLOQ

Abbreviations: APRI = aspartate amino transferase to platelet ratio index; HBV = hepatitis B virus; HCV = hepatitis C virus; IFN = interferon; LLOQ = lower limit of quantification; NR = not reported; PedsQL = Pediatric Quality of Life Inventory; RNA = ribonucleic acid; SD = standard deviation; SF = short form; SVR = sustained virologic response; U.K. = United Kingdom; U.S. = United States. Study names are not acronyms.

Appendix B Table 8. Key Questions 6–8: Direct Acting Antiviral Therapy in Adolescents – Effectiveness and Harms

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Efficacy Results	Subgroup Efficacy Results	Clinical Outcomes	Adverse Events	Funding Source
Abdel Ghaffar 2019[201] Egypt *Fair*	Sofosbuvir 200-400 mg + daclatasvir 30-60 mg	Treatment duration: 12 weeks Timing of assessments: 12 weeks post treatment	SVR: 98% (39/40)	NR	NR	Any adverse event: NR Serious adverse events: NR Withdrawal due to adverse events: NR Headache: 3% (1/40) Fatigue: 5% (2/40) Vomiting: 3% (1/40)	The Egyptian Cure Bank non-governmental organization; Society of Friends of Liver Patients in the Arab World
Balistreri 2017[175] and Younossi 2018[172] Australia, U.K., U.S. *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg	Treatment duration: 12 weeks Timing of assessments: 12 weeks post treatment	SVR: 98% (98/100)	Treatment-naïve: 98% (78/80) Treatment-experienced: 100% (20/20)	Mortality: 0% (0/100) PedsQL-4.0-SF-15 Score, mean change from baseline at post-treatment week 24 (scale 0-100, positive mean change = improvement in quality of life): Physical functioning: caregiver report: 2.14, p=0.49, self-report: -0.49, p=0.97 Emotional functioning: caregiver report 9.32, p<0.001; self-report 3.66, p=0.04 Social functioning: caregiver report 4.79, p=0.18; self-report 3.02, p=0.33 School functioning: caregiver report 4.79, p=0.18; self-report 3.02, p=0.33 Total score: caregiver report: 5.25, p=0.009; self-report: 1.89, p=0.12	Any adverse event: 71% (71/100) Serious adverse events: 0% (0/100) Withdrawals due to adverse events: 0% (0/100) Headache: 27% (27/100) Fatigue: 13% (13/100) Nausea: 11% (11/100) Vomiting: 11% (11/100)	Gilead

Appendix B Table 8. Key Questions 6–8: Direct Acting Antiviral Therapy in Adolescents – Effectiveness and Harms

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Efficacy Results	Subgroup Efficacy Results	Clinical Outcomes	Adverse Events	Funding Source
El-Karaksy 2018[202] Egypt *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg	Treatment duration: 12 weeks Timing of assessments: 12 weeks post treatment	SVR: 100% (40/40)	NR	NR	Headache: 48% (19/40) Fatigue: 53% (21/40) Nausea: 28% (11/40) Diarrhea: 23% (9/40) Insomnia: 23% (9/40)	NR; described as "treatment provided by charity"
Jonas 2019[171] DORA Multinational *Fair*	Glecaprevir 300 mg + pibrentasvir 120 mg	Treatment duration: 8 to 16 weeks (94% of study population treated for 8 weeks) Timing of assessments: 12 weeks post treatment	SVR: 100% (47/47)	NR	PedsQL total score, mean change from baseline (N=44): 2.3 (SD 7.7); p=NR	Any adverse event: 87% (41/47) Serious adverse events: 0% Withdrawal due to adverse events: 0% Headache: 17% (8/47) Fatigue: 11% (5/47)	AbbVie
Leung 2018[203] ZIRCON Multinational *Fair*	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + weight-based ribavirin	Treatment duration: 12 weeks Timing of assessments: 12 weeks post treatment	SVR: 100% (38/38)	Genotype 1a: 100% (16/16) Genotype 1b: 100% (15/15) Genotype 4: 100% (7/7) Treatment naïve: 100% (25/25) Treatment experienced: 100% (13/13)	NR	Any adverse event: 84% (32/38) Serious adverse events: 0% (0/38) Withdrawal due to adverse events: 0% (0/38) Headache: 21% (8/38) Fatigue: 18% (7/38)	AbbVie
Wirth 2017[173] and Younossi 2018[174] Australia, Belgium, Germany, Italy, New Zealand, Russia, U.K., U.S. *Fair*	Sofosbuvir 400 mg + weight-based ribavirin	Treatment duration: 12 (genotype 2) or 24 (genotype 3) weeks Timing of assessments: 12 weeks post treatment	SVR: 98% (51/52)	Genotype 2: 100% (13/13) Genotype 3: 97% (38/39)	Mortality: 0% (0/52) PedsQL-4.0-SF-15 Score, mean change from baseline at post-treatment week 24 (positive mean change=improvement in quality of life): 7.26 (SD 2.99); p=0.01	Any adverse event: 81% (41/52) Serious adverse events: 2% (1/52) Withdrawal due to adverse events: 0% (0/52) Headache: 23% (12/52) Fatigue: 12% (6/52) Nausea: 27% (14/52) Diarrhea: 6% (3/52)	Gilead

Appendix B Table 8. Key Questions 6–8: Direct Acting Antiviral Therapy in Adolescents – Effectiveness and Harms

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Efficacy Results	Subgroup Efficacy Results	Clinical Outcomes	Adverse Events	Funding Source
Yakoot 2018[176] Egypt *Good*	Weight-based sofosbuvir + daclatasvir	Treatment duration: 12 weeks Timing of assessments: 12 weeks post treatment	SVR: 97% (29/30)	NR	Mortality: 0% (0/30)	Any adverse event: 27% (8/30) Serious adverse events: 0% (0/30) Withdrawal due to adverse events: 0% (0/30) Headache: 10% (3/30) Fatigue: 13% (4/30) Nausea: 10% (3/30)	NR

Abbreviations: NR = not reported; PedsQL = Pediatric Quality of Life Inventory; SD = standard deviation; SF = short form; SVR = sustained virologic response; U.K. = United Kingdom; U.S. = United States. Study names are not acronyms.

Appendix B Table 9. Key Questions 6–8: Quality Assessment of Studies of Direct Acting Antiviral Therapy in Adolescents

Author year	Single or multi-arm study?	Non-randomized studies: Enrolled all (or a random sample of) patients meeting inclusion criteria?	Randomized studies: Randomization adequate?	Randomized studies: Allocation concealment adequate?	Groups similar at base-line?	Eligibility criteria specified?	Primary outcome pre-specified and reported?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and with-drawals reported?	Loss to followup: differential (>10%)/ high (>20%)?	Analyze people in the groups in which they were random-ized?	Quality
Abdel Ghaffar 2019[201]	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Balistreri 2017[175]	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
El-Karaksy 2018[202]	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Jonas 2019[171]	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Leung 2018[203]	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Wirth 2017[173]	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Yakoot 2018[176]	Single	Yes	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Good

Abbreviation: NA = not applicable.

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Abergel 2016a[142] France *Fair*	Adults>18 Patients with cirrhosis were eligible for inclusion, based on liver biopsy, FibroScan >12.5 kPa, or FibroTest >0.75 + APRI >2 Genotype 4 Treatment-naïve arm only Patients with HBV infection excluded	March 2014 to November 2014	22 (treatment-naïve population only)	Mean age 52 years 50% female 86% white; 14% black Fibrosis stage NR; cirrhosis: 5% Genotype 4: 100% Treatment-naïve: 100%	0% (0/22)	HCV RNA level <15 IU/mL
Abergel 2016b[141] France *Good*	Adults>18 Patients with cirrhosis were eligible for inclusion, based on liver biopsy, FibroScan >12.5 kPa, or FibroTest >0.75 + APRI >2 Genotype 5 Treatment-naïve arm only Patients with HBV infection excluded	March 2014 to June 2014	21 (treatment-naïve population only)	Mean age 61 years 48% female 100% white Fibrosis stage NR; cirrhosis: 14% Genotype 5: 100% Treatment-naïve: 100%	0% (0/21)	HCV RNA level <15 IU/mL

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Afdhal 2014[185] ION-1 U.S. and Europe *Fair*	Age >18 years 20% of population could have cirrhosis based on liver biopsy, Fibroscan >12.5kPa, or FibroTest >0.75 and APRI >2 Genotype 1 Patients with HBV infection excluded	October 2012 to May 2013	431 A=214 B=217	A vs. B <u>12-week intervention group (n=214)</u> Mean age 52 vs. 52 years 41% vs. 41% female 87% vs. 87% white; 11% vs. 12% black; <1% vs. 0% Asian; 1% vs. 1% other Fibrosis stage NR; cirrhosis: 16% vs. 15% Genotype 1a: 67%; 1b: 31%, Other 2% Treatment-naive: 100% vs. 100% <u>24-week intervention group (n=217)</u> Mean age 53 vs. 53 years 36% vs. 45% female 82% vs. 84% white; 15% 12% black; 2% vs. 2% Asian; 1% vs. 1% other Fibrosis stage NR; cirrhosis: 15% vs. 17% Genotype 1a: 67% vs. 66%; 1b: 31% vs. 33%, Other 1% vs. 1% Treatment-naive: 100% vs. 100%	0.9% (4/431)	HCV RNA <25 IU/mL
Ahmed 2018[195] Egypt *Fair*	Age ≥18 years Fibrosis/cirrhosis NR; Child-Pugh >8 excluded Genotype 4 Treatment-naïve HBV status NR	January 2015 to NR	100	Mean age 51 years 35% female Race/ethnicity NR Fibrosis stage NR Genotype 4: 100% Treatment-naïve: 100%	0% (0/100)	HCV RNA <15 IU/mL
Andreone 2014[186] PEARL-II Austria, Belgium, Italy, The Netherlands, Portugal, Puerto Rico, Sweden, Switzerland, U.S. *Fair*	Age 18 to 70 years Fibrosis stage NR; patients were required to have no cirrhosis Genotype 1b Prior failure of pegylated IFN + ribavirin treatment Patients with HBV infection excluded	August 2012 to January 2014	186 A=91 B=88	A vs. B Mean age 54 vs. 54 years 40% vs. 50% female 91% vs. 92% white; 6% vs. 3% black; 2% vs. 4% Hispanic Fibrosis stage F0 and F1: 64% vs. 70%; F2: 22% vs. 14%; F3: 13% vs. 14% Genotype 1b: 100% vs. 100% Treatment-naïve: 0% vs. 0% Treatment-experienced: 100% vs. 100% (pegylated IFN + ribavirin)	0.5% (1/186)	HCV RNA <25 IU/mL

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Asselah 2018[196] SURVEYOR II Part 4, Multinational (Asia, Europe, U.S. [specific countries NR]) *Fair*	Age >18 years No cirrhosis based on liver biopsy, FibroScan <12.5 kPa or FibroTest ≤0.48 and APRI <1 Genotype 2, 4, 5 or 6 Treatment naïve or experienced Patients with HBV excluded	October 2014 to October 2016	203 (8-week intervention groups only)	Mean age 52 years 52% female 75% white; 10% black; 11% Asian Fibrosis stage F0 and F1: 84%; F2: 6%; F3: 10% Genotype 2: 71%; 4: 23%; 5: 1%; 6: 5% Treatment-naïve: 87% Treatment-experienced (IFN or peg IFN, with ribavirin, with or without sofosbuvir): 13%	0.5% (1/203)	HCV RNA <LLOQ
Asselah 2019[143] ENDURANCE-5 Multinational (Australia, Belgium, Canada, France, New Zealand, Singapore, South Africa, Vietnam, U.S.) *Fair*	Age ≥18 years Cirrhosis allowed based on liver biopsy, FibroScan <12.5 kPa or FibroTest ≤0.48 Genotype 5 Treatment naïve or experienced Patients with HBV excluded	January 2017 to December 2017	23	Mean age 68 years 57% female 91% white; 4% Asian, 4% black Fibrosis stage F0 and F1: 74%; F2: 13%; F3: 0%; F4 (cirrhosis): 13% Genotype 5: 100% Treatment-naïve: 83% Treatment-experienced (IFN or peg IFN): 17%	0% (0/23)	HCV RNA <15 IU/mL
Asselah 2019[143] ENDURANCE-6 (same publication as ENDURANCE-5) *Fair*	Age ≥18 years Cirrhosis allowed based on liver biopsy, FibroScan <12.5 kPa or FibroTest ≤0.48 Genotype 6 Treatment naïve or experienced Patients with HBV excluded	See Asselah 2019 ENDURANCE-5	61	Mean age 54 years 52% female 7% white; 92% Asian, 0% black; 1% other Fibrosis stage F0 and F1: 74%; F2: 2%; F3: 15%; F4 (cirrhosis): 10% Genotype 6: 100% Treatment-naïve: 93% Treatment-experienced (IFN or peg IFN): 7%	0% (0/61)	See Asselah 2019 ENDURANCE-5

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Brown 2018[144] C-SCAPE (Genotype 4 only) Multinational (Australia, Belgium, France, Israel, Spain, U.K., U.S.) *Fair*	Age ≥18 years No cirrhosis based on liver biopsy, FibroScan <12.5 kPa or FibroTest ≤0.48 Genotype 2, 4, 5 or 6 Treatment-naive Patients with HBV excluded	October 2013 to December 2014	20 (Genotype 4 only; total population n=38)	*Total population (genotypes 2, 4, 5, 6)* A vs. B Mean age 52 vs. 53 years 58% vs. 37% female 74% vs. 68% white; 26% vs. 32% other race Fibrosis stage F0 to F2: 79% vs. 90%; F3: 21% vs. 5%; unknown: 0% vs. 5% Treatment-naïve: 100% vs. 100%	0% (0/20)	HCV RNA <25 IU/mL
Chayama 2018[197] CERTAIN-1 (Arm A only) Japan *Fair*	Age ≥18 years No cirrhosis based on liver biopsy or FibroScan <12.5 kPa or FibroTest >0.73 and APRI ≤2 Genotype 1 Treatment naïve or experienced Patients with HBV excluded	February 2016 to June 2016	129	Median age 64 years 64% female Race/ethnicity NR Fibrosis stage NR Genotype 1: 100% Treatment-naïve: 73% Treatment-experienced (IFN with/without ribavirin): 27%	0.8% (1/129)	HCV RNA <15 IU/mL
Chuang 2016[145] Taiwan *Fair*	Age ≥20 years ≤20% enrolled participants could meet cirrhosis criteria, based on Metavir score 4, Ishak score ≥5, or Fibroscan >12.5 kPa Genotype 1 Patients with HBV infection excluded	December 2013 to March 2014	85	Mean age 55 years 58% female 100% Asian Fibrosis stage: NR Genotype: 1: 1%; 1a: 12%; 1b: 87% Cirrhosis: 11% Treatment-naïve: 51%	0% (0/85)	HCV RNA <25 IU/mL

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Dore 2016[137] MALACHITE-1 Australia, Canada, Europe, South America *Good*	Age 18 to 65 years No cirrhosis, based on FibroTest ≤0.72 and APRI ≤2; or FibroScan <9.6 kPa; or liver biopsy within 24 months Genotype 1 Treatment-naïve Patients with HBV infection excluded	March to November 2014	309 <u>Genotype 1a</u> A=69 B=34 <u>Genotype 1b</u> C=84 D=83 E=41	A vs. B vs. C vs. D vs. E Mean age 46 vs. 45 vs. 46 vs. 47 vs. 46 years 39% vs. 59% vs. 55% vs. 52% vs. 59% female 17% vs. 9% vs. 14% vs. 18% vs. 7% Hispanic/Latino; other race/ethnicity NR Fibrosis stage F0 and F1: 72% vs. 71% vs. 83% vs. 72% vs. 76%; F2: 18% vs. 21% vs. 8% vs. 13% vs. 10%; F3: 10% vs. 9% vs. 8% vs. 14% vs. 15% Treatment-naive: 100% across all groups	0% (0/311)	HCV RNA <25 IU/mL
Dore 2016[137] MALACHITE-2 Australia, Canada, Europe, South America *Good*	Age 18 to 65 years No cirrhosis, based on FibroTest ≤0.72 and APRI ≤2; or FibroScan <9.6 kPa; or liver biopsy within 24 months Genotype 1 Treatment-experienced (pegylated IFN + ribavirin) Patients with HBV infection excluded	March to November 2014	148 A=101 B=47	A vs. B Mean age 47 vs. 45 46% vs. 40% female 100% vs. 100% white 12% vs. 4% Hispanic/Latino Fibrosis F0 and F1: 78% vs. 68%; F2: 17% vs. 23%; ≥F3: 5% vs. 9% Treatment-naive: 0% Treatment-experienced: 100% (peginterferon and ribavirin)	0% (0/148)	HCV RNA <25 IU/mL

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Everson 2015 (Part A)[146] U.S. *Good*	Age ≥18 years Fibrosis stage: NR; participants could not have cirrhosis, based on: liver biopsy within 2 years of screening; or FibroTest ≤0.48 and AST:platelet index ≤1 during screening; or Fibroscan ≤12.5 kPa within 6 months of baseline Genotype 1-6 Treatment naïve Patients with HBV infection excluded	August 2013 to August 2014	377 A=27 B=28 C=27 D=28 E=23 F=22	A vs. B vs. C vs. D vs. E vs. F Mean age 49 vs. 49 vs. 52 vs. 50 vs. 48 vs. 54 48% vs. 39% vs. 33% vs. 37% vs. 26% vs. 32% female 85% vs. 89% vs. 81% vs. 96% vs. 83% vs. 73% white; 15% vs. 4% vs. 15% vs. 0% vs. 9% vs. 5% black; 0% vs. 7% vs. 4% vs. 4% vs. 9% vs. 23% other Fibrosis/METAVIR score: NR Groups A & B: Genotype 1; Groups C & D: Genotype 3; Groups E & F: Genotypes 2; 4 to 6 Treatment naive: 100% across all groups	0% (0/377)	HCV RNA <LLOQ 12 weeks post-treatment
Feld 2014[187] SAPPHIRE-1 Australia, New Zealand; Austria, France, Germany, Hungary, Great Britain, Italy, Spain, Sweden, Switzerland; Canada, U.S. *Good*	Adults >18 Fibrosis Stage NR Genotype 1 Treatment naïve or experienced Patients with HBV infection excluded	November 2012 to May 2013	477	Mean age 49 43% female 91% white; 6% black; 4% other METAVIR score F0 or F1: 77%; F2: 15%; F3: 8.4% Genotype 1a: 69% Genotype 1b: 32% Treatment-naive: 68% Treatment-experienced: 32% (9.0% protease inhibitor, peginterferon, and ribavirin; 20% pegylated IFN and ribavirin; 3.7% nonpegylated IFN with or without ribavirin)	0.4% (2/477)	HCV RNA level <25 IU/mL

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Feld 2015[139] ASTRAL-1 U.S., Canada, Europe, Hong Kong *Good*	Age ≥18 years Fibrosis stage NR; up to 20% could have cirrhosis based on: liver biopsy (Metavir stage 4 or Ishak score 5 or 6), FibroTest score >0.75, AST:platelet ratio >2, or FibroScan >12.5 kPa) Genotype 1, 2, 4, 5, 6 Treatment-naive or experienced Patients with HBV infection excluded	July 2014 to December 2014	706 A=624 B=116	A vs. B Mean age 54 vs. 53 years 40% vs. 59% female 79% vs. 78% white; 8% vs. 9% black; 10% vs. 9% Asian; 2% vs. 3% other Fibrosis stage/METAVIR score NR Genotype 1a: 34% vs. 40%; 1b: 19% vs. 16%; 2: 17% vs. 18%; 4: 19% vs. 19%; 5: 6% vs. 0%; 6: 7% vs. 7% Compensated cirrhosis: 19% vs. 18% Treatment-naive: 72% vs. 68% Treatment-experienced: 28% vs. 32% (5% vs. 9% protease inhibitor, peginterferon, and ribavirin; 21% vs. 20% pegylated IFN and ribavirin; 3% vs. 4% nonpegylated IFN with or without ribavirin)	0.1% (1/706)	HCV RNA level <15 IU/mL at 12 weeks post-treatment
Ferenci 2014[188] PEARL III Austria, Belgium, Hungary, Israel, Italy, Poland, Portugal, Romania, Russia, Spain, U.S. *Good* *Same publication as PEARL IV*	Age 18 to 70 years No cirrhosis based on liver biopsy with 24 months, Fibro Scan (NR) or FibroTest (NR) Genotype 1b Patients with HBV infection excluded	NR	419 A=209 B=210	A vs. B Mean age 49 vs. 48 years 59% vs. 49% female 94% vs. 94% white; 5% vs. 5% black; 1% vs. 1% other; 2% vs. 1% Hispanic Fibrosis score F0 or F1: 68% vs. 71%; F2: 23% vs. 18%; F3: 10% vs. 11% Treatment-naïve: 100% vs. 100%	0% (0/419)	HCV RNA <25 IU/mL
Ferenci 2014[188] PEARL IV Canada, U.K., U.S. *Good* *Same publication as PEARL III*	Age 18 to 70 years No cirrhosis based on liver biopsy with 24 months, Fibro Scan (NR) or FibroTest (NR) Genotype 1a Treatment naive Patients with HBV infection excluded	NR	305 A=205 B=100	A vs. B Mean age 51 vs. 52 years 37% vs. 30% female 83% vs. 86% white; 13% vs. 10% black; vs. 4% 4% other; 11% vs. 11% Hispanic Fibrosis score F0 and F1: 64% vs. 63%; F2: 17% vs. 21%; F3: 19% vs. 16% Treatment-naïve: 100% vs. 100%	1% (3/305)	HCV RNA <25 IU/mL

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Foster 2015[147] ASTRAL-2 U.S. *Fair*	Age ≥18 years Fibrosis stage NR; up to 20% could have compensated cirrhosis based on: liver biopsy (Metavir stage 4 or Ishak score 5 or 6), FibroTest score >0.75, AST:platelet ratio >2, or FibroScan >12.5 kPa) Genotype 2 Patients with HBV infection excluded	October 2014 to December 2014	269 A=134 B=132	A vs. B Mean age 57 vs. 57 years 36% vs. 45% female 93% vs. 84% white; 4% vs. 9% black; 1% vs. 4% Asian; 2% vs. 3% other Fibrosis stage NR; 14% vs. 14% cirrhosis Genotype 2: 100% vs. 100% Treatment-naïve: 86% vs. 85% Treatment experienced: 14% vs. 15% (IFN-containing regimen)	0.4% (1/269)	HCV RNA <15 IU/mL
Foster 2015[147] ASTRAL-3 U.S. *Fair* *Same publication as ASTRAL-2*	Age ≥18 years Fibrosis stage NR; up to 20% could have compensated cirrhosis based on: liver biopsy (Metavir stage 4 or Ishak score 5 or 6), FibroTest score >0.75, AST:platelet ratio >2, or FibroScan >12.5 kPa) Genotype 3 Patients with HBV infection excluded	Same as Foster 2015 ASTRAL-2	558 A=278 B=280	A vs. B Mean age 49 vs. 50 years 39% vs. 37% female 90% vs. 87% white; 1% vs. <1% black; 8% vs. 11% Asian; <1% vs. 2% other Fibrosis stage NR; 29% vs. 30% cirrhosis Genotype 3: 100% vs. 100% Treatment-naïve: 74% vs. 74% Treatment-experienced: 26% vs. 26% (IFN-containing regimen)	1.4% (4/280)	Same as Foster 2015 ASTRAL-2
Gane 2015[148] New Zealand (Genotype 6 subset) *Fair*	Age ≥18 years Up to 40% of enrolled patients could have cirrhosis diagnosis based on liver biopsy, Fibroscan >12.5 kPa, or FibroTest >0.75 and APRI >2 Genotype 6 Patients with HBV infection excluded	April 2013 to October 2014	25	Mean age 51 years 36% female 16% white; 84% Asian Fibrosis stage NR Cirrhosis: 8% Genotype 6c-1: 68%; 6a or 6b: 32% Treatment-naïve: 92% Treatment-experienced: 8% (previous treatment not described)	0% (0/25)	HCV RNA <15 IU/mL

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Grebely 2018a[150] SIMPLIFY Multinational (Australia, Canada, New Zealand, Norway, Switzerland, U.K., U.S.) *Fair*	Age ≥18 years Cirrhosis allowed, based on Fibroscan >14.6 kPa Genotype 1 to 6 Treatment-naïve (DAA only; prior IFN treatment NR) IVDU within 6 months of study entry Patients with HBV excluded	March 2016 to October 2016	103	Mean age 48 years 28% female Race/ethnicity NR Fibrosis stage F0 and F1: 61%; F2 and F3: 28%; F4 (cirrhosis): 9% Genotype 1a: 34%; 1b: 1%; 2: 5%; 3: 58%; 4: 2% No IVDU in last 30 days: 26%, less than daily IVDU in last 30 days: 48%, at least daily IVDU in the last 30 days: 26% Injection drugs used in the last 30 days: 55% heroin, 13% cocaine, 30% methamphetamine, 21% other opioids, 7% other drugs History of opioid substitution therapy: 82%	2% (2/103)	HCV RNA <LLOQ
Grebely 2018b[149] D3FEAT Multinational (Australia, Canada, France, New Zealand, Norway, Switzerland) *Fair*	Age >18 years Cirrhosis allowed based on FibroScan >14.6 kPa or FIB-4 >3.25 Genotype 1 Treatment naive IVDU within 6 months of study entry or use of opioid substitution therapy Patients with HBV excluded	June 2016 to February 2017	87	Mean age 48 years 23% female Race/ethnicity NR Fibrosis stage F0 and F1: 77%; F2 and F3: 13%; F4 (cirrhosis): 8% Genotype 1a: 90%; 1b: 10% Treatment-naïve: 100% IVDU in last 6 months: 61% Non-IVDU in last 6 months: 43% History of opioid substitution therapy: 85%	1% (1/87)	HCV RNA <LLOQ
Hezode 2015[189] PEARL I (Treatment-naïve population) France, Hungary, Italy, Poland, Romania, Spain, Turkey, U.S. *Good* *See also Lawitz 2015[155] (PEARL I - Genotype 1b)*	Age 18 to 70 years No cirrhosis based on liver biopsy in the past 24 months or FibroTest ≤0.72 or APRI ≤2 or FibroScan <9.6 kPa Genotype 4 Patients with HBV infection excluded	August 2012 to March 2014	42	Mean age 44 years 33% female Race/ethnicity NR; 86% European; 14% North American Fibrosis stage F0 and F1: 79%; F2: 14%; F3: 7% Genotype 4: 100% Treatment-naïve: 100%	0% (0/42)	HCV RNA <25 IU/mL

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Hezode 2015[189] PEARL I (Treatment experienced population) France, Hungary, Italy, Poland, Romania, Spain, Turkey, U.S. *Good* *See also Lawitz 2015[155] (PEARL I - Genotype 1b)*	Same as Hezode 2015 (Treatment naïve population)	Same as Hezode 2015 (Treatment naïve population)	49	Mean age 51 years 26% female Race/ethnicity NR; 86% European; 14% North American Fibrosis stage F0 and F1: 67%; F2: 22%; F3: 10% Genotype 4: 100% Treatment-naïve: 0%	0% (0/49)	Same as Hezode 2015 (Treatment naïve population)
Kowdley 2014a[190] ION-3 U.S. *Fair*	Age ≥18 years No cirrhosis based on liver biopsy in the past 24 months or FibroTest ≤0.48 and APRI ≤1 Genotype 1 Patients with HBV infection excluded	May 2013 to June 2013	431	<u>8-week intervention group (n=215)</u> Mean age 53 years 40% female 76% white; 21% black; 3% other; 6% Hispanic; 93% non-Hispanic; 1% NR Fibrosis stage F0 to F2: 59%; F3: 13%; 28% NR Genotype 1a: 80%; 1b: 20%; unconfirmed subtype: 0.5% Treatment-naive: 100% <u>12-week intervention group (n=216)</u> Mean age 53 years 41% female 77% white; 19% black; 3% other; 6% Hispanic; 94% non-Hispanic Fibrosis stage F0 to F2: 59%; F3: 13%; 28% NR Genotype 1a: 80%; 1b: 20% Treatment-naive: 100%	2% (8/431)	HCV RNA <25 IU/mL

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Kowdley 2014b[191] AVIATOR Australia, Canada, France, Germany, New Zealand, Puerto Rico, Spain, U.K., U.S. *Good*	Age 18 to 70 years FibroTest ≤0.72 and APRI ≤2 at screening; or FibroScan <9.6 kPa, or the absence of cirrhosis based on a liver biopsy within 36 months Genotype 1 Patients with HBV infection excluded	October 2011 to April 2012	158 A=79 B=79	A vs. B Mean age 48 vs. 50 years 43% vs. 44% female 17% vs. 16% black; other races NR; 9% vs. 8% Hispanic Fibrosis score F2 or F3: 25% vs. 32% Genotype 1a: 67% vs. 69% Treatment-naïve: 100% vs. 100%	2.5% (4/158)	HCV RNA <25 IU/mL 24 weeks after the end of treatment Primary efficacy endpoint; 12-week post-treatment results reported in online supplement
Kumada 2017 (Part 2 only)[152] Japan *Good*	Age 20 to 80 years Fibrosis stage NR; patients with cirrhosis were eligible for study inclusion Genotype 1 Patients with HBV infection excluded	August 2014 to October 2015	Part 2 only 227	Mean age 61 years 62% female 100% Asian (Japanese) Fibrosis stage/METAVIR score NR Genotype 1a: 2%; 1b: 98% Treatment-naïve: 66% Treatment-experienced: 34% (IFN-containing regimen)	NR	HCV RNA undetectable
Kumada 2015[151] GIFT-1 (Substudy 1) Japan *Fair*	Age 18 to 75 years Liver biopsy within 24 months of study with METAVIR or New Inuyama Score ≤3; or if no biopsy FibroTest score of ≤0.72 and APRI ≤2, screening transient elastography (e.g., FibroScan) <12.5 kPa; or screening Discriminant Score <0 Genotype 1b Patients with HBV infection excluded	December 2013 through 2014	321 A=215 B=106	A vs. B Mean age 61 vs. 62 years 63% vs. 56% female Race NR Fibrosis stage: F0 and F1: 60% vs. 74%; F2: 21% vs. 3%; F3: 20% vs. 23%; NR: 62% vs. 71% Genotype 1b: 100% Treatment-naïve: 65% vs. 64% Treatment-experienced: 35% vs. 36% (IFN-containing regimen)	0% (0/321)	HCV RNA <LLOQ 12 weeks post-treatment

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Kwo 2016[153] OPTIMIST-1 Canada, U.S. *Fair*	Age 18 to 70 years FibroScan ≤12.5 kPa within 6 months of screening or between screening and day 1; or, FibroTest ≤0.48 + AST:platelet ratio index ≤1 at screening; or, liver biopsy within 2 years of screening or between screening and day 1 Genotype 1 Patients with HBV infection excluded	April 2014 to January 2015	155	Mean age 56 years 47% female 78% white; 20% black; 1% Asian; <1% other METAVIR Score F0 to F2: 43%; F3: 10%; NR: 47% Genotype 1a: 75%; 1b: 25% Treatment-naive: 74% Treatment-experienced: 26% (IFN-containing regimen)	0% (0/310)	HCV RNA <25 IU/mL or undetectable
Lalezari 2015[192] U.S. *Fair*	Age 18 to 70 years Fibrosis stage NR; no cirrhosis (undefined) Genotype 1 Patients with HBV infection excluded Stable opioid replacement therapy with either methadone or buprenorphine	April 2013 to December 2013	38	Mean age 48 years 34% female 95% white; 3% Hispanic/Latino Fibrosis stage F0-F1: 79%; F2: 16%; F3: 5% Genotype 1a: 84%; other subgenotypes NR Opioid replacement therapy, methadone: 50%; buprenorphine: 50% Treatment-naïve: 95% Treatment-experienced: 5% (pegylated IFN + ribavirin)	0% (0/38)	HCV RNA <15 IU/mL
Lawitz 2014a[154] COSMOS U.S. *Fair*	Age ≥18 years METAVIR F0-F2; previous nonresponders to peginterferon and ribavirin Genotype 1 Patients with HBV infection excluded	November 2011 to January 2014	41 A=14 B=27	A vs. B Median age 56 vs. 55 years 42% vs. 26% female 79% vs. 70% white; 21% vs. 30% black/African American; 14% vs. 15% Hispanic/Latino Fibrosis stage F0 and F1: 57% vs. 41%; F2: 43% vs. 59% Genotype 1a: 71% vs. 78%; 1b: 29% vs. 22% Treatment-naive: 0% vs. 0% Treatment-experienced: 100% vs. 100%	0% (0/41)	HCV RNA <25 IU/mL

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Lawitz 2014b[193] LONESTAR (Cohort A) U.S. *Fair*	Age >18 years No cirrhosis, based on liver biopsy Genotype 1 Patients with HBV infection excluded	November 2012 to December 2012	60 A=20 B=19 C=21	A vs. C <u>8-week intervention group</u> Mean age 48 vs. 50 years 30% vs. 43% female 20% vs. 0% black; 80% vs. 100% non-black 15% vs. 57% Hispanic; 85% vs. 43% non-Hispanic Fibrosis stage NR; cirrhosis: 0% vs. 0% Genotype 1a: 85% vs. 90%; 1b: 15% vs. 10% Treatment-naive: 100% vs. 100% B <u>12-week intervention group</u> Mean age 46 years 42% female 5% black; 95% non-black 47% Hispanic; 53% non-Hispanic Fibrosis stage NR; cirrhosis: 0% Genotype 1a: 89% Treatment-naive: 100%	2% (1/60)	HCV RNA <25 IU/mL or undetectable
Lawitz 2015[155] PEARL-1 France, Hungary, Italy, Poland, Puerto Rico, Romania, Spain, Turkey, U.S. *Fair*	Age 18 to 70 years No cirrhosis, based on liver biopsy or FibroScan ≥14.6 kPa Genotype 1b Patients with HBV infection excluded	August 2012 to March 2014	82 (without cirrhosis; 42 treatment naïve, 40 prior null responder)*	Mean age 55 years 51% female 80% white; 15% black; 5% Asian; <1% American Indian/Alaska Native Fibrosis stage F0 and F1: 63%; F2: 23%; F3: 14% Genotype 1b: 100% Treatment naïve: 51%Treatment-experienced: 49% (pegylated IFN + ribavirin)	1% (1/82)	HCV RNA <25 IU/mL

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Lim 2016[156] Korea *Fair*	Age ≥18 years Up to 20%of enrolled patients could have cirrhosis, based on liver biopsy Treatment-naïve arm only Genotype 1 Patients with HBV infection excluded	NR	46	Mean age 54 years 61% female 100% Asian Fibrosis stage NR; 9% cirrhosis Genotype 1a: 4%; 1b: 96% Treatment-naïve: 100%	0% (0/46)	HCV RNA <25 IU/mL
Nelson 2015[157] ALLY-3 U.S. *Fair*	Age ≥18 years Fibrosis stage NR; patients with compensated cirrhosis were eligible for inclusion Genotype 3 Patients with HBV infection excluded	NR	101 (treatment-naïve population only)	Mean age 53 years 43% female 91% white; 4% black; 5% Asian FibroTest F0 to F3: 76%; F4: 22% Genotype 3: 100% Cirrhosis: 19% Treatment-naïve: 100%	0% (0/101)	HCV RNA <25 IU/mL
Pianko 2015[158] Australia, New Zealand, U.S. *Fair*	Age ≥18 years No cirrhosis, based on liver biopsy, FibroTest >0.75 and APRI >2.0, or FibroScan >12.5 kPa Genotype 3 Treatment experienced (IFN + ribavirin) Patients with HBV infection excluded	June 2013 to August 2014	53 A=27 B=26	A vs. B Mean age 55 vs. 56 33% vs. 35% female 93% vs. 92% white; 0% vs. 4% black Fibrosis stage NR; 0% vs. 0% cirrhosis Genotype 3: 100% vs. 100% Treatment naïve: 0% vs. 0% Treatment-experienced: 100% vs. 100%	0% (0/53)	HCV RNA <LLOQ

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Poordad 2017[194] MAGELLAN-1 U.S. *Fair*	Age 18 to 70 years Liver biopsy with 24 months, FibroScan <12.5 kPa, or FibroTest ≤0.48 and APRI <1 Genotype 1 Prior DAA treatment failure Patients with HBV infection excluded	NR	50 A=6 B=22 C=22	A vs. B vs. C Mean age 59 vs. 59 vs. 56 years 50% vs. 18% vs. 9% female 33% vs. 45% vs. black; other race/ethnicity NR Fibrosis stage F0-F1: 67% vs. 50% vs. 77%; F2: 17% vs. 27% vs. 0%; F3: 17% vs. 23% vs. 23% Genotype 1a: 67% vs. 82% vs. 91%; 1b: 33% vs. 18% vs. 9% Treatment-experienced: 100% vs. 100% vs. 100%	0% (0/50)	HCV RNA <15 IU/mL
Pott-Junior 2019 (Group A - daclatasvir/ sofosbuvir arm)[159] Brazil *Good*	Age ≥18 years Fibrosis stage 3 based on liver biopsy or FibroScan ≥9.6 but <12.5; no cirrhosis Genotype 1 Treatment-naïve or experienced Patients with HBV excluded	NR	65	Mean age 56 years 53% female Race/ethnicity NR Mean FibroScan 9.9 kPa Genotype 1: 100% Treatment-naïve: 60% Treatment-experienced (pegylated IFN): 40%	0% (0/65)	HCV RNA <LLOQ
Pott-Junior 2019 (Group B - simeprevir/ sofosbuvir arm)[159] Brazil *Good*	See Pott-Junior 2019 Group A	See Pott-Junior 2019 Group A	60	Mean age 53 years 48% female Race/ethnicity NR Mean FibroScan 10.2 kPa Genotype 1: 100% Treatment-naïve: 60% Treatment-experienced (pegylated IFN): 40%	0% (0/60)	See Pott-Junior 2019 Group A
Sperl 2016[198] and Ng 2018[138] C-EDGE Head-2-Head (elbasvir/grazoprevir arm only) Multinational (Europe, Turkey) *Fair*	Age NR Cirrhosis allowed; criteria NR Genotype 1, 4 or 6 Treatment naïve or experienced Patients with HBV excluded	NR	129	Mean age 48 years 57% female 99% white; other races NR Fibrosis stage NR; 17% cirrhosis Genotype 1a: 14%; 1b: 81%; 4: 5% Treatment-naïve: 78% Treatment-experienced (peg IFN + ribavirin): 22%	0.8% (1/129)	HCV RNA <15 IU/mL

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Sulkowski 2014[161] A1444040 Study U.S. *Fair*	Age 18 to 70 years No cirrhosis based on liver biopsy within 24 months or FibroTest ≤0.72 and APRI ≤2 Genotype 1, 2 or 3 Patients with HBV infection excluded	June 2011 to November 2012	82 A=41 B=41	A vs. B Median age 55 vs. 54 years 51% vs. 49% female 80% vs. 80% white; 12% vs. 17% black; 7% vs. 2% other Fibrosis stage F0 and F1: 37% vs. 32%; F2 and F3:46% vs. 54%; F4: 15% vs. 12% Genotype 1a: 83% vs. 80%; 1b: 17% vs. 20% Treatment-naïve: 100% vs. 100%	0% (0/82)	HCV RNA <25 IU/mL
Sulkowski 2015[160] C-WORTHY Australia, Canada, Denmark France, Hungary, Israel, New Zealand, Puerto Rico, Spain, Sweden, Turkey, U.S. *Fair*	Age ≥18 years Fibrosis stage NR; patients with HCC or decompensated liver disease excluded Genotype 1 Patients with HBV infection excluded	February 2013 to July 2014	129 A=44 B=85	A vs. B Mean age 52 vs. 51 years 48% vs. 53% female 82% vs. 95% white; 18% vs. 5% non-white; 11% vs. 9% Hispanic Fibrosis stage F0 to F2: 89% vs. 95%; F3: 11% vs. 5% Genotype 1a: 68% vs. 61%; 1b: 32% vs. 37% Treatment-naïve: 100% vs. 100%	0% (0/129)	HCV RNA <25 IU/mL
Toyoda 2018[199] CERTAIN-2 (Arm A only) Japan *Fair*	Age ≥18 years No cirrhosis based on liver biopsy, FibroScan <12.5 kPa or FibroTest ≤0.72 Genotype 2 Patients with HBV excluded	February 2016 to July 2016	90 (Arm A only)	Mean age 57 years 53% female Race/ethnicity NR Median fibrosis stage 1.6 Genotype 2a: 72%; 2b: 28% Treatment-naïve: 83% Treatment-experienced (IFN): 17%	1% (1/90)	HCV RNA <15 IU/mL
Waked 2016[162] AGATE-II Egypt *Good*	Age ≥18 years No cirrhosis based on liver biopsy in the past 24 months or FibroTest ≤0.72 or APRI ≤2 or FibroScan >12.5 kPa Genotype 4 Patients with HBV infection excluded	November 2014 to March 2015	100 (treatment-naïve population only)	Mean age 49 years 30% female 98% white; 2% black Fibrosis F0 and F1: 68%; F2: 11%; F3: 19%; F4: 2% Genotype 4: 100% Treatment-naïve: 100%	0% (0/100)	HCV RNA <LLOQ

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Wei 2018[163] China *Fair*	Age ≥20 years Cirrhosis allowed, based on liver biopsy or FibroScan >12.5 kPa Genotype 1 Treatment naïve or experienced Patients with HBV excluded	May 2016 to July 2017	206	Mean age 47 years 50% female Race/ethnicity NR Fibrosis stage NR; 16% cirrhosis Treatment-naïve: 52% Treatment-experienced: 48%	0% (0/206)	HCV RNA <LLOQ
Wei 2019a[164] C-CORAL (Genotype 1 and 4 only) Multinational (Australia, China, Korea, Russia, Taiwan, Thailand, Vietnam) *Good*	Age >18 years Cirrhosis allowed, based on liver biopsy or FibroScan >12.5 kPa Genotype 1 or 4 Treatment naïve Patients with HBV excluded	March 2015 to September 2016	486 (efficacy; 435 excluding Genotype 6); 609 (harms)	Mean age 48 years 56% female 72% Asian, 28% white, 0.2% other Fibrosis stage F0 to F2: 70%; F3: 11%; F4: 19% Genotype 1a: 8%; 1b: 80%; other type 1: 1%; 4: 0.6% Treatment-naïve: 100%	0.2% (1/486)	HCV RNA <LLOQ
Wei 2019b[165] Multinational (China, Malaysia, Singapore, Thailand, Vietnam) *Fair*	Age ≥18 years Cirrhosis allowed, based on liver biopsy or FibroScan or FibroTest and APRI Genotype 1-6 Treatment naïve or experienced Patients with HBV excluded	April 2016 to June 2017	375	Median age 45 years 47% female Race/ethnicity NR Fibrosis stage NR; 18% cirrhosis Genotype 1: 34%; 2: 17%; 3: 22%; 6: 26% Treatment-naïve: 82% Treatment-experienced (primarily IFN or peg IFN + ribavirin): 18%	0.3% (1/375)	HCV RNA <15 IU/mL
Zeuzem 2015[166] C-EDGE Multinational (Australia, Czech Republic, France, Germany, Israel, Puerto Rico, South Korea, Taiwan, U.S.) *Good*	Age >18 years Fibrosis stage NR; 20% cirrhosis planned enrollment Genotype 1, 4 or 6; 15% genotype 4 or 6 planned enrollment Patients with HBV infection excluded	June 2014 to March 2015	246 (immediate treatment group only, without cirrhosis)	*Total population (n=316; 22% cirrhosis)* Mean age 52 years 46% female 17% Asian; 19% black; 60% white; 4% other Fibrosis F0 to F2: 67%; F3: 11%; F4: 22% Genotype 1a: 50%; 1b: 42%; 4: 6%; 6: 3% Treatment-naïve: 100%	*Total population* 0.6% (2/316)	HCV RNA unquantifiable

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Zeuzem 2018[167] ENDURANCE-1 Multinational (Australia, Austria, Belgium, Canada, Chile, France, Germany, Hungary, Israel, Italy, Lithuania, Mexico, New Zealand, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Spain, South Korea, Sweden, Switzerland, Taiwan, U.K., U.S.) *Fair*	Age ≥18 years No cirrhosis based on liver biopsy, serum markers or transient elastography Genotype 1 Treatment naïve or experienced (IFN or sofosbuvir) Patients with HBV infection excluded	October 2015 to May 2016	667	8-week intervention group (n=351) Median age 53 years 52% female 4% black; 82% white; other race/ethnicity NR Fibrosis stage F0 or F1: 85%; F2: 6%; F3: 9% Genotype 1a: 43% Treatment-naïve: 62% Treatment- experienced: 38% (99% IFN; 1% sofosbuvir) People who inject drugs: 28% Opioid substitution therapy: 3% HIV coinfection: 4% 12-week intervention group (n=352) Median age 52 years 50% female 4% black; 86% white; other race/ethnicity NR Fibrosis stage F0 or F1: 85%; F2: 7%; F3: 17% Genotype 1a: 41% Treatment-naive: 62%Treatment-experienced: 38% (99% IFN; 1% sofosbuvir) People who inject drugs: 28% Opioid substitution therapy: 5% HIV coinfection: 5%	0.3% (1/351)	HCV RNA <15 IU/mL

Appendix B Table 10. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Study Characteristics

Author year **Country** ***Quality***	**Eligibility** Age Fibrosis stage Genotype(s) HBV status	**Study Recruitment Dates**	**Sample Size**	**Baseline Characteristics**	**Loss to Followup**	**Definition of SVR**
Zeuzem 2018[167] ENDURANCE-3 (same publication as ENDURANCE-1) *Fair*	Age ≥18 years No cirrhosis based on liver biopsy, serum markers or transient elastography Genotype 3 Treatment naïve or experienced (IFN or sofosbuvir) Patients with HBV infection excluded	Same as Zeuzem 2018	505 A=157 B=233 C=115	A vs. B vs. C Median age 47 vs. 48 vs. 49 years 41% vs. 48% vs. 55% female 2% vs. 2% vs. 3% black; 85% vs. 8*% vs. 90% white; other race/ethnicity NR Fibrosis stage F0 or F1: 78% vs. 86% vs. 84%; F2: 5% vs. 5% vs. 7%; F3: 17% vs. 9% vs. 9% Genotype 3: 100% vs. 100% vs. 100% Treatment-naïve: 100% vs. 100% vs. 100% People who inject drugs: 66% vs. 64% vs. 63% Opioid substitution therapy: 20% vs. 16% vs. 15%	0.6% (3/505)	Same as Zeuzem 2018

Note: *Excluding patients who withdrew or were lost to follow up.
Abbreviations: APRI = aspartate amino transferase to platelet ratio index; AST = aspartate amino transferase; DAA = direct acting antiviral; HBV = hepatitis B virus; HCV = hepatitis C virus; HCC = hepatocellular carcinoma; IFN = interferon; IVDU = injection drug use; LLOQ = lower limit of quantification; NR = not reported; RNA = ribonucleic acid; SVR = sustained virologic response; U.K. = United Kingdom; U.S. = United States. Study names are not acronyms.

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Abergel 2016a[142] France *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	SVR: 96% (21/22)	Genotype 4: 96% (21/22)	NR
Abergel 2016b[141] France *Good*	Ledipasvir 90 mg + sofosbuvir 400 mg	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	SVR: 95% (20/21)	Genotype 5: 95% (20/21)	NR

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Afdhal 2014[185] ION-1 U.S. and Europe *Fair*	A. Ledipasvir 90 mg + sofosbuvir 400 mg B. Ledipasvir 90 mg + sofosbuvir 400 mg + ribavirin	Treatment duration: 12 to 24 weeks Timing of assessment: 12 weeks post-treatment	A vs. B 12-week intervention group SVR: 99% (211/214) vs. 97% (211/217) 24-week intervention group SVR: 98% (212/217) vs. 99% (215/217)	A vs. B SVR, 12-week intervention group* Genotype 1a: 99% (141/142) vs. 100% (143/143) Genotype 1b: 100% (66/66) vs. 100% (67/67) Other: 100% (4/4) vs. 100% (1/1) SVR, 24-week intervention group* Genotype 1a: 100% (143/143) vs. 100% (141/141) Genotype 1b: 97% (66/68) vs. 100% (71/71) Other: 100% (3/3) vs. 100% (3/3)	A vs. B SVR, 12-week intervention group* <65 years: 99% (196/197) vs. 100% (189/189) ≥65 years: 100% (15/15) vs. 100% (22/22) Male: 99% (125/126) vs. 100% (124/124) Female: 100% (86/86) vs. 100% (87/87) Black: 100% (24/24) vs. 100% (26/26) Non-Black: 99.5% (187.188) vs. 100% (184/184) Hispanic: 100% (26/26) vs. 100% (19/19) Non-Hispanic: 99.5% (184/185) vs. 100% (192/192) No cirrhosis: 100% (179/179) vs. 100% (178/178) Cirrhosis: 97% (32/33) vs. 100% (33/33) SVR, 24-week intervention group* <65 years: 99.5% (191/192) vs. 100% (202/202) ≥65 years: 96% (21/22) vs. 100% (13/13) Male: 99% (136/138) vs. 100% (118/118) Female: 100% (76/76) vs. 100% (97/97) Black: 94% (29/31) vs. 100% (26/26) Non-Black: 100% (183/183) vs. 100% (188/188) Hispanic: 100% (29/29) vs. 100% (26/26) Non-Hispanic: 100% (183/183) vs. 100% (188/188) No cirrhosis: 99.5% (181/182) vs. 100% (179/179) Cirrhosis: 97% (31/32) vs. 100% (36/36)
Ahmed 2018[195] Egypt *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg	Treatment duration: 12 weeks Timing of assessments: 12 weeks post-treatment	SVR: 99% (99/100)	Genotype 4: 99% (99/100)	NR

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Andreone 2014[186] PEARL-II Austria, Belgium, Italy, The Netherlands, Portugal, Puerto Rico, Sweden, Switzerland, U.S. *Fair*	A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day B. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + ribavirin	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	A vs. B SVR: 100% (91/91) vs. 97% (85/88)	A vs. B Genotype 1b: 100% (91/91) vs. 97% (85/88)	A vs. B Male: 100% (54/54) vs. 95% (41/43) Female: 100% (37/37) vs. 98% (44/45) Black: 100% (5/5) vs. 100% (3/3) Other: 100% (86/86) vs. 97% (82/85)
Asselah 2018[196] SURVEYOR II Part 4, Multinational (Asia, Europe, U.S. [specific countries NR]) *Fair*	Glecaprevir 300 mg + pibrentasvir 120 mg	Treatment duration: 8 weeks Timing of assessments: 12 weeks post-treatment	SVR: 97% (196/203)	Genotype 2: 98% (142/145) Genotype 4: 93% (43/46) Genotype 5: 100% (2/2) Genotype 6: 90% (9/10)	NR
Asselah 2019[143] ENDURANCE-5 Multinational (Australia, Belgium, Canada, France, New Zealand, Singapore, South Africa, Vietnam, U.S.) *Fair*	Glecaprevir 300 mg + pibrentasvir 120 mg	Treatment duration: 8 weeks Timing of assessments: 12 weeks post-treatment	SVR: 96% (22/23)	Genotype 5: 96% (22/23)	NR (reported for combined genotypes only)
Asselah 2019[143] ENDURANCE-6 (same publication as ENDURANCE-5) *Fair*	See Asselah 2019 ENDURANCE-5	See Asselah 2019 ENDURANCE-5	SVR: 98% (60/61)	Genotype 6: 98% (60/61)	See Asselah 2019 ENDURANCE-5
Brown 2018[144] C-SCAPE (Genotype 4 only) Multinational (Australia, Belgium, France, Israel, Spain, U.K., U.S.) *Fair*	A. Elbasvir 50 mg + grazoprevir 100 mg (n=10) B. Elbasvir 50 mg + grazoprevir 100 mg + ribavirin (n=10)	Treatment duration: 12 weeks Timing of assessments: 12 weeks post-treatment	A vs. B SVR: 90% (9/10) vs. 100% (10/10)	NR	NR

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Chayama 2018[197] CERTAIN-1 (Arm A only) Japan *Fair*	Glecaprevir 300 mg + pibrentasvir 120 mg	Treatment duration: 8 weeks Timing of assessments: 12 weeks post-treatment	SVR: 99% (128/129)	Genotype 1: 99% (128/129)	NR
Chuang 2016[145] Taiwan *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	SVR: 98% (83/85)	Genotype 1: 98% (83/85)	Treatment-naïve: 100% (42/42) Treatment experienced: 95% (41/43)

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Dore 2016[137] MALACHITE-1 Australia, Canada, Europe, South America *Good*	Genotype 1a A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + weight-based ribavirin B. Telaprevir 750 mg 3x/day + subcutaneous pegylated IFN 180 ug 1/week + weight-based ribavirin Genotype 1b C. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + weight-based ribavirin D. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day E. Telaprevir 750 mg 3x/day + subcutaneous pegylated IFN 180 ug 1/week + weight-based ribavirin	Treatment duration: 12 weeks; some patients in groups B and D received up to 48 weeks of pegylated IFN / ribavirin Timing of assessment: 12 weeks post-treatment	Genotype 1a A vs. B SVR: 97% (67/69) vs. 82% (28/34) Genotype 1b C vs. D vs. E SVR: 99% (83/84) vs. 98% (81/83) vs. 78% (32/41)	Genotype 1a A vs. B SVR: 97% (67/69) vs. 82% (28/34) Genotype 1b C vs. D vs. E SVR: 99% (83/84) vs. 98% (81/83) vs. 78% (32/41)	NR

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Dore 2016[137] MALACHITE-2 Australia, Canada, Europe, South America *Good*	A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + weight-based ribavirin B. Telaprevir 750 mg 3x/day + subcutaneous pegylated IFN 180 ug 1/week + weight-based ribavirin	Treatment duration: 12 weeks; some patients in group B and D received up to 48 weeks of pegylated IFN / ribavirin Timing of assessment: 12 weeks post-treatment	A vs. B SVR: 99% (100/101) vs. 66% (31/47)	A vs. B Genotype 1a: 100% (19/19) vs. 57% (4/7) Genotype 1b: 99% (81/82) vs. 68% (27/40)	NR
Everson 2015 (Part A)[146] U.S. *Good*	Part A (trial phase) A. Sofosbuvir 400 mg + velpatasvir 25 mg (Genotype 1) B. Sofosbuvir 400 mg + velpatasvir 100 mg (Genotype 1) C. Sofosbuvir 400 mg + velpatasvir 25 mg (Genotype 3) D. Sofosbuvir 400 mg + velpatasvir 100 mg (Genotype 3) E. Sofosbuvir 400 mg + velpatasvir 25 mg (Genotype 2; 4-6) F. Sofosbuvir 400 mg + velpatasvir 100 mg (Genotype 2; 4-6)	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	A vs. B vs. C vs. D vs. E vs. F SVR: 96% (26/27) vs. 100% (28/28) vs. 93% (25/27) vs. 93% (25/27) vs. 96% (22/23) vs. 95% (21/22)	A vs. B vs. C vs. D vs. E vs. F Genotype 1, Group A: 96% (26/27) Genotype 1, Group B: 100% (28/28) Genotype 3, Group C: 93% (25/27) Genotype 3, Group D: 93% (25/27) Genotype 2 or 4-6, Group E: 96% (22/23) Genotype 2 or 4-5, Group F: 95% (21/22)	NR

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Feld 2014[187] SAPPHIRE-1 Australia, New Zealand; Austria, France, Germany, Hungary, Great Britain, Italy, Spain, Sweden, Switzerland; Canada, U.S. *Good*	A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x day + weight-based ribavirin B. Placebo for 12 weeks followed by open-label ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x day + weight-based ribavirin	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	SVR: 96% (455/473)	Genotype 1a: 95% (307/322) 1b: 98% (148/151)	Age <55 years: 97% (95% CI, 94.5 to 98.7); (280/290) Age ≥55 years: 96% (95% CI, 92.7 to 98.6); (175/183) Male: 95% (95% CI, 92.7 to 97.8); (258/271) Female: 98% (95% CI, 95.4 to 99.7); (197/202) Black: 96% (95% CI, 89.6 to 100.0); (27/28) Non-Black: 96% (95% CI, 94.4 to 98.0); (428/445) F0 or F1: 97%(95% CI, 95.2 to 98.7); (352/363) F2: 94% (95% CI, 88.9 to 99.7); (66/70) F3: 93% (95% CI, 84.3 to 100.0); (37/40) History of diabetes: 100% (95% CI, 100.0-100.0); (19/19) No history of diabetes: 96% (95% CI, 94.2 to 97.8); (436/454)

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Feld 2015[139] ASTRAL-1 U.S., Canada, Europe, Hong Kong *Good*	A. Sofosbuvir 400 mg + velpatasvir 100 mg B. Placebo	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	A vs. B SVR: 99% (618/624) vs. 0% (0/116)	*Group A only* Genotype 1: 99% (323/328) 1a: 98% (206/210) 1b: 99% (117/118) 2: 100% (104/104) 4: 100% (116/116) 5: 97% (34/35) 6: 100% (41/41)	*Group A only* Age <65 years: 99% (530/536) -Genotype 1: 98% (287/292); Genotype 2: 100% (79/79); Genotype 4: 100% (116/116); Genotype 5: 95% (18/19); Genotype 6: 100% (41/41) Age ≥65 years: 100% (88/88) -Genotype 1: 100% (36/36); Genotype 2: 100% (25/25); Genotype 4: 100% (11/11); Genotype 5: 100% (16/16); Genotype 6: 0/0 Male: 99% (369/374) -Genotype 1: 98% (193/197); Genotype 2: 100% (57/57); Genotype 4: 100% (86/86); Genotype 5: 93% (13/14); Genotype 6: 100% (21/21) Female: 99.6% (249/250) -Genotype 1: 99% (130/131); Genotype 2: 100% (47/47); Genotype 4: 100% (30/30); Genotype 5: 100% (21/21); Genotype 6: 100% (21/21) White: 99% (488/493) -Genotype 1: 99% (275/279); Genotype 2: 100% (82/82); Genotype 4: 100% (96/96); Genotype 5: 97% (34/35); Genotype 6: 100% (1/1) Black: 98% (51/52) -Genotype 1: 96% (24/25); Genotype 2: 100% (13/13); Genotype 4: 100% (14/14); Genotype 5 & 6: 0/0 Other: 100% (76/76) -Genotype 1: 100% (22/22); Genotype 2: 100% (8/8); Genotype 4: 100% (6/6); Genotype 5 & 6: 0/0 No cirrhosis: 99% (496/501) -Genotype 1: 98% (251/255); Genotype 2: 100% (93/93); Genotype 4: 100% (89/89); Genotype 5: 97% (28/29); Genotype 6: 100% (35/35) Cirrhosis: 99% (120/121) -Genotype 1: 99% (72/73); Genotype 2: 100% (10/10); Genotype 4: 100% (27/27); Genotype 5: 100% (5/5); Genotype 6: 100% (6/6) Treatment-naïve: 99% (418/423) -Genotype 1: 98% (214/218; Genotype 1a: 97% [128/132]; Genotype 1b: 100% [86/86]); Genotype 2: 100% (79/79); Genotype 4: 100% (64/64); Genotype 5: 96% (23/24); Genotype 6: 100% (38/38) Treatment-experienced: 99.5% (200/201) -Genotype 1: 99% (109/110; Genotype 1a: 100% [78/78]; Genotype 1b: 97% [31/32]); Genotype 2: 100% (25/25); Genotype 4: 100% (52/52); Genotype 5: 100% (11/11); Genotype 6: 100% (3/3)

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Ferenci 2014[188] PEARL III Austria, Belgium, Hungary, Israel, Italy, Poland, Portugal, Romania, Russia, Spain, U.S. *Good* *Same publication as PEARL IV*	A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day B. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + ribavirin	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	SVR: 99% (207/209) vs. 99.5% (209/210)	Genotype 1b: 99% (207/209) vs. 99.5% (209/210)	NR
Ferenci 2014[188] PEARL IV Canada, U.K., U.S. *Good* *Same publication as PEARL III*	A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day B. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + ribavirin	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	A vs. B SVR: 90% (185/205) vs. 97% (97/100)	Genotype 1a: 90% (185/205) vs. 97% (97/100)	NR
Foster 2015[147] ASTRAL-2 U.S. *Fair*	A. Sofosbuvir 400 mg + velpatasvir 100 mg B. Sofosbuvir 400 mg + ribavirin	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	A vs. B SVR: 99% (133/134) vs. 94% (124/132)	Genotype 2: SVR: 99% (133/134) vs. 94% (124/132)	NR

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Foster 2015[147] ASTRAL-3 U.S. *Fair* *Same publication as ASTRAL-2*	Same as Foster 2015 ASTRAL-2	Treatment duration: 12 (group A) or 24 (group B) weeks Timing of assessment: 12 weeks post-treatment	A vs. B SVR: 95% (264/277) vs. 80% (221/275)	A vs. B Genotype 3: 95% (264/277) vs. 80% (221/275)	A vs. B Age <65 years: 95% (257/270) vs. 81% (210/261) Age ≥65 years: 100% (7/7) vs. 79% (11/14) Male: 94% (159/170) vs. 76% (132/175) Female: 98% (105/107) vs. 88% (89/101) Black: 100% (3/3) vs. 100% (1/1) White: 95% (238/250) vs. 78% (187/239) Other: 96% (23/24) vs. 94% (32/34) No cirrhosis: 97% (191/197) vs. 87% (163/187) Cirrhosis: 91% (73/80) vs. 66% (55/83) Missing data: 0% vs. 60% (3/5) Treatment-naive: 97% (200/206) vs. 86% (176/204) Treatment-experienced: 90% (64/71) vs. 63% (45/71) No cirrhosis + treatment-naive: 98% (160/163) vs. 90% (141/156) No cirrhosis + treatment-experienced: 91% (31/34) vs. 71% (22/31)
Gane 2015[148] New Zealand (Genotype 6 subset) *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	SVR: 96% (24/25)	Genotype 6: 96% (24/25)	NR
Grebely 2018a[150] SIMPLIFY Multinational (Australia, Canada, New Zealand, Norway, Switzerland, U.K., U.S.) *Fair*	Sofosbuvir 400 mg + velpatasvir 100 mg	Treatment duration: 12 weeks Timing of assessments: 12 weeks post-treatment	SVR: 94% (97/103)	NR	Male: 92% (68/74) Female: 100% (29/29) Age ≤41 years: 93% (26/28) Age >41 years: 95% (71/75) F0 and F1: 97% (57/59) F2 and F3: 93% (25/27) Cirrhosis: 78% (7/9) Current opioid substitution therapy: 96% (43/45) No current opioid substitution therapy: 93% (54/58) Recent IVDU: 95% (72/76) No recent IVDU: 93% (25/27)

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Grebely 2018b[149] D3FEAT Multinational (Australia, Canada, France, New Zealand, Norway, Switzerland) *Fair*	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg + 1000 to 1200 mg ribavirin	Treatment duration: 12 weeks Timing of assessments: 12 weeks post-treatment	SVR: 91% (79/87)	Genotype 1: 91% (79/87)	Male: 91% (61/67) Female: 90% (18/20) Age ≤54 years: 89% (59/66) Age >54 years: 95% (20/21) F0 and F1: 90% (61/68) F2 and F3: 100% (12/12) Cirrhosis: 86% (6/7) Recent IVDU: 93% (39/42) No recent IVDU: 89% (40/45)
Hezode 2015[189] PEARL I (Treatment-naïve population) France, Hungary, Italy, Poland, Romania, Spain, Turkey, U.S. *Good* *See also Lawitz 2015[155] (PEARL I - Genotype 1b)*	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + ribavirin (weight-based; dose NR)	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	SVR: 100% (42/42)	Genotype 4: 100% (42/42)	NR
Hezode 2015[189] PEARL I (Treatment experienced population) France, Hungary, Italy, Poland, Romania, Spain, Turkey, U.S. *Good* *See also Lawitz 2015[155] (PEARL I - Genotype 1b)*	Same as Hezode 2015 (Treatment naïve population)	Same as Hezode 2015 (Treatment naïve population)	SVR: 100% (49/49)	Genotype 4: 100% (49/49)	NR

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Kowdley 2014a[190] ION-3 U.S. *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg	Treatment duration: 8 to 12 weeks Timing of assessment: 12 weeks post-treatment	8-week intervention group SVR: 94% (202/215) 12-week intervention group SVR: 95% (206/216)	8-week intervention group Genotype 1a: 93% (159/171) Genotype 1b: 98% (42/43) Unconfirmed subtype: 100% (1/1) 12-week intervention group Genotype 1a: 95% (163/172) Genotype 1b: 98% (43/44)	8-week intervention group <65 years: 94% (185/196) ≥65 years: 90% (17/19) Male: 92% (119/130) Female: 98% (83/85) Black: 91% (41/45) Non-black: 95% (161/170) Hispanic: 100% (13/13) Non-Hispanic: 94% (187/200) 12-week intervention group <65 years: 95% (189/199) ≥65 years: 100% (17/17) Male: 95% (122/128) Female: 96% (84/85) Black: 95% (40/42) Non-black: 95% (165/173) Hispanic: 93% (13/14) Non-Hispanic: 96% (193/202)
Kowdley 2014b[191] AVIATOR Australia, Canada, France, Germany, New Zealand, Puerto Rico, Spain, U.K., U.S. *Good*	A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 150 mg + dasabuvir 800 mg B. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100-150 mg + dasabuvir 800 mg + ribavirin 1000-1200 mg	Treatment duration: 12 weeks Timing of assessment: 24 weeks post-treatment	A vs. B SVR, 12 weeks post-treatment: 91% (72/79) vs. 99% (78/79) SVR, 24 weeks post-treatment: 89% (70/79) vs. 96% (76/79)	A vs. B Genotype 1a + treatment naive: 83% (43/52) vs. 94% (51/54) Genotype 1b + treatment naive: 100% (25/25) vs. 100% (25/25)	A vs. B Black: 100% (13/13) vs. 100% (13/13) Non-black: 86% (57/66) vs. 96% (63/66)
Kumada 2017 (Part 2 only)[152] Japan *Good*	Elbasvir 50 mg + grazoprevir 100 mg	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	SVR: 97% (219/227)	Genotype 1a: 100% (4/4) Genotype 1b: 96% (215/223)	<65 years: 99% (122/123) 65-74 years: 93% (70/75) ≥75 years: 93% (27/29) Male: 98% (85/87) Female: 96% (134/140) Treatment-naïve: 97% (144/149) Treatment-experienced: 96% (75/78)

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Kumada 2015[151] GIFT-1 (Substudy 1) Japan *Fair*	A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg (double-blind treatment) B. Placebo for 12 weeks, followed by ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg (open-label treatment)	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	A vs. B SVR: 95% (204/215) vs. 98% (104/106)	A vs. B Genotype 1b: 95% (204/215) vs. 98% (104/106)	A vs. B Treatment-naïve: 94.2% (131/139) vs. 98/5% (67/68) Treatment-experienced: 96.1% (73/76) vs. 97.4% (37/38)
Kwo 2016[153] OPTIMIST-1 Canada, U.S. *Fair*	Simeprevir 150 mg + sofosbuvir 400 mg	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	SVR: 97% (150/155)	Genotype 1a: 97% (112/116) Genotype 1b: 97% (38/39)	Treatment-naïve: 97% (112/115) Treatment experienced: 95% (38/40)
Lalezari 2015[192] U.S. *Fair*	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + ribavirin 1000-1200 mg	Treatment duration: 12 weeks Timing of assessment: 12 and 24 weeks post treatment	SVR, 12 weeks: 97.4% (37/38) SVR, 24 weeks: 97.4% (37/38)	Genotype 1, 12 weeks: 97.4% (37/38) Genotype 1, 24 weeks: 97.4% (37/38)	NR
Lawitz 2014a[154] COSMOS U.S. *Fair*	A. Simeprevir 150 mg + sofosbuvir 400 mg B. Simeprevir 150 mg + sofosbuvir 400 mg + ribavirin	Treatment duration: 12 weeks Timing of assessment: 12 weeks post treatment	SVR: 92.9% (13/14) vs. 96% (26/27)	Genotype 1: 92.9% (13/14) vs. 96% (26/27)	Treatment-naïve: (4/4) vs. (5/6)

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Lawitz 2014b[193] LONESTAR (Cohort A) U.S. *Fair*	A. Ledipasvir 90 mg + sofosbuvir 400 mg, 8 weeks B. Ledipasvir 90 mg + sofosbuvir 400 mg, 12 weeks C. Ledipasvir 90 mg + sofosbuvir 400 mg + ribavirin	Treatment duration: 8 and 12 weeks Timing of assessment: 12 weeks post treatment	A vs. C 8-week intervention group SVR: 95% (19/20) vs. 100% (21/21) B 12-week intervention group SVR: 95% (18/19)	A vs. C 8-week intervention group Genotype 1: 95% (19/20) vs. 100% (21/21) B 12-week intervention group Genotype 1: 95% (18/19)	NR
Lawitz 2015[155] PEARL-1 France, Hungary, Italy, Poland, Puerto Rico, Romania, Spain, Turkey, U.S. *Fair*	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	SVR: 92.7% (76/82)	Genotype 1b: 92.7% (76/82)	Treatment-naïve: 95.2% (40/42) Treatment-experienced: 90.0% (36/40)
Lim 2016[156] Korea *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg	Treatment duration: 12 weeks Timing of assessments: 12 weeks post treatment	SVR: 100% (46/46)	Genotype 1: 100% (46/46)	Age <65 years: 100% (33/33) Age ≥65 years: 10% (13/13)
Nelson 2015[157] ALLY-3 U.S. *Fair*	Daclatasvir 60 mg + sofosbuvir 400 mg	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	SVR: 90% (91/101)	Genotype 3: 90% (91/101)	Age <65 years: 90% (128/142)† Age ≥65 years: 70% (7/10)† Male gender: 86% (77/90)† Female gender: 94% (58/62)† F0-F3: 95% (72/76) F4: 73% (16/22) Treatment-naïve: 97% (73/75) Treatment-experienced: 94% (32/34)

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Pianko 2015[158] Australia, New Zealand, U.S. *Fair*	A. Sofosbuvir 400 mg + velpatasvir 100 mg (Group 3) B. Sofosbuvir 400 mg + velpatasvir 100 mg + ribavirin (Group 4)	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	A vs. B SVR: 100% (27/27) vs. 100% (26/26)	A vs. B Genotype 3: 100% (27/27) vs. 100% (26/26)	NR
Poordad 2017[194] MAGELLAN-1 U.S. *Fair*	A. Glecapravir 200 mg + pibrentasvir 80 mg B. Glecapravir 200 mg + pibrentasvir 120 mg C. Glecapravir 200 mg + pibrentasvir 120 mg + ribavirin	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	A vs. B vs. C SVR: 100% (6/6) vs. 86% (19/22) vs. 95% (21/22)	A vs. B vs. C Genotype 1: 100% (6/6) vs. 86% (19/22) vs. 95% (21/22)	NR
Pott-Junior 2019 (Group A - daclatasvir/ sofosbuvir arm)[159] Brazil *Good*	Daclatasvir 60 mg + sofosbuvir 400 mg	Treatment duration: 12 weeks Timing of assessments: 12 weeks post-treatment	SVR: 100% (65/65)	Genotype 1a: 100% (27/27) Genotype 1b: 100% (35/35)	Treatment-naïve: 100% (39/39) Treatment-experienced: 100% (26/26)
Pott-Junior 2019 (Group B - simeprevir/ sofosbuvir arm)[159] Brazil *Good*	Simeprevir 150 mg + sofosbuvir 400 mg	See Pott-Junior 2019 Group A	SVR: 93% (56/60)	Genotype 1a: 90% (28/31) Genotype 1b: 96% (27/28)	Treatment-naïve: 97% (35/36) Treatment-experienced: 88% (21/24)
Sperl 2016[198] and Ng 2018[138] C-EDGE Head-2-Head (elbasvir/grazoprevir arm only) Multinational (Europe, Turkey) *Fair*	Elbasvir 50 mg + grazoprevir 100 mg	Treatment duration: 12 weeks Timing of assessments: 12 weeks post-treatment	SVR: 99% (128/129)	Genotype 1a: 100% (18/18) Genotype 1b: 99% (104/105) Genotype 4: 100% (6/6)	Male: 100% (55/55) Female: 99% (73/74) Age ≤40 years: 100% (37/37) Age 41 to 50 years: 100% (31/31) Age 51 to 60 years: 98% (40/41) Age 61 to 70 years: 100% (20/20) No cirrhosis: 99% (106/107) Cirrhosis: 100% (22/22) Treatment-naive: 99% (99/100) Treatment-experienced: 100% (29/29)

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Sulkowski 2014[161] A1444040 Study U.S. *Fair*	A. Sofosbuvir 400 mg + daclatasvir 60 mg B. Sofosbuvir 400 mg + daclatasvir 60 mg + ribavirin	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	A vs. B SVR: 100% (41/41) vs. 95% (39/41)	NR	NR
Sulkowski 2015[160] C-WORTHY Australia, Canada, Denmark France, Hungary, Israel, New Zealand, Puerto Rico, Spain, Sweden, Turkey, U.S. *Fair*	A. Grazoprevir 100 mg + elbasvir 50 mg B. Grazoprevir 100 mg + elbasvir 50 mg + ribavirin	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	A vs. B SVR: 98% (43/44) vs. 93% (79/85)	A vs. B Genotype 1: 98% (43/44) vs. 93% (79/85)	NR
Toyoda 2018[199] CERTAIN-2 (Arm A only) Japan *Fair*	Glecaprevir 300 mg + pibrentasvir 120 mg	Treatment duration: 8 weeks Timing of assessments: 12 weeks post-treatment	SVR: 98% (88/90)	Genotype 2: 98% (88/90)	NR
Waked 2016[162] AGATE-II Egypt *Good*	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + 1000 to 1200 mg ribavirin	Treatment duration: 12 weeks Timing of assessment: 12 weeks post-treatment	SVR: 94% (94/100)	Genotype 4: 94% (94/100)	NR
Wei 2018[163] China *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg +	Treatment duration: 12 weeks Timing of assessments: 12 weeks post-treatment	SVR: 100% (206/206)	Genotype 1: 100% (206/206)	Treatment-naïve: 100% (106/106) Treatment-experienced: 100% (100/100)

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Wei 2019a[164] C-CORAL (Genotype 1 and 4 only) Multinational (Australia, China, Korea, Russia, Taiwan, Thailand, Vietnam) *Good*	A. Elbasvir 50 mg + grazoprevir 100 mg (n=326) B. Placebo (n=123; harms assessment only)	Treatment duration: 12 weeks Timing of assessments: 12 weeks post-treatment	SVR-12: 94% (459/486) SVR-24: 94% (458/486)	SVR-12 Genotype 1a: 92% (34/37) Genotype 1b: 98% (382/389) Genotype 1-other: 100% (6/6) Genotype 4: 100% (3/3) SVR-24 Genotype 1a: 92% (34/37) Genotype 1b: 98% (381/389) Genotype 1-other: 100% (6/6) Genotype 4: 100% (3/3)	SVR-12 Male: 96% (207/216) Female: 93% (252/270) Asian: 93% (325/350) White: 99% (133/135) Other: 1005 (1/1) Hispanic/Latino: 100% (5/5) Non-Hispanic/Latino: 94% (454/481) Age <65 years: 95% (420/444) Age ≥65 years: 93% (39/42) No cirrhosis: 95% (375/396) Cirrhosis: 93% (84/90) SVR-24 Male: 95% (206/216) Female: 93% (252/270) Asian: 93% (324/350) White: 99% (133/135) Other: 1005 (1/1) Hispanic/Latino: 100% (5/5) Non-Hispanic/Latino: 94% (453/481) Age <65 years: 95% (420/444) Age ≥65 years: 91% (38/42) No cirrhosis: 95% (375/396) Cirrhosis: 93% (84/90)
Wei 2019b[165] Multinational (China, Malaysia, Singapore, Thailand, Vietnam) *Fair*	Sofosbuvir 400 mg + velpatasvir 100 mg	Treatment duration: 12 weeks Timing of assessments: 12 weeks post-treatment	SVR: 97% (362/375)	Genotype 1a: 100% (22/22) Genotype 1b: 100% (107/107) Genotype 2: 100% (64/64) Genotype 3a and unconfirmed subtype: 95% (40/42) Genotype 3b: 76% (32/42) Genotype 6: 99% (97/98)	Male: 94% (186/197) Female: 99% (176/178) Age <65 years: 96% (340/353) Age ≥65 years: 100% (22/22) No cirrhosis: 98% (302/308) Cirrhosis: 90% (60/67) Treatment-naive: 97% (297/307) Treatment-experienced: 96% (65/68)

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Zeuzem 2015[166] C-EDGE Multinational (Australia, Czech Republic, France, Germany, Israel, Puerto Rico, South Korea, Taiwan, U.S.) *Good*	Grazoprevir 100 mg + elbasvir 50 mg	Treatment duration: 12 weeks Timing of assessments: 14 weeks post treatment	*Patients without cirrhosis only* SVR: 94% (231/246)	Genotype 1a: 92% (144/157) Genotype 1b: 98% (129/131) Genotype 4: 100% (18/18)	NR
Zeuzem 2018[167] ENDURANCE-1 Multinational (Australia, Austria, Belgium, Canada, Chile, France, Germany, Hungary, Israel, Italy, Lithuania, Mexico, New Zealand, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Spain, South Korea, Sweden, Switzerland, Taiwan, U.K., U.S.) *Fair*	Glecaprevir 300 mg + pibrentasvir 120 mg	Treatment duration: 8 weeks Timing of assessments: 12 and 24 weeks post-treatment	8-week intervention group SVR-12 (includes n=15 with HIV coinfection and n=1 with prior sofosbuvir treatment): 99% (348/351) SVR-12 (excluding HIV positive patients and those with prior sofosbuvir treatment): 99% (332/335) SVR-24: 98% (343/351) 12-week intervention group SVR-12 (includes n=18 with HIV co-infection and n=2 with prior sofosbuvir treatment): 99.7% (351/352) SVR-12 (excluding HIV positive patients and those with prior sofosbuvir treatment): 99.7% (331/332) SVR-24: 98% (345/352)	8-week intervention group Genotype 1a: 98% (150/153) Other genotype 1: 100% (198/198) 12-week intervention group Genotype 1a: 99% (148/149)Other genotype 1: 100% (203/203)	8-week intervention group Male: 99% (165/167) Female: 99% (183/184) Black race: 100% (14/14) Other race: 99% (334/337) Age <65 years: 99% (306/309) Age ≥65 years: 100% (42/42) Treatment-naive: 99% (217/219) Treatment-experienced: 99% (131/132) People who inject drugs (recent or history): 98% (96/98) Not people who inject drugs: 99.6% (252/253) No current opioid substitution therapy: 99% (336/339) Current opioid substitution therapy: 100% (12/12) 12-week intervention group Male: 100% (176/176) Female: 99% (175/176) Black race: 92% (12/13) Other race: 100% (339/339) Age <65 years: 99.7% (316/317) Age ≥65 years: 100% (35/35) Treatment-naive: 99.5% (216/217) Treatment-experienced: 100% (135/135) People who inject drugs (recent or history): 100% (97/97) Not people who inject drugs: 99.7% (254/255) No current opioid substitution therapy: 100% (336/336) Current opioid substitution therapy: 94% (15/16)

Appendix B Table 11. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Sustained Virologic Response Outcomes

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Treatment Duration and Assessments	Overall SVR Results	Genotype SVR Results	Other Subgroup SVR Results
Zeuzem 2018[167] ENDURANCE-3 (same publication as ENDURANCE-1) *Fair*	A. Glecaprevir 300 mg + pibrentasvir 120 mg, 8 weeks B. Glecaprevir 300 mg + pibrentasvir 120 mg, 12 weeks 3. Sofosbuvir 400 mg + daclatasvir 60 mg. 12 weeks	Treatment duration: 8 to 12 weeks Timing of assessments: 12 and 24 weeks post-treatment	A vs. B vs. C SVR-12: 95% (149/157) vs. 95% (222/233) vs. 97% (111/115) SVR-24: 91% (143/157) vs. 92% (214/233) vs. 96% (110/115)	Genotype 3a: 95% (148/156) vs. 96% (220/230) vs. 97% (111/115) Other genotype 3: 100% (1/1) vs. 67% (2/3) vs. NA	Male: 93% (86/92) vs. 93% (112/121) vs. 92% (48/52) Female: 97% (63/65) vs. 98% (110/112) vs. 100% (63/63) Black race: 100% (3/3) vs. 100% (4/4) vs. 75% (3/4) Not Black race: 95% (146/154) vs. (218/229) vs. 97% (108/111) Age <65 years: 95% (144/152) vs. 95% (213/224) vs. 96% (107/111) Age ≥65 years: 100% (5/5) vs. 100% (9/9) vs. 100% (4/4) People who inject drugs (recent or history): 94% (98/104) vs. 93% (139/149) vs. 96% (70/73) Not people who inject drugs: 96% (51/53) vs. 99% (83/84) vs. 98% (41/42) No current opioid substitution therapy: 94% (119/126) vs. 96% (188/195) vs. 96% (94/98) Current opioid substitution therapy: 97% (30/31) vs. 90% (34/38) vs. 100% (17/17)

*Excluding patients who withdrew or were lost to follow up.
†Based on total study population (treatment naïve and experienced combined).
Abbreviations: IFN = interferon; IVDU = injection drug use; NR = not reported; SVR = sustained virologic response; U.K. = United Kingdom; U.S. = United States. Study names are not acronyms.

Appendix B Table 12. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Clinical Outcomes and Adverse Events

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Abergel 2016a[142] France *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg	Mortality: 0% (0/21)	*Entire study cohort (n=44; 23% cirrhosis)* Any adverse event: 71% (31/44) Serious adverse events: 0% Withdrawal due to adverse events: 0% Headache: 25% (11/44) Fatigue: 20% (9/44) Nausea: 9% (4/44) Diarrhea: 9% (4/44) Hemoglobin 10.0 to 10.9 g/dL: 2% (1/44) ALT >1.25-2.50x ULN: 2% (1/44) Bilirubin >1.0-1.5x ULN: 5% (2/44)	Gilead
Abergel 2016b[141] France *Good*	Ledipasvir 90 mg + sofosbuvir 400 mg	Mortality: 0% (0/22)	*Entire study cohort (n=41; 22% cirrhosis)* Any adverse event: 80% (33/41) Serious adverse events: 2% (1/41; worsening depression) Withdrawal due to adverse events: 0% Headache: 27% (11/41) Fatigue: 10% (4/41) Diarrhea: 7% (3/41) Hemoglobin 100-109 g/dL: 2% (1/41) Bilirubin >1.0-1.5 ULN: 10% (4/41)	Gilead

Appendix B Table 12. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Clinical Outcomes and Adverse Events

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Afdhal 2014[185] ION-1 U.S. and Europe *Fair*	A. Ledipasvir 90 mg + sofosbuvir 400 mg B. Ledipasvir 90 mg + sofosbuvir 400 mg + ribavirin	NR	A vs. B 12-week intervention group Any adverse event: 79% (169/214) vs. 85% (185/217) Serious adverse event*: 0.5% (1/214) vs. 3% (7/217) Withdrawal due to adverse events: 0% vs. 0% Headache: 25% (53/214) vs. 23% (49/217) Fatigue: 21% (44/214) vs. 36% (79/217) Nausea: 11% (24/214) vs. 17% (37/217) Diarrhea: 11% (24/214) vs. 8% (18/217) Insomnia: 8% (17/214) vs. 21% (45/217) Anemia: 0% vs. 12% (25/217) Rash: 7% (16/214) vs. 10% (21/217) 24-week intervention group Any adverse event: 82% (178/217) vs. 92% (200/217) Serious adverse event*: 8% (8% (18/217) vs. 3% (7/217) Withdrawal due to adverse events: 2% (4/217) vs. 3% (6/217) Headache: 24% (54/217) vs. 30% (65/217) Fatigue: 24% (24% (53/217) vs. 38% (82/217) Nausea: 13% (29/217) vs. 15% (32/217) Diarrhea: 11% (24/217) vs. 6% (14/217) Insomnia: 12% (26/217) vs. 22% (47/217) Anemia: 0% vs. 10% (22/217) Rash: 7% (16/217) vs. 12% (25/217)	Gilead
Ahmed 2018[195] Egypt *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg	NR	Any adverse event: 26% (26/100) Headache: 2% (2/100) Fatigue: 18% (18/100) Nausea: 2% (2/100) Diarrhea: 1% (1/100) Insomnia: 2% (2/100)	NR
Andreone 2014[186] PEARL-II Austria, Belgium, Italy, The Netherlands, Portugal, Puerto Rico, Sweden, Switzerland, U.S. *Fair*	A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day B. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + ribavirin	NR	A vs. B Any adverse event: 77.9% (74/95) vs. 79% (72/91) Withdrawals due to adverse events: 0% (0/95) vs. 2% (2/91) Serious adverse events (Pancreatitis, cellulitis, nephrolithiasis, osteoarthritis): 2% (2/95) vs. 2% (2/91) Headache: 23.3% (22/95) vs. 24.2% (22/91) Fatigue: 15.8% (15/95) vs. 31.9% (29/91) Nausea: 6.3% (6/95) vs. 20.9% (19/91) Diarrhea: 12.6% (12/95) vs. 13.2 (12/91) Anemia: 0% (0/95) vs. 11% (10/91) Rash: 1% (1/95) vs. 9% (8/91)	AbbVie

Appendix B Table 12. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Clinical Outcomes and Adverse Events

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Asselah 2018[196] SURVEYOR II Part 4, Multinational (Asia, Europe, U.S. [specific countries NR]) *Fair*	Glecaprevir 300 mg + pibrentasvir 120 mg	NR	Any adverse event: 63% (128/203) Serious adverse events (cholecystitis, urosepsis): 1% (2/203) Withdrawal due to adverse events: 0% (0/203) Headache: 18% (37/203) Fatigue: 14% (28/203) Nausea: 11% (23/203)	AbbVie
Asselah 2019[143] ENDURANCE-5 Multinational (Australia, Belgium, Canada, France, New Zealand, Singapore, South Africa, Vietnam, U.S.) *Fair*	Glecaprevir 300 mg + pibrentasvir 120 mg	Mortality: 0% (0/23)	*Total population (n=84, genotype 5 and 6 combined)* Any adverse event: 55% (46/84) Serious adverse events (gastric ulcer, pyelonephritis, giardiasis and depression, pulmonary tuberculosis, viral infection): 6% (5/84) Withdrawal due to Adverse events: 0% (0/84) Headache: 13% (11/84) Fatigue:13% (11/84)	AbbVie
Asselah 2019[143] ENDURANCE-6 (same publication as ENDURANCE-5) *Fair*	See Asselah 2019 ENDURANCE-5	Mortality: 0% (0/61)	See Asselah 2019 ENDURANCE-5	See Asselah 2019 ENDURANCE-5
Brown 2018[144] C-SCAPE (Genotype 4 only) Multinational (Australia, Belgium, France, Israel, Spain, U.K., U.S.) *Fair*	A. Elbasvir 50 mg + grazoprevir 100 mg (n=10) B. Elbasvir 50 mg + grazoprevir 100 mg + ribavirin (n=10)	Mortality: 0% (0/20)	*Total population (genotypes 2, 4, 5, 6)* Any adverse event: 79% (15/19) vs. 95% (18/19) Serious adverse events: 0% (0/19) vs. 0% (0/19) Withdrawal due to adverse events: 5% (1/19) vs. 0% (0/19) Headache: 26% (5/19) vs. 32% (6/19) Fatigue: 16% (3/19) vs. 26% (5/19) Nausea: 5% (1/19) vs. 11% (2/19) Asthenia: 21% (4/19) vs. 16% (3/19)	Merck
Chayama 2018[197] CERTAIN-1 (Arm A only) Japan *Fair*	Glecaprevir 300 mg + pibrentasvir 120 mg	NR	Any adverse event: 57% (74/129) Serious adverse events: 0% (0/129) Withdrawal due to adverse events: 0% (0/129) Headache: 5% (6/129) Rash: 2% (3/129)	AbbVie
Chuang 2016[145] Taiwan *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg	*Total population (treatment-naïve and treatment-experienced)* Mortality: 0% (0/85)	*Total population (treatment-naïve and treatment-experienced)* Any adverse event: 60% (51/60) Withdrawals due to adverse events: 1% (1/85) Headache: 14% (12/85) Fatigue: 9% (8/85) Nausea: 6% (5/85)	Gilead

Appendix B Table 12. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Clinical Outcomes and Adverse Events

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Dore 2016[137] MALACHITE-1 Australia, Canada, Europe, South America *Good*	<u>Genotype 1a</u> A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + weight-based ribavirin B. Telaprevir 750 mg 3x/day + subcutaneous pegylated IFN 180 ug 1/week + weight-based ribavirin <u>Genotype 1b</u> C. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + weight-based ribavirin D. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day E. Telaprevir 750 mg 3x/day + subcutaneous pegylated IFN 180 ug 1/week + weight-based ribavirin	<u>Genotype 1a</u> A vs. B SF-36 mental component score, mean change from baseline at 12 weeks post-treatment: -1.1 (SD 12) vs. -2.1 (SD 10.1) SF-36 physical component score, mean change from baseline at 12 weeks post-treatment: 3.1 (SD 8.7) vs. 0.7 (SD 7.6) <u>Genotype 1b</u> C vs. D vs. E SF-36 mental component score, mean change from baseline at 12 weeks post-treatment: 1.9 (SD 9.6) vs. 1.4 (SD 8.1) vs. -0.3 (SD 10.3) SF-36 physical component score, mean change from baseline at 12 weeks post-treatment: 2.3 (SD 5.3) vs. 2.5 (SD 5.7) vs. 1.0 (SD 8.4)	(A + C [with ribavirin]) vs. D (without ribavirin) vs. (B + E [telaprevir]) Any adverse event: 75% (115/153) vs. 49% (41/83) vs. 99% (74/75); (A+C) vs. (B+E): RR 0.76 (95% CI, 0.69 to 0.84); D vs. (B+E): RR 0.50 (95% CI, 0.40 to 0.62) Withdrawals due to adverse events: 1% (1/153) vs. 0% (0/83) vs. 8% (6/75); (A+C) vs. (B+E): RR 0.08 (95% CI, 0.01 to 0.67) Serious adverse events (one each: prostate cancer, overdose, anemia, cough, chest pain, hematochezia, retinopathy, toxic skin eruption, cellulitis): 1% (1/153) vs. 0% (0/83) vs. 12% (9/75); (A+C) vs. (B+E): RR 0.05 (95% CI, 0.007 to 0.42); D vs. (B+E): RR 0.05 (95% CI, 0.003 to 0.80) Headache: 27% (41/153) vs. 19% (16/83) vs. 31% (23/75); (A+C) vs. (B+E): RR 0.87 (95% CI, 0.57 to 1.34); D vs. (B+E): RR 0.63 (95% CI, 0.36 to 1.10) Fatigue: 14% (21/153) vs. 5% (4/83) vs. 31% (23/75); (A+C) vs. (B+E): RR 0.45, (95% CI, 0.27 to 0.76); D vs. (B +E): RR 0.16 (95% CI, 0.06 to 0.43) Nausea: 21% (32/153) vs. 8% (7/83) vs. 40% (30/75); (A+C) vs. (B+E): RR 0.52 (95% CI, 0.35 to 0.79); D vs. (B+E): RR 0.21 (95% CI, 0.10 to 0.45) Anemia: 7% (10/153) vs. 1% (1/83) vs. 45% (34/75); (A+C) vs. (B+E): RR 0.14 (95% CI, 0.08 to 0.28); D vs. (B+E): RR 0.03 (95% CI, 0.004 to 0.19) Rash: 8% (12/153) vs. 0% vs. 23% (17/75); (A+C) vs. (B+E): RR 0.37 (95% CI, 0.19 to 0.73); D vs. (B+E): RR 0.03 (95% CI, 0.00 to 0.42)	AbbVie

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Dore 2016[137] MALACHITE-2 Australia, Canada, Europe, South America *Good*	A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + weight-based ribavirin B. Telaprevir 750 mg 3x/day + subcutaneous pegylated IFN 180 ug 1/week + weight-based ribavirin	A vs. B SF-36 mental component score, mean change from baseline at 12 weeks post-treatment: 0.8 (SD 8.0) vs. -1.5 (SD 7.5) SF-36 physical component score, mean change from baseline at 12 weeks post-treatment: 3.0 (SD 6.4) vs. -1.3 (5.3)	A vs. B Any adverse event: 62% (63/101) vs. 91% (43/47); RR 0.68 (95% CI, 0.57 to 0.81) Serious adverse events (epilepsy, anemia [2 people], abdominal pain, infectious diarrhea, staphylococcal : 1% (1/101) vs. 5% (11/47); RR 0.04 (95% CI, 0.006 to 0.32) Withdrawal due to adverse events: 0% (0/101) vs. 11% (5/47); RR 0.04 (95% CI, 0.002 to 0.76) Headache: 29% (29/101) vs. 45% (21/47); RR 0.64 (95% CI, 0.41 to 1.00) Fatigue: 12% (12/101) vs. 26% (12/47); RR 0.47 (95% CI, 0.23 to 0.96) Nausea: 10% (10/101) vs. 43% (20/47); RR 0.23 (95% CI, 0.12 to 0.46) Insomnia: 6% (6/101) vs. 21% (10/47); RR 0.28 (95% CI, 0.11 to 0.72) Anemia: 3% (3/101) vs. 34% (16/47); RR 0.09 (95% CI, 0.03 to 0.28) Rash: 3% (3/101) vs. 17% (8/47); RR 0.06 (95% CI, 0.02 to 0.21)	AbbVie
Everson 2015 (Part A)[146] U.S. *Good*	<u>Part A (trial phase)</u> A. Sofosbuvir 400 mg + velpatasvir 25 mg (Genotype 1) B. Sofosbuvir 400 mg + velpatasvir 100 mg (Genotype 1) C. Sofosbuvir 400 mg + velpatasvir 25 mg (Genotype 3) D. Sofosbuvir 400 mg + velpatasvir 100 mg (Genotype 3) E. Sofosbuvir 400 mg + velpatasvir 25 mg (Genotype 2; 4-6) F. Sofosbuvir 400 mg + velpatasvir 100 mg (Genotype 2; 4-6)	A vs. B vs. C vs. D vs. E vs. F Mortality: 0% (0/27) vs. 0% (0/28) vs. 0% (0/27) vs. 0% (0/27) vs. 4% (1/23) vs. 0% (0/22)	(A + C + E) vs. (B + D + F) Any adverse event: 68% (52/77) vs. 70% (54/77) Withdrawal due to adverse events: 0% (0/77) vs. 0% (0/77) Serious adverse events (not described): 3% (2/77) vs. 1% (1/77) Headache: 21% (16/77) vs. 18% (14/77) Fatigue: 25% (19/77) vs. 18% (14/77) Nausea: 13% (10/77) vs. 10% (8/77) Diarrhea: 6% (5/77) vs. 9% (7/77) Constipation: 12% (9/77 vs. 8% (6/77) Insomnia: 4% (3/77) vs. 6% (5/77) Hemoglobin <100g/L: 0% vs. 0% Bilirubin >2.5x ULN: 0% vs. 0% Rash: 5% (4/77) vs. 5% (4/77)	Gilead

Appendix B Table 12. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Clinical Outcomes and Adverse Events

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Feld 2014[187] SAPPHIRE-1 Australia, New Zealand; Austria, France, Germany, Hungary, Great Britain, Italy, Spain, Sweden, Switzerland; Canada, U.S. *Good*	A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x day + weight-based ribavirin B. Placebo for 12 weeks followed by open-label ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x day + weight-based ribavirin	NR	A vs. B Any adverse event: 86% (414/473) vs. 73% (116/158); RR 1.19 (95% CI, 1.08 to 1.32) Withdrawal due to adverse event: 0.6% (3/473) vs. 0.6% (1/158); RR 1.00 (95% CI, 0.10 to 9.56) Serious adverse events (appendicitis, lobar pneumonia, cholecystitis, lumbar vertebral fracture in one patient each; aortic stenosis and postoperative wound infection in one; overdose and encephalopathy in one; mediastinal mass and non–small-cell lung cancer in one; acute respiratory failure and hypoxemia in one; abdominal pain, sinus tachycardia, diarrhea, chills, vomiting, nausea, and ventricular extrasystoles in one; and anemia and noncardiac chest pain in one): 2% (10/473) vs. 0%; RR 7.04 (95% CI, 0.42 to 120) Diarrhea: 14% (65/473) vs. 7% (11/158); RR 1.97 (95% CI, 1.07 to 3.64) Fatigue: 35% (164/473) vs. 29% (45/158); RR 1.22 (95% CI, 0.92 to 1.60) Headache: 33% (156/473) vs. 27% (42/158); RR 1.24 (95% CI, 0.93 to 1.66) Nausea: 24% (112/473) vs. 13% (21/158); RR 1.78 (95% CI, 1.16 to 2.74) Insomnia: 14% (66/473) vs. 8% (12/158); RR 1.84 (95% CI, 1.02 to 3.31) Grade 3 or 4 hemoglobin: 0% vs. 0% Rash: 11% (51/473) vs. 6% (9/158); RR 1.89 (95% CI, 0.95 to 3.76)	AbbVie
Feld 2015[139] ASTRAL-1 U.S., Canada, Europe, Hong Kong *Good*	A. Sofosbuvir 400 mg + velpatasvir 100 mg B. Placebo	A vs. B Mortality: 0.2% (1/624) vs. 0% (0/116) Mean change from baseline in patient-reported outcomes (composite SF-36, FACIT-F, CLDQ-HCV, WPAI:SHP; scale 0 to 100), 24-weeks post-treatment: 5.4; p<0.05 for all individual components except WPAI:SHP work productivity and WPAI:SHP absenteeism	A vs. B Any adverse event: 78% (485/624) vs. 77% (89/116); RR 1.01, 95% CI, 0.91 to 1.13 Serious adverse events (19 events in 15 patients: abscess limb, acute myocardial infarction, appendicitis, bronchitis, cellulitis, chronic obstructive pulmonary disease, epilepsy, extremity necrosis, gastroenteritis, influenza, ligament sprain, lung cancer, mania, palpitations, rotatorcuff syndrome, small intestinal obstruction, sudden death from unknown cause, upper limb fracture, and vestibular neuronitis): 2% (15/624) vs. 0% (0/116); RR 5.80, 95% CI, 0.35 to 96 Withdrawals due to adverse events: 0.2% (1/624) vs. 2% (2/116); RR 0.09 (95% CI, 0.01 to 1.02) Headache: 29% (182/624) vs. 28% (33/116); RR 1.03 (95% CI, 0.75 to 1.40) Fatigue: 20% (126/624) vs. 20% (23/116); RR 1.02 (95% CI, 0.68 to 1.52) Nausea: 12% (75/624) vs. 11% (13/116) Diarrhea: 8% (48/624) vs. 7% (8/116); RR 1.12 (95% CI, 0.54 to 2.30) Insomnia: 8% (50/624) vs. 9% (11/116); RR 0.84 (95% CI, 0.45 to 1.57) Hemoglobin <10 g/dL: 0.4% (2/624) vs. 0% (0/116); RR 2.21 (95% CI, 0.11 to 46)	Gilead

Appendix B Table 12. Key Questions 6–8: Direct Acting Antiviral Therapy in Adults – Clinical Outcomes and Adverse Events

Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Ferenci 2014[188] PEARL III Austria, Belgium, Hungary, Israel, Italy, Poland, Portugal, Romania, Russia, Spain, U.S. *Good* *Same publication as PEARL IV*	A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day B. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + ribavirin	NR	A vs. B Any adverse event: 67.0% (140/209) vs. 80% (168/210) Serious adverse events (coronary artery disease, atrial fibrillation, nephrolithiasis, epididymitis, arthritis, breast lesion, uterine polyp, myalgia): 2% (4/209) vs. 2% (4/210) Withdrawal due to adverse events: none Headache: 23% (49/209) vs. 24% (51/210) Fatigue: 23% (48/209) vs. 21% (45/210) Nausea: 4% (9/209) vs. 23% (11/210) Diarrhea: 6% (13/209) vs. 4% (9/210) Rash: 3% (8/209) vs. 6% (12/210)	AbbVie
Ferenci 2014[188] PEARL IV Canada, U.K., U.S. *Good* *Same publication as PEARL III*	A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day B. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + ribavirin	NR	Any adverse event: 82% (169/205) vs. 92.0% (92/100) Serious adverse events (pancreatitis, anemia, intestinal obstruction, diverticulitis): 0.5% (1/205) vs. 3.0% (3/100) Withdrawal due to adverse events: none Headache: 28% (58/205) vs. 25.0% (25/100) Fatigue: 35% (72/205) vs. 46.0% (46/100) Nausea: 14% (28/205) vs. 21.0% (21/100) Diarrhea: 16.1% (33/205) vs. 14.0% (14/100) Rash: 5% (10/205) vs. 5% (5/100)	AbbVie
Foster 2015[147] ASTRAL-2 U.S. *Fair*	A. Sofosbuvir 400 mg + velpatasvir 100 mg B. Sofosbuvir 400 mg + ribavirin	A vs. B Mortality: 1% (2/134) vs. 0% (0/132)	A vs. B Any adverse event: 69% (92/134) vs. 77% (101/132) Serious adverse events (pneumonia, enteritis, abdominal pain, arthralgia, depression): 1% (2/134) vs. 2% (2/132) Withdrawals due to adverse events: 1% (1/134) vs. 0% (0/132) Dyspepsia: 1% (1/134) vs. 4% (5/132) Headache: 18% (24/134) vs. 22% (29/132) Fatigue: 15% (20/134) vs. 35% (47/132) Nausea: 10% (14/134) vs. 14% (19/132) Grade 3 or 4 bilirubin elevation: 0% (0/134) vs. 0% (0/132) Insomnia: 4% (6/134) vs. 14% (18/132	Gilead

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Foster 2015[147] ASTRAL-3 U.S. *Fair* *Same publication as ASTRAL-2*	Same as Foster 2015 ASTRAL-2	A vs. B Mortality: 0% (0/278) vs. 0.7% (2/280)	A vs. B Any adverse event: 88% (245/277) vs. 95% (260/275) Serious adverse events (myocardial infarction, bursitis, cellulitis, cardiovascular accident, cholecystitis, chronic obstructive pulmonary disease, depression, food poisoning, gunshot wound, hematochezia, overdose, intervertebral disc protrusion, aneurysm, lung infection, ovarian cyst rupture, stenosis, infection, psychotic disorder, rash): 2% (6/277) vs. 5% (15/275) Withdrawal due to adverse events: 0% (0/277) vs. 3% (9/275) Dyspepsia: 3% (9/277) vs. 11% (30/275) Headache: 32% (90/277) vs. 32% (89/275) Fatigue: 26% (71/277) vs. 38% (105/275) Nausea: 17% (46/277) vs. 21% (58/275) Insomnia: 11% (31/277) vs. 27% (74/275)	Gilead
Gane 2015[148] New Zealand (Genotype 6 subset) *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg	Mortality: 0% (0/25)	Any adverse event: 84% (21/25) Serious adverse events (not described): 4% (1/25) Withdrawal due to adverse events: 0% (0/25) Headache: 8% (2/25) Fatigue: 24% (6/25) Nausea: 0% (0/25) Diarrhea: 16% (4/25) Gastroenteritis: 0% (0/25) Vomiting: 0% (0/25) Hemoglobin 7.0 to <9.0 g/dL: 0% (0/25) Total bilirubin >2.5 to 5x ULN: 0% (0/25) ALT elevation >5 to 10x ULN: 4% (1/25) AST elevation >5 to 10x ULN: 4% (1/25) Rash: 8% (2/25)	Gilead
Grebely 2018a[150] SIMPLIFY Multinational (Australia, Canada, New Zealand, Norway, Switzerland, U.K., U.S.) *Fair*	Sofosbuvir 400 mg + velpatasvir 100 mg	Mortality: 4% (4/103)	Any adverse event: 83% (85/103) Serious adverse events (rhabdomyolysis; other serious adverse events NR): 7% (7/103) Withdrawal due to adverse events: 1% (1/103) Headache: 18% (19/103) Fatigue: 22% (23/103) Nausea: 14% (14/103) Vomiting: 4% (4/103) Diarrhea: 4% (4/103) Insomnia: 9% (9/103)	Gilead

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Grebely 2018b[149] D3FEAT Multinational (Australia, Canada, France, New Zealand, Norway, Switzerland) *Fair*	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg + 1000-1200 mg ribavirin	Mortality: 3% (3/87)	Any adverse event: 61% (53/87) Serious adverse events (NR): 6% (5/87) Withdrawal due to adverse events: 0% (0/87) Headache: 5% (12/87) Fatigue: 10% (25/87) Nausea: 8% (20/87) Vomiting: 4% (11/87) Anemia: 5% (12/87) Insomnia: 4% (11/87)	AbbVie
Hezode 2015[189] PEARL I (Treatment-naïve population) France, Hungary, Italy, Poland, Romania, Spain, Turkey, U.S. *Good* *See also Lawitz 2015[155] (PEARL I - Genotype 1b)*	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + ribavirin (weight-based; dose NR)	NR	Any adverse event: 88% (37/42) Serious adverse events: 0% Withdrawal due to adverse events: 0% Headache: 33% (14/42) Fatigue: 12% (5/42) Nausea: 17% (7/42) Diarrhea: 14% (6/42) Insomnia: 10% (4/42) Hemoglobin <100 g/L: 2% (1/42) Total bilirubin, grade 3 elevation: 0% ALT elevation >5x ULN and ≥2x baseline: 0% AST elevation >5x ULN and ≥2x baseline: 0%	AbbVie
Hezode 2015[189] PEARL I (Treatment experienced population) France, Hungary, Italy, Poland, Romania, Spain, Turkey, U.S. *Good* *See also Lawitz 2015[155] (PEARL I - Genotype 1b)*	Same as Hezode 2015 (Treatment naïve population)	NR	Any adverse event: 88% (43/49) Serious adverse events: 0% Withdrawal due to adverse events: 0% Headache: 29% (14/49) Fatigue: 18% (9/49) Nausea: 12% (6/49) Diarrhea: 6% (3/49) Insomnia: 16% (8/49) Hemoglobin <100 g/L: 2% (1/49) Total bilirubin, grade 3 elevation: 6% (3/49) ALT elevation >5x ULN and ≥2x baseline: 0% AST elevation >5x ULN and ≥2x baseline: 0%	AbbVie

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Kowdley 2014a[190] ION-3 U.S. *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg	NR	8-week intervention group Any adverse event: 67% (145/215) Serious adverse events (anaphylaxis, colitis, inadequately controlled diabetes, gastrointestinal hemorrhage, hypertension, pituitary tumor): 2% (4/215) Withdrawal due to adverse events: 0% Headache: 14% (30/215) Fatigue: 21% (45/215) Nausea: 7% (15/215) Diarrhea: 7% (15/215) Insomnia: 5% (11/215) Anemia: 1% (2/215) Rash: 1% (3/215) 12-week intervention group Any adverse event: 69% (149/216) Serious adverse events (abdominal pain, bile duct stone, hemothorax, hypoglycemia, intestinal perforation, mental illness, respiratory failure, rhabdomyolysis, traffic accident, bone injury, lung cancer): 2% (5/216) Withdrawal due to adverse events: 1% (2/216) Headache: 15% (33/216) Fatigue: 23% (49/216) Nausea: 11% (24/216) Diarrhea: 4% (9/216) Insomnia: 7% (15/216) Anemia: 1% (2/216) Rash: 2% (5/216)	Gilead

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Kowdley 2014b[191] AVIATOR Australia, Canada, France, Germany, New Zealand, Puerto Rico, Spain, U.K., U.S. *Good*	A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 150 mg + dasabuvir 800 mg B. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100-150 mg + dasabuvir 800 mg + ribavirin 1000-1200 mg	NR	A vs. B Any adverse event: NR Serious adverse events (affective disorder, animal bite, arthralgia, acute cholecystitis, and facial paresis (occurring in one patient each); increased blood creatinine level and bronchitis occurring in the same patient; the cervicobrachial syndrome, neck pain, and osteoarthritis of the spine occurring in the same patient; lung disorder and pneumonia occurring in the same patient): 3% (2/79) vs. 1% (1/79) Withdrawals due to adverse events: 0% (0/79) vs. 3% (2/79) Headache: 19% (15/79) vs. 27% (21/79) Fatigue: 20% (16/79) vs. 28% (22/79) Nausea: 14% (11/79) vs. 24% (19/79) Diarrhea: 16% (13/79) vs. 13% (10/79) Grade 3 or 4 bilirubin elevation: 0% (0.79) vs. 5% (4/79) Grade 3 or 4 ALT elevation: 0% (0/79) vs. 1% (1/79) Anemia: 1% (1/79) vs. 9% (7/79)	AbbVie
Kumada 2017 (Part 2 only)[152] Japan *Good*	Elbasvir 50 mg + grazoprevir 100 mg	Mortality: 0% (0/227)	Serious adverse events (not described): 5% (11/227) Withdrawal due to adverse events: 1% (3/227) Clinically significant adverse event: 4% (8/227)	Merck
Kumada 2015[151] GIFT-1 (Substudy 1) Japan *Fair*	A. Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg (double-blind treatment) B. Placebo for 12 weeks, followed by ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg (open-label treatment)	A vs. B Mortality: 0% (0/255 vs. 0% (0/106)	A vs. B (placebo-controlled phase only) Any adverse event: 68.8% (148/215) vs. 56.6% (60/106); RR 1.22 (95% CI, 1.01 to 1.47) Serious adverse events (not described): 3.3% (7/215) vs. 1.9% (2/106); RR 1.73 (95% CI, 0.36 to 8.16) Withdrawals due to adverse events: 0.9% (2/215) vs. 0% (0/106); RR 2.48 (95% CI, 0.12 to 51) Headache: 8.8% (19/215) vs. 9.4% (10/106); RR 0.94 (95% CI, 0.45 to 1.94) Nausea: 4.3% (9/215) vs. 3.8% (4/106); RR 1.11 (95% CI, 0.35 to 3.52) Hemoglobin <8g/dL: 0% vs. 0%	AbbVie

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Kwo 2016[153] OPTIMIST-1 Canada, U.S. *Fair*	Simeprevir 150 mg + sofosbuvir 400 mg	Mortality: 0% (0/155) Quality of life, mean change from baseline (among 141/155 with SVR) - -HCV-SIQv4 overall body symptom score -3.9 (SE 0.96) -Fatigue Severity Scale: -0.5 (SE 0.15) -Center for Epidemiologic Studies-Depression Scale: -0.2 (SE 0.73) -EQ-5D VAS: 4.1 (SE 1.4)	Any adverse event: 66% (103/155) Serious adverse events (colitis): 1% (1/155) Withdrawals due to adverse events: 0% (0/155) Nausea: 15% (23/155) Headache: 14% (22/155) Fatigue: 12% (19/155) Increased bilirubin: 1% (1/155) Rash: 6% (10/155)	Janssen
Lalezari 2015[192] U.S. *Fair*	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + dasabuvir 250 mg 2x/day + ribavirin 1000-1200 mg	NR	Any adverse event: 92.1% (35/38) Serious adverse events (cerebrovascular accident, sarcoma, acute myeloid leukemia): 7.9% (3/38) Withdrawal due to adverse events: 2.6% (1/38) Headache: 31.6% (12/38) Fatigue: 47.4% (18/38) Nausea: 50% (19/38) Vomiting: 10.5% (4/38) Insomnia: 18.4% (7/38) Anemia: 10.5% (4/38) Rash: 15.8% (6/38)	AbbVie
Lawitz 2014a[154] COSMOS U.S. *Fair*	A. Simeprevir 150 mg + sofosbuvir 400 mg B. Simeprevir 150 mg + sofosbuvir 400 mg + ribavirin	Mortality: 0% (0/81)	Any adverse event: 79% (11/14) vs. 89% (24/27) Serious adverse events: 0% vs. 0% Withdrawals due to adverse events: 0% vs. 0% Anemia: 0% vs. 0% Rash: 7% (1/14) vs. 22% (6/27)	Janssen

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Lawitz 2014b[193] LONESTAR (Cohort A) U.S. *Fair*	A. Ledipasvir 90 mg + sofosbuvir 400 mg, 8 weeks B. Ledipasvir 90 mg + sofosbuvir 400 mg, 12 weeks C. Ledipasvir 90 mg + sofosbuvir 400 mg + ribavirin	NR	8-week intervention group Any adverse event: 45% (9/20) Serious adverse events: 0% Withdrawal due to adverse events: 0% Headache: 10% (2/20) Nausea: 10% (2/20) Rash: 5% (1/20) 12-week intervention group Any adverse event: 42% (8/19) Serious adverse events (exacerbation of peptic ulcer disease): 5% (1/19) Withdrawal due to adverse events: 0% Headache: 0% Nausea: 5% (1/19) Rash: 0%	Gilead
Lawitz 2015[155] PEARL-1 France, Hungary, Italy, Poland, Puerto Rico, Romania, Spain, Turkey, U.S. *Fair*	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg	Mortality: 0% (0/82)	Any adverse event: 76.8% (63/82) Serious adverse events (unclear; NR according to treatment group): 2.4% (2/82) Severe adverse events: 2.4% (2/82) Withdrawals due to adverse events: 0% (0/82) Asthenia: 6.1% (5/82) Diarrhea: 7.3% (6/82) Dry skin: 8/5% (7/82) Fatigue: 7.2% (6/82) Headache: 29.3% (24/82) Hypertension: 1.2% (1/82) Nausea: 9.8% (8/82) Pruritus: 7.3% (6/82)	AbbVie
Lim 2016[156] Korea *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg	*Includes all patients (n=93, including treatment experienced, 28% cirrhosis)* Mortality: 0% (093)	*Includes all patients (n=93, including treatment experienced, 28% cirrhosis)* Any adverse event: 49% (46/93) Serious adverse event (contact dermatitis, erysipelas, inguinal hernia): 3% (3/93) Withdrawals due to adverse events: (1/93) Headache: 8% (7/93) Fatigue: 6% (6/93)	Gilead
Nelson 2015[157] ALLY-3 U.S. *Fair*	Daclatasvir 60 mg + sofosbuvir 400 mg	Mortality: 0% (0/152)	Any adverse event: NR Serious adverse events (gastrointestinal hemorrhage): 0.7% (1/152) Headache: 20% (30/152) Fatigue: 19% (29/152) Nausea: 12% (18/152) Diarrhea: 9% (13/152) Insomnia: 6% (9/152)	Bristol-Myers Squibb

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Pianko 2015[158] Australia, New Zealand, U.S. *Fair*	A. Sofosbuvir 400 mg + velpatasvir 100 mg (Group 3) B. Sofosbuvir 400 mg + velpatasvir 100 mg + ribavirin (Group 4)	*Includes Genotype 3 patients with cirrhosis and Genotype 1 patients* A vs. B Mortality: 0% (0/80)	*Includes Genotype 3 patients with cirrhosis and Genotype 1 patients (n=80; 41% cirrhosis)* A vs. B Any adverse event: 79% (63/80) vs. 86% (69/80) Serious adverse events (group A only: cholecystitis, suicide, rib fracture, contusion; group B not described): 5% (4/80) vs. 4% (3/80) Withdrawal due to adverse events: 0% (0/80) vs. 0% (0/80) Headache: 23% (18/80) vs. 30% (24/80) Fatigue: 24% (19/80) vs. 34% (27/80) Nausea: 9% (7/80) vs. 23% (18/80) Diarrhea: 11% (9/80) vs. 5% (4/80) Insomnia: 8% (6/80) vs. 20% (16/80) Rash: 3% (2/80) vs. 11% (9/80)	Gilead
Poordad 2017[194] MAGELLAN-1 U.S. *Fair*	A. Glecapravir 200 mg + pibrentasvir 80 mg B. Glecapravir 200 mg + pibrentasvir 120 mg C. Glecapravir 200 mg + pibrentasvir 120 mg + ribavirin	NR	A vs. B vs. C Any adverse event: 83.3% (5/6) vs. 81.8% (18/22) vs. 86.4% (19/22) Serious adverse events (fracture, breast cancer): 16.7% (1/6) vs. 0% vs. 4.5% (1/22) Withdrawal due to adverse events: 0% vs. 0% vs. 0% Headache: 16.7% (1/6) vs. 36.4% (8/22) vs. 22.7% (5/22) Fatigue: 16.7% (1/6) vs. 18.2% (4/22) vs. 36.4% (8/22) Nausea: 16.7% (1/6) vs. 13.6% (3/22) vs. 27.3% (6/22) Insomnia: 0% vs. 0% vs. 27.3% (6/22) ALT >3x ULN: 0% vs. 0% vs. 0% AST >3x ULN: 0% vs. 0% vs. 0% Bilirubin >3x ULN: 0% vs. 0% vs. 0% Hemoglobin <10 g/dL: 0% vs. 0% vs. 0%	AbbVie
Pott-Junior 2019 (Group A - daclatasvir/ sofosbuvir arm)[159] Brazil *Good*	Daclatasvir 60 mg + sofosbuvir 400 mg	Mortality: 0% (0/127)	Headache: 15% (10/65) Fatigue: 23% (15/65) Nausea: 6% (4/65) Vomiting: 2% (1/65) Insomnia: 6% (4/65) Rash: 2% (1/65)	Federal University of São Paulo
Pott-Junior 2019 (Group B - simeprevir/ sofosbuvir arm)[159] Brazil *Good*	Simeprevir 150 mg + sofosbuvir 400 mg	See Pott-Junior 2019 Group A	Headache: 28% (17/60) Fatigue: 28% (17/60) Nausea: 13% (8/60) Vomiting: 5% (3/60) Insomnia: 10% (6/60) Rash: 10% (6/60)	See Pott-Junior 2019 Group A

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Sperl 2016[198] and Ng 2018[138] C-EDGE Head-2-Head (elbasvir/grazoprevir arm only) Multinational (Europe, Turkey) *Fair*	Elbasvir 50 mg + grazoprevir 100 mg	SF-36 physical component score, mean change from baseline: 2.0 SF-36 mental component score, mean change from baseline: 2.0 FACIT-F score, mean change from baseline: 1.75	Any adverse event: 52% (67/129) Serious adverse events (type of adverse event NR): 0.8% (1/129) Withdrawal due to adverse events: 0.8% (1/129)	Merck
Sulkowski 2014[161] A1444040 Study U.S. *Fair*	A. Sofosbuvir 400 mg + daclatasvir 60 mg B. Sofosbuvir 400 mg + daclatasvir 60 mg + ribavirin	Mortality: 0% (0/41)	Any adverse event: 93% (38/41) Serious adverse events (psychiatric disorder): 2% (1/41) Withdrawal due to adverse events: 0% Headache: 34% (14/41) Fatigue: 39% (16/41) Nausea: 20% (8/41) Vomiting: 2% (1/41) Diarrhea: 5% (2/41) Insomnia: 10% (4/41) Grade 3 or 4 lab abnormality: 0%	Bristol-Myers Squibb; Gilead
Sulkowski 2015[160] C-WORTHY Australia, Canada, Denmark France, Hungary, Israel, New Zealand, Puerto Rico, Spain, Sweden, Turkey, U.S. *Fair*	A. Grazoprevir 100 mg + elbasvir 50 mg B. Grazoprevir 100 mg + elbasvir 50 mg + ribavirin	Mortality: 0% (0/44)	Any adverse event: NR; drug-related adverse events 56% (24/43[†]) Serious adverse events: 0% Withdrawal due to adverse events: 0% Headache: 35% (15/43) Fatigue: 23% (10/43) Nausea: 16% (7/43) Diarrhea: 12% (5/43) Hemoglobin <8.5 g/dL: 0% ALT >2.5x baseline value: 0% AST >2.5x baseline value: 0% Bilirubin >5x baseline value: 0%	Merck
Toyoda 2018[199] CERTAIN-2 (Arm A only) Japan *Fair*	Glecaprevir 300 mg + pibrentasvir 120 mg	NR	Any adverse event: 48% (43/90) Serious adverse events (pneumothorax, unstable angina): 2% (2/90) Withdrawal due to adverse events: 1% (1/90) Headache: 7% (6/90) Nausea: 3% (3/90) Anemia: 0% (0/90)	AbbVie

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Waked 2016[162] AGATE-II Egypt *Good*	Ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg + 1000-1200 mg ribavirin	Mortality: 1% (1/100)	Any adverse event: 80% (80/100) Serious adverse events (deep venous thrombosis, cardiac arrest): 2% (2/100) Headache: 41% (41/100) Fatigue: 35% (35/100) Dyspepsia: 17% (17/100) Insomnia: 9% (9/100) Grade 2 hemoglobin abnormality: 7% (7/100) Grade ≥2 total bilirubin elevation: 19% (19/100)	AbbVie
Wei 2018[163] China *Fair*	Ledipasvir 90 mg + sofosbuvir 400 mg +	Mortality: 0% (0/206)	Any adverse event: 58% (120/206) Serious adverse events (epicondylitis, asthma, bone contusion): 1% (3/206) Withdrawal due to adverse events: 0% (0/206)	Gilead
Wei 2019a[164] C-CORAL (Genotype 1 and 4 only) Multinational (Australia, China, Korea, Russia, Taiwan, Thailand, Vietnam) *Good*	A. Elbasvir 50 mg + grazoprevir 100 mg (n=326) B. Placebo (n=123; harms assessment only)	A vs. B Mortality: 0.2% (1/486) vs. 0% (0/123)	A vs. B Any adverse event: 47% (230/486) vs. 50% (62/123) Serious adverse events (suicide, contusion, Evans syndrome, lymphoma, enteritis vs. influenza, fracture): 2% (8/486) vs. 2% (2/123) Withdrawal due to adverse events: 0.6% (3/486) vs. 2% (2/123) Headache: 6% (27/486) vs. 5% (6/123) Fatigue: 5% (22/486) vs. 7% (9/123)	Merck
Wei 2019b[165] Multinational (China, Malaysia, Singapore, Thailand, Vietnam) *Fair*	Sofosbuvir 400 mg + velpatasvir 100 mg	Mortality: 0% (0/375)	Any adverse event: 50% (189/375) Serious adverse events (foot infection, pneumonia, ligament rupture): 1% (3/375) Withdrawal due to adverse events: 0% (0/375) Headache: 5% (18/375)	Gilead
Zeuzem 2015[166] C-EDGE Multinational (Australia, Czech Republic, France, Germany, Israel, Puerto Rico, South Korea, Taiwan, U.S.) *Good*	Grazoprevir 100 mg + elbasvir 50 mg	*Patients without cirrhosis only* Mortality: 0.4% (1/246)	*Patients without cirrhosis only* Any adverse event: 71% (175/246) Serious adverse events (not described): 3% (7/246) Withdrawal due to adverse event: 0.8% (2/246)	Merck

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Zeuzem 2018[167] ENDURANCE-1 Multinational (Australia, Austria, Belgium, Canada, Chile, France, Germany, Hungary, Israel, Italy, Lithuania, Mexico, New Zealand, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Spain, South Korea, Sweden, Switzerland, Taiwan, U.K., U.S.) *Fair*	Glecaprevir 300 mg + pibrentasvir 120 mg	8-week intervention group Mortality: 0% (0/351) 12-week intervention group Mortality: 0.3% (1/352)	8-week intervention group Any adverse event: 62% (216/351) Serious adverse events (suicide attempt, unstable angina, fracture, uterine leiomyoma, transient ischemic attack): 1% (5/351) Withdrawal due to adverse events: 0% (0/351) Headache: 19% (68/351) Fatigue: 9% (31/351) Nausea: 5% (19/351) 12-week intervention group Any adverse event: 66% (234/352) Serious adverse events (irritable bowel syndrome, pneumonia/death, bronchitis, atrial fibrillation): 1% (4/352) Withdrawal due to adverse events: 0.3% (1/352) Headache: 18% (62/352) Fatigue: 12% (43/352) Nausea: 8% (29/352)	AbbVie
Zeuzem 2018[167] ENDURANCE-3 (same publication as ENDURANCE-1) *Fair*	A. Glecaprevir 300 mg + pibrentasvir 120 mg, 8 weeks B. Glecaprevir 300 mg + pibrentasvir 120 mg, 12 weeks 3. Sofosbuvir 400 mg + daclatasvir 60 mg. 12 weeks	A vs. B vs. C Mortality: 0.6% (1/157) vs. 0% (0/233) vs. 0.9% (1/115)	A vs. B vs. C Any adverse event: 62% (98/157) vs. 76% (177/233) vs. 70% (80/115) Serious adverse events (ulcerative keratitis, overdose, substance-abuse dependence): 2% (3/157) vs. 2% (5/233) vs. 2% (2/115) Withdrawal due to adverse events: 0% (0/157) vs. 1% (3/233) vs. 0.9% (1/115) Headache: 20% (31/157) vs. 26% (60/233) vs. 20% (23/115) Fatigue: 13% (20/157) vs. 19% (44/233) vs. 14% (16/115) Nausea: 12% (19/157) vs. 14% (32/233) vs. 13% (15/115)	Same as Zeuzem 2018

*****Serious adverse events occurring in more than one person (each occurred in 2 people; NR by intervention group): cellulitis, chest pain, gastroenteritis, hand fracture, noncardiac chest pain, pneumonia.

†One patient excluded from analysis due to receiving the ineligible intervention.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate amino transferase; CI = confidence interval; CLDQ-HCV = Chronic Liver Disease Questionnaire-Hepatitis C Version; EQ-5D VAS = EuroQoL 5-Dimensions questionnaire visual analog scale; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; HCV-SIQv4 = Hepatitis C Symptom and Impact Questionnaire; NR = not reported; RR = relative risk; SD = standard deviation; SE = standard error; SF = short form; SVR = sustained virologic response; U.K. = United Kingdom; ULN = upper limit of normal; U.S. = United States; WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem. Study names are not acronyms.

Appendix B Table 13. Key Questions 6–8: Quality Assessment of Studies of Direct Acting Antiviral Therapy in Adults

Author year	Single- or multi-arm study?	Non-randomized studies: Enrolled all (or a random sample of) patients meeting inclusion criteria?	Randomized studies: Random-ization adequate?	Randomized studies: Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Primary outcome pre-specified and reported?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential (>10%)/ high (>20%)?	Analyze people in the groups in which they were assigned?	Quality
Abergel 2016a[142]	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Abergel 2016b[141]	Single	Yes	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Good
Afdhal 2014[185]	Multi	NA	Unclear	No (open label)	Yes	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Ahmed 2018[195]	Single	Yes	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Andreone 2014[186]	Multi	NA	Unclear	No (open label)	Yes	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Asselah 2018[196] SURVERYOR II	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Asselah 2019[143] ENDURANCE-5 and 6	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Brown 2018[144] C-SCAPE	Single	NA	Unclear	No (open label)	No	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Chayama 2018[197] CERTAIN-1	Single	Yes	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Chuang 2016[145]	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Dore 2016[137] MALACHITE 1	Multi	NA	Yes	No (open label)	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Good
Dore 2016[137] MALACHITE 2	Multi	NA	Yes	No (open label)	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Good
Everson 2015[146]	Multi	NA	Yes	No (open label)	Yes	Yes	Yes	NA	No	No	Yes	No	Yes	Good
Feld 2014[187]	Multi	NA	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	Good

Appendix B Table 13. Key Questions 6–8: Quality Assessment of Studies of Direct Acting Antiviral Therapy in Adults

Author year	Single- or multi-arm study?	Non-randomized studies: Enrolled all (or a random sample of) patients meeting inclusion criteria?	Randomized studies: Random-ization adequate?	Randomized studies: Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Primary outcome pre-specified and reported?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential (>10%)/ high (>20%)?	Analyze people in the groups in which they were assigned?	Quality
Feld 2015[139]	Multi	NA	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	Good
Ferenci 2014[188] PEARL 3	Multi	NA	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	Good
Ferenci 2014[188] PEARL 4	Multi	NA	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	Good
Foster 2015[147] ASTRAL 2	Multi	NA	Unclear	No (open label)	Yes	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Foster 2015[147] ASTRAL 3	Multi	NA	Unclear	No (open label)	Yes	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Gane 2015[148]	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Grebely 2018a[150] SIMPLIFY	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Grebely 2018b[149] D3FEAT	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Hezode 2015[189]	Multi	NA	Yes	No (open label)	Yes	Yes	Yes	NA	No	No	Yes	No	Yes	Good
Kowdley 2014a[190]	Multi	NA	Unclear	No (open label)	Yes	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Kowdley 2014b[191]	Multi	NA	Yes	No (open label)	Yes	Yes	Yes	NA	No	No	Yes	No	Yes	Good
Kumada 2015[151]	Multi	NA	Unclear	Unclear	Yes	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	Fair
Kumada 2017[152]	Multi	NA	Yes	Yes	Yes	Yes	Yes	NA	Unclear	Yes	Yes	No	Yes	Good
Kwo 2016[153]	Multi	NA	Unclear	No (open label)	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Fair
Lalezari 2015[192]	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair

Appendix B Table 13. Key Questions 6–8: Quality Assessment of Studies of Direct Acting Antiviral Therapy in Adults

Author year	Single- or multi-arm study?	Non-randomized studies: Enrolled all (or a random sample of) patients meeting inclusion criteria?	Randomized studies: Random-ization adequate?	Randomized studies: Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Primary outcome pre-specified and reported?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential (>10%)/ high (>20%)?	Analyze people in the groups in which they were assigned?	Quality
Lawitz 2014a[154]	Multi	NA	Yes	No (open label)	No	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Lawitz 2014b[193]	Multi	NA	Yes	No (open label)	No	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Lawitz 2015[155]	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Lim 2016[156]	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Nelson 2015[157]	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Pianko 2015[158]	Multi	NA	Yes	No (open label)	Yes	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Poordad 2017[194]	Multi	NA	Unclear	No (open label)	No	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Pott-Junior 2019[159]	Multi	NA	Yes	Yes	Yes	Yes	Yes	NA	No	No	Yes	No	Yes	Good
Sperl 2016[198] C-EDGE	Single	Yes	NA	NA	NA	Yes	Yes	No	No	No	Yes	No	Yes	Fair
Sulkowski 2014[161]	Multi	NA	Unclear	No (open label)	Yes	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Sulkowski 2015 [160]	Multi	NA	Unclear	No (open label)	Yes	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Toyoda 2018[199] CERTAIN-2	Single	Yes	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Waked 2016[162]	Single	Yes	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Good
Wei 2018[163]	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Wei 2019a[164] C-CORAL	Multi	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Wei 2019b[165]	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Zeuzem 2015[166]	Multi	NA	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	Good

Appendix B Table 13. Key Questions 6–8: Quality Assessment of Studies of Direct Acting Antiviral Therapy in Adults

Author year	Single- or multi-arm study?	Non-randomized studies: Enrolled all (or a random sample of) patients meeting inclusion criteria?	Randomized studies: Random-ization adequate?	Randomized studies: Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Primary outcome pre-specified and reported?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential (>10%)/ high (>20%)?	Analyze people in the groups in which they were assigned?	Quality
Zeuzem 2018[167] ENDURANCE-1	Multi	NA	Yes	No	Yes	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Zeuzem 2018[167] ENDURANCE-3	Single	Yes	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair

Abbreviation: NA = not applicable. Study names are not acronyms.

Appendix B Table 14. Key Question 9: Association of Sustained Virologic Response and Clinical Outcomes – Study Characteristics

Author year *Quality*	Study type	Country Dates of enrollment Number of centers (location)	Inclusion criteria
Arase 2007[204] *Fair*	Cohort*	Japan 1989 to 2004 Single Center (Toranomon Hospital)	≥60 years of age; ALT elevation greater than double upper limits within 6 months; no corticosteroids or antiviral agents in last 6 months; no HBV surface antigen, antinuclear antibodies, or antimitochondrial antibodies; leukocytes >3000/mm^3, platelet count >80,000/mm^3, and bilirubin <2.0 mg/mL; IFN therapy >4 weeks Excluded: History of alcohol abuse or advanced cirrhosis, encephalopathy, bleeding esophageal varices, or ascites
Asahina 2010[217] *Fair*	Cohort†	Japan 1992 to 2008 Single center (Musashino Red Cross Hospital)	HCV infection with histologically proven chronic hepatitis or cirrhosis
Backus 2011[69] *Fair*	Cohort‡	U.S. (VA) 2001 to 2008 Multicenter (national)	HCV genotype 1, 2, or 3; treated with pegylated interferon + ribavirin Exclusion: HIV infection, HCC prior to treatment
Butt 2017[205] *Fair*	Cohort‡	U.S. (VA) Enrollment dates NR Multicenter (national)	HCV infected initiating paritaprevir + ritonavir + ombitasvir + dasabuvir or ledipasvir + sofosbuvir
Carrat 2019[168] French National Agency for Research on AIDS CO22 Hepather Cohort *Fair*	Cohort (prospective)	France 2012 to 2015 32 centers	Patients with chronic HCV infection recruited from 32 hepatology centers in France. Excluded: HBV, HIV coinfection, previous HCC diagnosis, history of decompensated cirrhosis, liver transplant recipient
Cozen 2013[206] San Francisco VA Cohort *Fair*	Cohort‡	U.S. 1992 to 2007 Two centers (San Francisco VA and University of California at San Francisco)	>18 years of age, HCV infection, underwent liver biopsy and follow-up liver imaging study , biopsy, or clinic visit
Cozen 2013[206] University of California at San Francisco Cohort *Fair*	Cohort‡	U.S. 1992 to 2007 Two centers (San Francisco VA and University of California at San Francisco)	>18 years of age, HCV infection, underwent liver biopsy and follow-up liver imaging study , biopsy, or clinic visit
Dieperink 2014[207] *Fair*	Cohort‡	U.S. (VA) 1997 to 2009 Single center (Minneapolis VA)	Chronic HCV infection, initiated antiviral therapy
Dohmen 2013[218] *Fair*	Cohort (prospective)	Japan 2004 to 2010 Multicenter (10 centers, primarily in Fukuoka)	Chronic HCV infection with viral load ≥5 log IU/mL; HBV negative Excluded: history of HCC or HCC developed in the first 6 months
El-Serag 2014[215] *Fair*	Cohort‡	U.S. (VA) 1999 to 2010 Multicenter (national)	HCV infection, ≥1 year followup in VA
Ikeda 1999[219] *Fair*	Cohort*	Japan 1974-1995 Single center (Toronoman Hospital)	Included: age 15 to 86 Excluded: HBV, HCC, cirrhosis

Appendix B Table 14. Key Question 9: Association of Sustained Virologic Response and Clinical Outcomes – Study Characteristics

Author year *Quality*	Study type	Country Dates of enrollment Number of centers (location)	Inclusion criteria
Imai 1998[220] *Fair*	Cohort	Japan 1992 to 1993 Multicenter (8 centers, primarily in Osaka, Japan)	Included: adults with HCV, Childs A cirrhosis Excluded: HCC
Imazeki 2003[208] *Fair*	Cohort[§]	Japan 1986 to 1998 Single center (Chiba University Hospital)	Chronic HCV infection, underwent liver biopsy Excluded: HCC detected within six months of liver biopsy
Innes 2011[209] *Fair*	Cohort	U.K. 1996 to 2007 Multicenter (throughout Scotland)	HCV infection, treatment naive Excluded: Nonsustained SVR (presence of viremia subsequent to meeting definition for SVR), liver transplant, HIV-positive, unknown treatment response
Ioannou 2018[221] *Fair*	Cohort[‖]	U.S. (VA) 1999 to 2015 Multicenter (national)	Initiation of antiviral regimen within VA from January 1999 to December 2015
Izumi 2005[222] *Fair*	Cohort[†]	Japan 1994 to 2001 Single center (Musashino Red Cross Hospital)	Chronic HCV infection, underwent interferon monotherapy
Kasahara 1998[223] *Fair*	Cohort[¶]	Japan 1989 to 1995 10 centers (primarily in Osaka)	Included: adults with HCV Excluded: HCC, cirrhosis
Kasahara 2004[210] *Fair*	Cohort[¶]	Japan Enrollment dates NR Multicenter (number and location of centers unclear)	Histological diagnosis of chronic hepatitis or cirrhosis; no clinical complications of cirrhosis; no evidence of HCC on ultrasonography and/or computed tomography Excluded: HBV; HIV; co-existing liver diseases such as autoimmune hepatitis or primary biliary cirrhosis; excessive alcohol consumption (>80 g/day)
Kurokawa 2009[224] *Fair*	Cohort [¶] (prospective)	Japan 2002 to 2005 Multicenter (number of centers unclear, primarily in Osaka)	All patients treated with interferon alfa-2a + ribavirin during study period Excluded: HBV, HIV positive; liver disease including history of HCC or HCC within 6 months after treatment cessation
Lee 2017[225] *Fair*	Cohort	South Korea 2004 to 2013 Single center (Inha University Hospital)	HCV positive treated during study period Excluded: HBV positive; liver disease
Maruoka 2012[211] *Fair*	Cohort[§]	Japan1986 to 2005Single center (Chiba University Hospital)	HCV positive, underwent liver biopsy Excluded: Other causes of chronic liver disease, HIV-positive, detection of HCC within 1 year of antiviral therapy, dropout within 1 year
Okanoue 2002[226] *Fair*	Cohort	Japan 1995 to 1998 Multicenter (15 centers)	HCV infection, 18 to 68 years of age Excluded: HBV infection, HIV infection, daily alcohol intake >60 g of ethanol for more than 5 years, ALT <30 IU/L

Appendix B Table 14. Key Question 9: Association of Sustained Virologic Response and Clinical Outcomes – Study Characteristics

Author year *Quality*	Study type	Country Dates of enrollment Number of centers (location)	Inclusion criteria
Osaki 2012[227] *Fair*	Cohort	Japan 2002 to 2010 Single center (Osaka Red Cross Hospital)	HCV infection, elevated liver enzymes, and ultrasound image demonstrating chronic liver damage Exclusion: neutrophil count <750 cells/uL, platelet count <50,000 cells/uL, hemoglobin level ≤9.0 g/dL, and renal insufficiency (serum creatinine levels >2 mg/dL), follow-up <24 weeks after the termination of the interferon therapy, previously treated for HCC, or occurrence of HCC during or within 24 weeks after treatment
Singal 2013[212] *Fair*	Cohort	U.S. 2001 to 2006 Single center (Parkland Health and Hospital System)	HCV infection, life expectancy >5 years, platelet count >50,000/uL
Sinn 2008[231] *Fair*	Cohort	South Korea 1994 to 2004 Single center (Sungkyunkwan University School of Medicine)	HCV infection
Tanaka 2000[228] *Fair*	Cohort	Japan 1980 to 1996 Multicenter (6 hospitals in Osaka)	Chronic HCV infection with liver biopsy Excluded: HBV infection, HCC or other liver disease such as alcoholic liver disease, autoimmune hepatitis, or primary biliary cirrhosis
Tateyama 2011[229] *Fair*	Cohort	Japan, 1992 to 2003 Single center (National Nagasaki Medical Center)	Chronic HCV infection
Tseng 2016[216] *Fair*	Cohort	Taiwan 2005 to 2011 Single center (Dalin Tzu Chi General Hospital)	Age ≥65 years, chronic HCV infection, treated with pegylated interferon; elevated ALT Excluded: Decompensated cirrhosis; malignant neoplasms; autoimmune diseases; HIV infection, neutropenia; thrombocytopenia; anemia; poorly controlled psychiatric diseases
Yoshida 1999[230] *Fair*	Cohort[#]	Japan 1986 to 1998 Multicenter (8 centers throughout Japan [Inhibition of Hepatocarcinogenesis by Interferon Therapy Study Group])	HCV positive with liver biopsy Excluded: HCC or other liver diseases (chronic HBV, alcoholic liver disease, autoimmune hepatitis, or primary biliary cirrhosis)
Yoshida 2002[213] *Fair*	Cohort[#]	Japan 1986 to 1998 Multicenter (8 centers throughout Japan [Inhibition of Hepatocarcinogenesis by Interferon Therapy Study Group])	HCV positive, underwent liver biopsy Exclusion: HBV co-infection, alcoholic liver disease, autoimmune hepatitis, or primary biliary cirrhosis
Yu 2006[214] *Fair*	Cohort	Taiwan 1991 to 2003 Multicenter (4 centers in Taiwan)	Biopsy-proven chronic HCV infection, with or without cirrhosis Excluded: HBV or HIV, autoimmune hepatitis, alcohol abuse (≥80 g ethanol per day), HCC at treatment initiation or within 6 months

* Study populations overlap.
† Study populations overlap.
‡ Study population appears to overlap with Ioannou 2018.
§ Study populations overlap.

Appendix B Table 14. Key Question 9: Association of Sustained Virologic Response and Clinical Outcomes – Study Characteristics

‖ Study population appears to overlap with Backus 2011, Butt 2017, Cozen 2013, Dieperink 2014, and El-Serag 2014.
¶ Study populations likely overlap.
# Study populations appear to overlap.
Abbreviations: ALT = alanine aminotransferase; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IFN = interferon; NR = not reported; SVR = sustained virologic response; U.K. = United Kingdom; U.S. = United States of America; VA = Veterans Affairs.

Appendix B Table 15. Key Question 9: Association of Sustained Virologic Response and Clinical Outcomes – Intervention Characteristics and Results

Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Arase 2007[204] *Fair**	Treatment duration: Median 165 days (range 28 to 730) Followup: Mean 7.4 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of long-term IFN therapy IFN-2a or IFN-2b monotherapy: 94% IFN plus ribavirin combination therapy: 6%	Antiviral treatment: n=500 SVR: n=140 No SVR: n=360 Mean age (years): 64 Female: 50% Race: NR Genotype 1b: 60% Genotype 2: 34% Other genotype: 8.0% F1: 36% F2: 31% F3: 7.0% F4: 14%	Liver fibrosis, sex, age, HCV genotype, AST, ALT, HCV viral load, liver histology (activity)	HCC, aHR SVR: 0.19 (95% CI, 0.08 to 0.45) No SVR: Reference Mortality, aHR SVR: 0.39 (95% CI, 0.16 to 0.93) No SVR: Reference Liver-related mortality, aHR SVR: 0.13 (95% CI, 0.03 to 0.59) No SVR: Reference	Okinaka Memorial Institute for Medical Research and Japanese Ministry of Health, Labor and Welfare
Asahina 2010[217] *Fair*†	Treatment: 24 or 48 weeks up to 2 to 5 years Followup: Mean 7.5 years (range 0.5 to 17 years)	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy IFN-alpha or beta monotherapy (n=1062) Combination therapy IFN-alpha and ribavirin (n=306) Pegylated IFN-alpha monotherapy (n=386) Combination pegylated IFN-alpha and ribavirin (n=412)	Antiviral treatment: n=2166 SVR: n=686 No-SVR: n=1356 Prolonged therapy: n=59 Undetermined response: n=65 Mean Age: 55.4 (SD±3.1) Female: 50% Race: NR F0: 1% F1: 40% F2: 34% F3: 21% F4: 5% Genotype 1a: 0.3% Genotype 1b: 70% Genotype 2a: 18% Genotype 2b: 10%	Age, sex, BMI, fibrosis stage, degree of steatosis, esophagogastric varices, genotype, albumin, ALT, AST, GGT, alkaline phosphatase, total bilirubin, total cholesterol, triglyceride, fasting blood sugar, white blood cell, red blood cell, platelet count, AFP (baseline and post treatment), viral load, IFN regimen	HCC, aHR, annual incidence SVR: 0.38 (95% CI, 0.18 to 0.83), 0.4% No SVR: Reference, 20.2%, 1.4%	Japanese Ministry of Education, Culture, Sports, Science, and Technology Japanese Ministry of Welfare, Health and Labor

Appendix B Table 15. Key Question 9: Association of Sustained Virologic Response and Clinical Outcomes – Intervention Characteristics and Results

Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Backus 2011[69] *Fair*‡	Treatment duration: 48 weeks for genotype 1, 24 weeks for genotypes 2 and 3 Followup: Median 3.8 years (IQR 2.6 to 5.2)	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy PEG-IFN (alfa-2a or alfa-2b) plus ribavirin	Antiviral treatment: n=16,864 SVR: n=7434 No SVR: n=9430 Mean age (years): 52 Female: 4% Non-White: 43% Genotype 1: 72% Genotype 2: 17% Genotype 3: 11% Fibrosis stage: NR Cirrhosis: 13%	Age, sex, albumin, AST, AST/ALT ratio, creatinine clearance, platelets, sodium, cirrhosis, chronic obstructive pulmonary disease, diabetes, hypertension, tobacco use, treatment duration <60% recommended, bilirubin, BMI, HBV co-infection, HCV viral load, hemoglobin, coronary artery disease, cancer, congestive heart failure, cerebrovascular disease, schizophrenia, recent alcohol abuse diagnosis, anxiety disorder, depression, hard drug use, post-traumatic stress disorder, socioeconomic status instability, multiple treatment courses, erythropoiesis stimulating agent use, granulocyte colony stimulating factor use, year of treatment start	All-cause mortality, aHR, 5-year mortality rate <u>Genotype 1</u> SVR: 0.70 (0.59 to 0.83), 6.7% No SVR: Reference, 14% <u>Genotype 2</u> SVR: 0.64 (0.46 to 0.88), 7.3% No SVR: Reference, 16% <u>Genotype 3</u> SVR: 0.51 (0.35 to 0.73), 8.0% No SVR: Reference, 24% SVR vs. no SVR (calculated): 0.66 (0.57 to 0.76)	VA, Veterans Health Administration, Office of Public Health and Environmental Hazards

Appendix B Table 15. Key Question 9: Association of Sustained Virologic Response and Clinical Outcomes – Intervention Characteristics and Results

Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Butt 2017[205] *Fair*‡	Treatment duration: NR Followup: 1.5 years	SVR vs. no SVR SVR not defined Paritaprevir + ritonavir + ombitasvir + dasabuvir (n=1,473) Ledipasvir + sofosbuvir (n=5,497)	Antiviral treatment: n=6,970 SVR: n=6,371 No SVR: n=599 Paritaprevir + ritonavir + ombitasvir + dasabuvir vs. ledipasvir + sofosbuvir Median age (years): 61 to 62 Female: 3% vs. 4% White: 47% vs. 55% Black: 32% vs. 26% Hispanic: 2% vs. 2% Genotype 1a: 61% vs. 64% Genotype 1b: 38% vs. 17% Child-Turcotte-Pugh class A: 94% vs. 90% Class B: 6% vs. 10% Class C: 0.1% vs. 0.5% FIB-4 score >3.5 (cirrhosis): 13% vs. 15%	Age, sex, race/ethnicity, BMI, FIB-4 score >3.5; diabetes, chronic kidney disease stage 3-5; alcohol use/dependence; drug abuse/dependence; HCV RNA, genotype, anemia	Mortality, aHR SVR: 0.57 (95% CI, 0.33 to 0.99) No SVR: Reference	VA, Pittsburgh

Appendix B Table 15. Key Question 9: Association of Sustained Virologic Response and Clinical Outcomes – Intervention Characteristics and Results

Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Carrat 2019[168] French National Agency for Research on AIDS CO22 Hepather Cohort *Fair*	Treatment duration: NR Followup: Median 33.4 months (IQR: 24.0 to 40.7)	SVR vs. no SVR SVR not defined DAA regimen (sofosbuvir + simeprevir +/- ribavirin; sofosbuvir + daclatasvir +/- ribavirin; sofosbuvir + ledipasvir +/- ribavirin; sofosbuvir + ribavirin; sofosbuvir + IFN alpha + ribavirin; sofosbuvir + velpatasvir +/- voxilaprevir; paritaprevir + ritonavir + ombitasvir +/- dasabuvir +/- ribavirin; elbasvir + grazoprevir +/- ribavirin) (n=4,521, non-cirrhosis only)	Antiviral treatment: 4,521 SVR: n=3,286 No SVR: n=146 Unknown SVR: n=1,089 No treatment: 2,329 Total study population (including 3,045 patients with cirrhosis) Treatment vs. no treatment Mean age: 57 vs. 54 Female: 44% vs. 54% Race NR Fibrosis stage: F0, F1, or F2: 41% vs. 84% F3: 17% vs. 6% F4: 42% vs. 10% Genotype 1: 67% vs. 64% Genotype 2: 6% vs. 10% Genotype 3: 13% vs. 9% Genotype 4: 13% vs. 14% Genotypes 5 to 7: 2% vs. 3%	Age, sex, BMI, geographical origin, infection route, fibrosis score, treatment history, genotype, alcohol consumption, diabetes, arterial hypertension, biological variables, time-dependent covariates of treatment response	<u>All-cause mortality, aHR, rate SVR</u>: 0.64 (95% CI, 0.33 to 1.23), 21/4,422 person-years No SVR: 0.47 (95% CI, 0.06 to 4.04), 1/239 person-years No treatment: Reference, 48/11,131 person-years <u>HCC, aHR, rate SVR:</u> 0.75 (95% CI, 0.23 to 2.40), 9/4,400 person-years No SVR: 3.46 (95% CI, 0.61 to 19.7), 3/234 person-years No treatment: Reference, 14/11,120 person-years <u>Liver mortality, aHR, rate SVR:</u> NR, 5/4,422 person-years No SVR: NR, 0/239 person-years No treatment: Reference, 6/11,131 person-years <u>Decompensated cirrhosis, aHR, rate SVR:</u> NR, 2/4,418 person-years No SVR: NR, 0/236 person-years No treatment: Reference, 4/11,131 person-years	French National Agency for Aids and Viral Hepatitis Research; French National Agency of Research; French Ministry of Social Affairs and Health; Merck Sharp & Dohme; Janssen; AbbVie; Bristol-Myers Squibb; Roche

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Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Cozen 2013[206] San Francisco VA Cohort *Fair*‡	Treatment duration: mean 40.45 weeks (SD 22.32) Followup: Mean 10 years	SVR vs. nonresponder vs. relapser SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy Relapser=Undetectable viral load during treatment with detectable virus at 6 month followup IFN alpha +/- ribavirin	San Francisco VA Cohort Antiviral treatment: n=159 SVR: n=69 Nonresponder: n=49 Relapser: n=22 Early treatment discontinuation/unknown: n=19 Never treated: 199 Mean Age 50.98 (SD 6.68) Female: 1.1% African-American: 20.2% Latino: 8.7% Asian: 5% Genotype 1: 68.7% Genotype 2: 14.5% Genotype 3: 8.4% Genotype 4: 1.7% Mixed genotype: 0.6% F0: 31% F1: 24% F2: 26% F3: 8.4% F4: 1.7%	Fibrosis stage, age, race/ethnicity, HCV genotype, alcohol use, substance use, psychiatric comorbidities, social stability	Cirrhosis, aHR, rate SVR: 0.68 (95 % CI 0.26 to 1.80), 11% (7/69) Nonresponder: 2.35 (95% CI, 1.18 to 4.69), 49% (20/49) Relapser: 1.00 (95% CI, 0.28 to 3.56), 22% (4/22) Never treated: Reference 14% (28/199) SVR vs. no SVR (calculated): 0.35 (95% CI, 0.11 to 1.10) Mortality, aHR, rate SVR: 0.23 (95% CI, 0.07 to 0.75), 8.7% (6/69) Nonresponder: 0.56 (95% CI, 0.24, to 1.32), 29% (14/49) Relapser 0.11 (95% CI, 0.01 to 0.95), 18.2% (4/22) Never treated: Reference, 24% (47/199) SVR vs. no SVR (calculated): 0.50 (95% CI, 0.12 to 2.10)	National Institutes of Health, VA merit award

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Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Cozen 2013[206] University of California, San Francisco Cohort *Fair*‡	Treatment duration: mean 40.45 weeks (SD 22.32) Followup: Mean 10 years	SVR vs. nonresponder vs. relapser SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy Relapser=Undetectable viral load during treatment with detectable virus at 6 month followup IFN alpha +/- ribavirin	University of California, San Francisco Cohort Antiviral treatment: n=131 SVR: n=43 Nonresponder: n=42 Relapser: n=21 Early treatment discontinuation/unknown: n=25 Mean age: 48.42 (SD 8.39) Female: 38.9% African-American: 9.9% Latino: 4.6% Asian: 13.0% Genotype 1: 63.3% Genotype 2: 18.3% Genotype 3: 12.2% Genotype 4: 0% Genotype 6: 1.5% F0: 11.5% F1: 23.7% F2: 30.5% F3: 19.1% F4: 15.3%	Fibrosis stage, age, race/ethnicity, HCV genotype, alcohol use, substance use, psychiatric comorbidities, social stability	Cirrhosis, aHR, rate SVR: 1.12 (0.12 to 10.33), 5.1% (2/43) Nonresponder: 5.90 (1.50 to 23.24), 36% (11/42) Relapser: 0.23 (0.02 to 2.27), 5.3% (1/21) Never treated: Reference, 7.8% (10/134) SVR vs. no SVR (calculated): 0.43 (95% CI, 0.03 to 5.35) Death or liver transplant University of California, San Francisco cohort, aHR, rate SVR: 0.24 (0.05 to 1.10), 7.0% (3/43) Nonresponder: 0.43 (0.13 to 1.38), 26% (11/42) Relapser: 0.80 (0.21 to 3.04), 19% (4/21) Never treated: Reference, 11% (15/134)	National Institutes of Health, VA merit award

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Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Dieperink 2014[207] *Fair*‡	Followup: Median 7.5 years (IQR 4.9 to 9.8)	SVR vs. no SVR SVR not defined PEG-IFN-alpha plus ribavirin (68%) IFN-alpha plus ribavirin (26%) IFN-alpha (3.0%) Consensus IFN and ribavirin (3.0%)	Antiviral Treatment: n=536 SVR: n=222 Non-SVR: n=314 Median age (years): 52 (range 36 to 72) Female: 2% Black: 10% White: 81% Hispanic: 0.4% Asian: 0.4% Native American: 1.5% Unknown/other race: 7.3% Genotype 1: 70% Genotype 2: 15% Genotype 3: 12% Genotype 4: 0.2 Unknown genotype: 2.6% Clinical cirrhosis: 7.1% F0: 2.6% F1: 12% F2: 22% F3: 22% F4: 21% No biopsy: 21%	SVR, integrated care, genotype, fibrosis stage, diabetes, thrombocytopenia, age, depression Not significant in univariate analyses (excluded from model): alcohol use diagnoses, substance use diagnoses, psychosis, number of antiviral treatments, cardiac disease	SVR vs. no SVR All-cause mortality, aHR, rate SVR: 0.47 (95% CI, 0.26 to 0.85), 9% (19/222) No SVR: Reference, 26% (81/314) Liver related mortality, rate SVR: 3% (6/222) No SVR: 18% (56/314) Liver transplant, rate SVR: <1% (2/222) No SVR: 4% (13/314) HCC, aHR, rate SVR: 0.41 (95% CI, 0.18 to 0.96), 4% (9/222) No SVR: Reference, 9% (29/314)	Supported by VA Research Service
Dohmen 2013[218] *Fair*	Treatment duration: Range 24-72 weeks Followup: median 4.75 years (range 1 to 6.25 years)	SVR vs. no SVR SVR=Undetectable HCV RNA by PCR at 24 weeks after completion of antiviral therapy Oral ribavirin plus subcutaneous PEG-IFN-α-2a or subcutaneous PEG-IFN-α-2b	Antiviral treatment: n=474 SVR: n=285 No SVR: n=189 Mean age: 55 years Female: 52% Race: NR Genotype 1: 67% Genotype 2: 33% Fibrosis stage: NR	Age, sex, genotype, hemoglobin, platelet count, albumin, ALT, viral load, alpha-fetoprotein level	HCC, aHR, rate SVR: 0.39 (calculated 95% CI, 0.24 to 0.64, p=0.0002), 2% (6/285) No SVR: Reference, 9% (17/189)	NR

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Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
El-Serag 2014[215] *Fair*‡	Treatment duration: NR Followup: Mean: 5.2 years	SVR vs. no SVR vs. undeterminable vs. no treatment SVR=Undetectable HCV RNA 12 weeks after completion of antiviral therapy Treatment NR	Demographics reported for all patients Antiviral treatment: n=16344 SVR: n=7577 No SVR: n=8767 Undeterminable: n=7188 No treatment: n=125875 Age: 52.5% Female: 2.9% White: 56% African American: 36% Hispanic: 6.0% Genotype 1: 55% Genotype 2: 8% Genotype 3: 5% Genotype 4: 1% Genotype 5/6: <1% Unknown genotype: 31% Fibrosis stage: NR	Age, sex, service period, HCV diagnosis year, genotype, diabetes, alcohol abuse, BMI, HIV coinfection, HBV coinfection	Cirrhosis, aHR SVR: 0.75 (95% CI, 0.69 to 0.82) No SVR: 2.07 (95% CI, 1.97 to 2.18) Undeterminable: 1.55 (95% CI, 1.45 to 1.66) No treatment: Reference SVR vs. no SVR (calculated): 0.36 (95% CI, 0.33 to 0.40) HCC, aHR SVR: 0.40 (95% CI, 0.32 to 0.50) No SVR: 1.34 (95% CI, 1.19 to 1.50) Undeterminable: 0.96 (95% CI, 0.82 to 1.12) No treatment: Reference SVR vs. no SVR (calculated): 0.30 (0.23 to 0.38)	National Institutes of Health grant - National Cancer Institute R01 116845 Houston VA Health Services Research & Development Center for Innovations in Quality, Effectiveness and Safety Texas Digestive Disease Center National Institutes of Health DK58338

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Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Ikeda 1999[219] *Fair**	Treatment duration:14 to 24 weeks Followup: Median 5.4 years (range 0.1 to 22.8)	Responder vs. nonresponder Complete response=Persistent undetectable HCV RNA 6 months after completion of antiviral therapy Incomplete responder=normal ALT values without elimination of HCV RNA for ≥6 months after treatment IFN alpha, beta or both	Antiviral treatment: n=1191 Responders: n=606 (461 complete responders and 145 incomplete [biochemical] responders) Nonresponders: n=585 No treatment: n=452 Median age (years): 50 (range15-86) Female 33% (389/1191) Race: NR Genotype 1a, 1b: 67% Genotype 2a, 2b: 28% Unknown genotype: 5% F1: 67% F2 and F3: 33% F4: 0%	Age, sex, alcohol intake, family history of HCC, history of blood transfusion, fibrosis stage, AST, ALT, albumin, bilirubin, globulin, gamma-glutamyl transferase, platelet count, indocyanine green retention rate at 15 minutes, HCV genotype, HCV viral load	HCC, aHR, rate Responder: 0.32 (95% CI, 0.13 to 0.78), 1.2% (7/606) Nonresponder: 0.96 (95% CI, 0.55 to 1.70), 3.6% (21/585) No treatment: Reference, rate NR SVR vs. no SVR (calculated): 0.33 (95% CI, 0.12 to 0.96)	NR
Imai 1998[220] *Fair*	Treatment duration: 24 weeks Follow-up: 47.6 months (range 3.3 to 65.2 months)	SVR vs. relapse vs. nonresponder SVR=Persistent normalization of ALT levels during treatment and followup Relapse=Normal ALT at end of treatment, but abnormally elevated levels after treatment Human lymphoblastoid IFN, recombinant IFN alpha 2a, recombinant IFN alpha 2b	Antiviral treatment: n=419 SVR: n=151 Relapse: n=120 Nonresponder: n=148 No treatment (historical control): 144 Age <60: 71% Female 33% Race: NR Genotype: NR F1: 30% F2: 33% F3: 29% F4: 8%	Age, sex, ALT, AFP, platelet count, fibrosis stage, Histologic Activity Index	HCC, aHR, rate SVR: 0.06 (95% CI, 0.01 to 0.46), 0.7% (1/151) Relapse: 0.51 (95% CI, 0.20 to 1.27), 6.1%, 5.8% (7/120) Nonresponder: 0.95 (95% CI, 0.48 to 1.84), 13% (20/148) No treatment: Reference, 13% (19/144) SVR vs. no SVR (calculated): 0.06 (95% CI, 0.01 to 0.48)	NR

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Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Imazeki 2003[208] *Fair*[§]	Treatment duration: Mean 167 (range 6 to 560) days Followup: Mean 8.2 years (range 7 to 183 months)	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy IFN-2a: 84% IFN-2b: 12% Both: 4%	Antiviral treatment: n=355 SVR: n=116 No SVR: 239 Mean age (years): 49 Female: 36% Race: NR Genotype 1: 74% F0/F1: 56% F2: 17% F3: 14% F4: 13%	Age, sex, fibrosis stage, AST, ALT, albumin, platelet count, alcohol consumption, duration of HCV infection	Liver-related mortality, aHR, rate SVR: 0.030 (95% CI, 0.003 to 0.27), 0.9% (1/116) No SVR: 0.26 (95% CI, 0.11 to 0.61), 7.5% (18/239) No treatment: Reference, 12% (12/104) SVR vs. no SVR (calculated): 0.12 (95% CI, 0.01 to 1.28) All-cause mortality, aHR, rate SVR: 0.22 (95% CI, 0.068 to 0.71), 3.4% (4/116) No SVR: 0.63 (95% CI, 0.32 to 1.26), 12% (29/239) No treatment: Reference, 14% (15/104) SVR vs. no SVR (calculated): 0.35 (95% CI, 0.09 to 1.36)	NR
Innes 2011[209] *Fair*	Treatment duration: Not specified Followup: Mean 5.3 years (range 27 days to 12.4 years)	SVR vs. no SVR SVR=Undetectable HCV RNA >6 months after completion of antiviral therapy PEG-IFN plus ribavirin: 61% PEG-IFN monotherapy: 1% IFN plus ribavirin: 21% IFN monotherapy: 18%	Antiviral treatment: n=1215 SVR: n=560 No SVR: n=655 Mean age (years): 42 Female: 31% Non-White: 7.8% Genotype 1: 36% Non-genotype 1: 55% Unknown genotype: 9.2% Fibrosis stage: NR Cirrhosis: 14%	Sex, age, race, IVDU, genotype, cirrhosis, alcohol-related hospitalization, elevated ALT	Liver-related mortality, aHR, rate SVR: 0.22 (95% CI, 0.09 to 0.58), 0.9% (5/560) No SVR: Reference, 7.6% (50/655) Liver-related hospital episode, aHR SVR: 0.22 (95% CI, 0.15 to 0.34) No SVR: Reference	Scottish Government

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Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Ioannou 2018[221] *Fair*‖	Treatment duration: NR Followup duration: mean 6.1 years	SVR vs. no SVR SVR=HCV RNA <lower limit of detection 12 weeks after completion of antiviral therapy IFN or pegylated IFN: 58% DAA + IFN: 7.3% DAA only: 35%	Antiviral treatment=50,886 (excluding persons with cirrhosis) SVR: 28,655 No SVR: 23,231 All patients (included persons with cirrhosis) Mean age: 55.8 (SD ±7.6) years Female: 3.4% White: 55.6% Black: 26.3% Hispanic: 6.0% Other: 1.6% Missing race/ethnicity: 10.5% Genotype 1: 77% Genotype 2: 14% Genotype 3: 8.3% Genotype 4: 0.8% Fibrosis stage: NR Cirrhosis: 16.8% (decompensated 4.7%)	Cirrhosis, decompensated cirrhosis, age, sex, race/ethnicity, BMI, HCV genotype, HCV viral load, HIV co-infection, HBV co-infection, type 2 diabetes mellitus, alcohol use disorders, substance abuse disorders, liver transplantation, platelet count, AST/ALT ratio, international normalized ratio, hemoglobin	HCC, aHR, rate <u>All regimens (excludes cirrhotics)</u> SVR: 0.32 (95% CI, 0.28 to 0.37), 1.1% (316/28,655) No SVR: Reference, 7.7% (1,778/23,231) <u>All regimens (includes cirrhotics)</u> SVR: 0.39 (95% CI, 0.35 to 0.43), 1.9% (642/34,660) No SVR: Reference, 9.5% (2629/27,694) <u>IFN-only (includes cirrhotics)</u> SVR: 0.32 (95% CI, 0.28 to 0.37), 2.5% (303/11,988) No SVR: Reference, 9.8% (2348/23,883) <u>DAA + IFN (includes cirrhotics)</u> SVR: aHR 0.48 (95% CI, 0.32 to 0.73), 2.1% (59/2763) No SVR: 6.5% (116/1772) <u>DAA only (includes cirrhotics)</u> SVR: HR 0.29 (95% CI, 0.23 to 0.37), 1.4% (280/19,909) No SVR: Reference, 8.1% (165/2039)	National Institutes of Health/National Cancer Institute grant R01CA196692 VA Clinical Science Research & Development grant I01CX001156

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Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Izumi 2005[222] *Fair*†	Treatment duration: 24 weeks Followup: Duration NR	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy IFN monotherapy	Antiviral therapy: n=495 SVR: n=155 No SVR: n=340 Mean age (years): 52 Female: 43% Race: NR Genotype 1b: 50% Genotype 2a: 13% Genotype 2b: 7.9% F1: 27% F2: 37% F3: 25% F4: 0.7%	Age, sex, and fibrosis stage reported as statistically significant predictors of outcomes in multivariate model, otherwise unclear	HCC, aHR, rate SVR: 0.36 (95% CI, 0.04 to 0.83), 1.9% (3/155) No SVR: Reference, 8.2% (28/340)	Japanese Ministry of Health Labor and Welfare
Kasahara 1998[223] *Fair*¶	Treatment duration: 14 to 52 weeks Follow up, mean: 37.4 months (range 13 to 97 months)	SVR vs. relapse vs. nonresponder SVR=Normalized ALT levels 24 weeks after completion of antiviral therapy Relapse=normalized ALT during therapy, abnormal ALT levels 24 weeks after therapy IFN alpha 2a, IFN alpha 2b, IFN beta, natural IFN alpha	Antiviral treatment: n=1022 SVR: n=313 Relapse: n=304 Non-responder: n=405 Mean age (years): 53 Female: 33% Race: NR Genotype 1: 58% Genotype 2: 18% Mixed or unclassified: 1.5% Genotype not tested: 23% METAVIR stage (mean): 1.9 to 2.3 Cirrhosis: Excluded	Age, gender, total histological score, Knodell's scores (periportal necrosis, intralobular or portal inflammation, and fibrosis), HCV genotype, HCV viral load, IFN dose, number of courses of IFN treatment, period of observation, ALT response	HCC, aHR, rate SVR: 0.13 (95% CI, 0.03 to 0.57), 1.6% (5/313) Non-responder: Reference, 7.9% (32/405) HCC, aHR, rate SVR: 0.32 (95% CI, 0.06 to 1.69), 1.6% (5/313) Relapse: Reference, 3.0% (9/304) HCC SVR vs. no SVR (calculated): 0.19 (95% CI, 0.06 to 0.58)	NR

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Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Kasahara 2004[210] *Fair*¶	Treatment duration: 4 to12 months Followup: Mean 5.7 (SD± 2.0) years vs. 5.8 (SD±1.9)	SVR vs. No SVR SVR=Normalized ALT levels 24 weeks after completion of antiviral therapy IFN	Antiviral Treatment: n=2698 SVR: n=738 No SVR: n=1930 No treatment: n=256 Median age (years): 53 (range 20 to 76) Female: 36% Race: NR Genotype: NR F0: 0.7% vs. 0.6% F1: 35% vs. 25% F2: 36% vs. 32% F3: 26% vs. 38% F4: 3% vs. 5%	Age, gender, fibrosis stage, liver biopsy date	All-cause mortality, aHR, rate SVR: 0.14 (95% CI, 0.06 to 0.35), 0.9% (7/738) No SVR: 0.59 (95% CI, 0.33 to 1.06), 4.9% (94/1930) No treatment: Reference, 20% (52/256) SVR vs. no SVR (calculated): 0.24 (95% CI, 0.08 to 0.68) Liver-related mortality SVR: 0.04 (95% CI, 0.005 to 0.30), 0.1% (1/738) No SVR: 0.76 (95% CI, 0.40 to 1.42), 3.5% (68/1930) No treatment: Reference, 16% (42/256) SVR vs. no SVR (calculated): 0.05 (95% CI, 0.01 to 0.45)	NR
Kurokawa 2009[224] *Fair*¶	Treatment duration: NR Followup: median 3 years (range 6 months to 5 years)	SVR vs. no SVR SVR=Undetectable HCV-RNA 24 weeks after completion of antiviral therapy Subcutaneous IFN-α-2b + oral ribavirin	Antiviral treatment: n=403 SVR: n=139 No SVR: n=264 Mean age (years): 55.8 (SD 10.9) Female: 36% Race: NR Genotype 1: 73% F0: 4% F1: 37% F2: 14% F3: 23% F4: 2%	Sex, age, fibrosis	HCC, aHR, rate SVR: 0.28 (95% CI, 0.08 to 0.96), 2.9% (4/139) No SVR: Reference, 8.0% (21/264)	NR

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Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Lee 2017[225] *Fair*	Treatment duration: NR Followup: Median 2.6 years (range 6 months to 12 years)	SVR vs. no SVR SVR=Undetectable HCV RNA 24 weeks after completion of antiviral therapy PEG-IFN + ribavirin: 93% IFN followed by PEG-IFN + ribavirin: 7%	Antiviral Treatment: n=489 SVR: n=306 No SVR: n=183 Median age (years): 46 Female: 36% Race: NR Genotype 1: 51% Genotype 2: 40% Mixed genotype 1 and 2: 0.2% Mixed genotype 3 or 4: 0.2% Fibrosis stage: NR Cirrhosis: 13%	Age, sex, BMI, cirrhosis, ALT, HCV RNA, HCV genotype	HCC, aHR, rate SVR: 0.09 (95% CI, 0.02 to 0.40), 1.1% (n/N unclear) No SVR: Reference, 9.8% (18/183)	Inha University Hospital
Maruoka 2012[211] *Fair*[§]	Treatment duration: Median 25 (range 1-267) weeks Followup: Mean 9.9±5.3 years	SVR vs. no SVR SVR=Undetectable HCV RNA >6 months after completion of antiviral therapy IFN-alfa or -beta monotherapy: 83% IFN-alfa or -beta sequential therapy: 3.3% IFN-alfa plus ribavirin combination therapy: 14%	Antiviral treatment: n=577 SVR: n=221 No SVR: n=356 No treatment: n=144 Mean age (years): 50 Female: 36% Race: NR Genotype 1: 73% Genotype 2: 27% F0 or F1: 53% F2: 23% F3: 14% F4: 10%	Sex, age, fibrosis stage, inflammatory grade, genotype, high viral load, genotype 1 and high viral load, ALT, platelets, albumin	All-cause mortality, aHR, rate SVR: 0.17 (95% CI, 0.075 to 0.40), 4.5% (10/221) No SVR: 0.84 (95% CI, 0.50 to 1.42), 21% (74/356) No treatment: Reference, 26% (37/144) SVR vs. no SVR (calculated): 0.20 (0.08 to 0.54) HCC, aHR, rate SVR: 0.14 (95% CI, 0.046 to 0.42), 2.3% (5/221) No SVR: 1.18 (95% CI, 0.69 to 2.01), 22% (80/356) No treatment: Reference, 24% (35/144) SVR vs. no SVR (calculated): 0.12 (95% CI, 0.03 to 0.41)	NR

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Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Okanoue 2002[226] *Fair*	Treatment duration: 16 to 26 weeks Followup: Mean 5.6 years	SVR vs. relapse vs. nonresponder SVR=Normalized ALT levels 6 months after completion of antiviral therapy Relapse=Normalized ALT during treatment, elevated levels 6 months after treatment Natural IFN Recombinant IFN2a Recombinant IFN2b Natural IFNB	Antiviral Treatment: n=1,370 SVR: n=426 Relapse: n=358 Nonresponder: n=586 Mean age 50.4 (SD±11.5) Female: 37% Race: NR Genotype: NR F1: 17% F2: 52% F3: 28% F4: 4%	Sex, age, fibrosis stage, serum ALT level, platelet count	HCC, aHR, rate SVR: 0.10 (95% CI, 0.04 to 0.28), 0.2% (1/426) Relapse: 0.55 (95% CI, 0.34 to 0.89), 2% (8/358) Non-responder: Reference, 7.5% (44/586) SVR vs. no SVR (calculated): 0.13 (95% CI, 0.06 to 0.27) All-cause mortality, rate SVR: 1% (2/426) Relapse: 3% (10/358) Non-responder: 6% (37/637)	Ministry of Education of Japan and Health and Welfare of Japan
Osaki 2012[227] *Fair*	Treatment: 48 to 72 weeks for HCV genotype 1 and serum HCV RNA >5 log IU/mL, 24 weeks otherwise Followup: Median 4.1 (range 0.1 to 8.4) years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy IFN + ribavirin (n=69) Or PEG-IFN + ribavirin (n=313)	Antiviral Treatment: n=382 SVR: n=185 No SVR: n=197 Median age (years): 59 (range 18-81) Female: 50% Race: NR Genotype 1b: 60% (genotype otherwise NR) Fibrosis stage: NR Cirrhosis: Excluded	Age, sex, HCV genotype, virological response, biochemical response, ALT, AFT, platelet count	HCC, aHR, rate SVR: 0.12 (95% CI, 0.01 to 0.94), 1% (1/185) No SVR: Reference, 11% (22/197)	Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labor and Welfare of Japan

Appendix B Table 15. Key Question 9: Association of Sustained Virologic Response and Clinical Outcomes – Intervention Characteristics and Results

Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Singal 2013[212] *Fair*	Treatment Duration: 48 weeks for genotypes 1,4, 6 and 24 weeks for genotypes 2 and 3 Followup: Median 72 months in SVR patients, 36-65 months in nonresponders	SVR vs. no SVR SVR=Undetectable HCV RNA 24 weeks after completion of antiviral therapy PEG-IFN α-2b and ribavirin	Antiviral treatment: n=242 SVR: n=83 No SVR: n=159 Median age: 48 (IQR 43-54) Female: 49% Caucasian: 47% African-American: 31% Hispanic: 14% Genotype 1: 68% Genotype: 2 or 3: 27% Other genotype: 5% Fibrosis stage: NR Clinical cirrhosis: 17% Biopsy cirrhosis: 21%	Genotype, age, gender, race, comorbidities, cirrhosis, albumin level, white blood cell level, platelet count, SVR	Mortality, aHR, rate SVR: 0.11 (95% CI, 0.03 to 0.47), 2% (2/83) No SVR: Reference, 27% (43/159)	Grants: KL2 RR024983-04 and Adjusted Clinical Group Junior Faculty Development Award
Sinn 2008[231] *Fair*	Treatment duration: NR Followup: Median 4.6 years	SVR vs. no SVR SVR not defined IFN monotherapy or combination therapy with pegylated IFN or IFN and ribavirin	Antiviral treatment: n=490 SVR: n=296 No SVR: n=194 Mean age: 48.4 (SD±10.8) Female: 58% (286/490) Race: NR Genotype (n=240) Genotype 1b: 44% Genotype 1, non-1b: 2% Genotype 2: 52% Genotype 3 and 6: 2% Fibrosis stage (n=122) F0 and 1: 52% F3 and 4: 48%	Age, gender, diabetes, alcohol intake, body weight, HCV duration, platelet level, ALT, AST, AST:platelet ratio, AFP, genotype, fibrosis stage	Disease progression (increase in Child-Pugh score of ≥2 points, HCC, spontaneous bacterial peritonitis, bleeding gastric or esophageal varices, hepatic encephalopathy, or liver death), aHR SVR: 0.32 (95% CI, 0.11 to 0.91) No SVR: Reference	NR

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Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Tanaka 2000[228] *Fair*	Treatment: 6 months Followup: Mean 55 to 68 months	SVR vs. relapse vs. nonresponders vs. no treatment SVR=Normalized ALT levels 24 weeks after completion of antiviral therapy Relapse=normalized ALT levels during treatment, elevated after 24 weeks of treatment IFN alpha 2a, recombinant IFN alpha 2b	Antiviral Treatment: n=594 SVR: n=175 Relapse: n=165 Nonresponders: n=254 No treatment: n=144 Mean age (years): 52 Female: 31% Race: NR Genotype 1: 75% Genotype 2: 25% F0: 2.4% F1: 54% F3: 40% F4: 2.9%	Age, sex, ALT, platelet count, fibrosis stage, HCV genotype, HCV viral load	HCC, aHR, rate SVR: 0.16 (95% CI, 0.04 to 0.62), 2% (3/175) Relapse: 0.27 (95% CI, 0.09 to 0.79), 3% (5/165) Non-responder: 0.74 (95% CI, 0.37 to 1.48),10% (25/254) No treatment: Reference, 12% (17/144) SVR vs. no SVR (calculated): 0.29 (95% CI, 0.07 to 1.28) SVR vs. relapse vs. non-responder All-cause mortality: 1.1% (2/175) vs. 0.6% (1/165) vs. 5.9% (15/254)	Osaka Prefectural Government and New Ten-Year Strategy for Center Control, Prevention of Cancer, from the Ministry of Health and Welfare of Japan
Tateyama 2011[229] *Fair*	Treatment duration:NR Followup: Mean: 8.2 (SD±4.4) years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy IFN monotherapy PEG-IFN monotherapy IFN and ribavirin combination PEG-IFN with ribavirin	Antiviral Treatment: n=373 SVR: n=139 No SVR: n=234 No treatment: n=334 (patient characteristics include untreated patients) Mean age (years): 57 Female: 50% Race: NR Genotype 1b: 72% Genotype 2: 28% Other genotype: 0.3% F0 or F1: 39% F2: 27% F3: 17% F4: 17%	Age, sex, alcohol consumption, fibrosis stage, platelet count, albumin, AST, ALT, AFP, HCV genotype	HCC, aHR, 10-year cumulative incidence SVR: 0.099 (95% CI, 0.03 to 0.33), 3.1% No SVR: 0.70 (95% CI, 0.45 to 1.09), 14.6% No treatment: Reference, 29.5% SVR vs. no SVR (calculated): 0.14 (95% CI, 0.04 to 0.52)	Ministry of health, Labor and Welfare of Japan

Appendix B Table 15. Key Question 9: Association of Sustained Virologic Response and Clinical Outcomes – Intervention Characteristics and Results

Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Tseng 2016[216] *Fair*	Treatment duration: 6 months Followup: mean 5.5 years (SD 2.5)	SVR vs. no SVR SVR=Undetectable HCV RNA 24 weeks after completion of antiviral therapy Subcutaneous PEG-IFN-α-2a or PEG-IFN-α-2b + oral ribavirin	Antiviral Treatment: n=145 SVR: n=95 No SVR: n=50 Mean age: 69 (SD±3.3) years Female: 56% Race: NR Genotype 1: 61% Fibrosis stage: NR Cirrhosis: NR	Sex, diabetes, HBV co-infection, alcoholism, fatty liver, HCV genotype	Cirrhosis, aHR, rate SVR: 0.29 (95% CI, 0.10 to 0.76), 15% (14/95) No SVR: Reference, 26% (13/50)	Dalin Tzu Chi General Hospital
Yoshida 1999[230] *Fair*[#]	Treatment: NR Followup: mean 4.3 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy IFN	Antiviral Treatment: n=2357 SVR: n=789 No SVR: n=1568 No antiviral treatment: n=490 Mean age, years: 49.5 (SD±11.3) Female: 36% F0: 2% F1: 28% F2: 37% F3: 24% F4: 10% Genotype 1: 70% Genotype 2: 30%	Age, sex, fibrosis stage	HCC, aHR, rate SVR: 0.20 (95% CI, 0.099 to 0.39), 0% (10/789) No SVR: 0.63 (0.43 to 0.92), 1% (76/1568) No treatment: Reference, 12.0% (59/490) SVR vs. no SVR (calculated): 0.32 (95% CI, 0.14 to 0.70)	The Japan Ministry of Health and Welfare

Appendix B Table 15. Key Question 9: Association of Sustained Virologic Response and Clinical Outcomes – Intervention Characteristics and Results

Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Yoshida 2002[213] *Fair*[#]	Treatment duration: Mean 137 days Followup: Mean 5.4±2.4 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy IFN alfa: 84% IFN beta: 14% Both: 2%	Antiviral treatment: n=2,430 SVR: n=817 No SVR: n=1613 No treatment: n=459 Mean age (years): 50 Female: 37% Race: NR Genotype: NR F0 or F1: 30% F2: 37% F3: 23% F4: 9.5%	Age, sex	Mortality, aHR, rate SVR: 0.15 (95% CI, 0.064 to 0.34), 0.9% (7/817) No SVR: 0.47 (95% CI, 0.29 to 0.76), 3.0% (49/1613) No treatment: Reference, 6.5% (30/459) SVR vs. no SVR (calculated): 0.32 (95% CI, 0.12 to 0.86) Liver-related mortality, aHR, rate SVR: 0.050 (95% CI, 0.012 to 0.22), 0.2% (2/817) No SVR: 0.39 (95% CI, 0.22 to 0.68), 2.0% (33/1613) No treatment: Reference, 5.0% (23/459) SVR vs. no SVR (calculated): 0.13 (95% CI, 0.03 to 0.61)	Ministry of Health, Labor, and Welfare of Japan and Ministry of Education, Culture, Sports, Science, and Technology of Japan

Appendix B Table 15. Key Question 9: Association of Sustained Virologic Response and Clinical Outcomes – Intervention Characteristics and Results

Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
Yu 2006[214] *Fair*	Treatment duration: 20-48 weeks Followup: Mean 5.18 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy IFN alpha, combination	Antiviral Treatment: n=1057 SVR: n=715 No SVR: n=342 No treatment: n=562 Mean age (years): 46.9 (SD±11.49) Female: 40% Race: NR Genotype 1: 46% Other Genotypes: 54% Fibrosis stage: NR Cirrhosis: 16%	Age, sex, ALT, fibrosis stage, HCV genotype	HCC, aHR, rate SVR: HR 0.24 (95% CI, 0.13 to 0.46), 0.4% (3/715) No SVR: 0.99 (95% CI, 0.64 to 1.51), 2.6% (9/342) No treatment: 1.1% (6/562) SVR vs. no SVR (calculated): 0.24 (95% CI, 0.11 to 0.52) Mortality, aHR, rate SVR: 0.37 (95% CI, 0.14 to 0.99), 0.6% (4/715) No SVR: 1.32 (95% CI, 0.56 to 3.06), 3.5% (12/342) No treatment: Reference, 1.8% (10/562) SVR vs. No SVR (calculated): 0.28 (95% CI, 0.08 to 1.02) Liver-related mortality, rate SVR: 0.4% (3/715) No SVR: 3.2% (11/342) No treatment: 1.8% (10/562)	Department of Health, Taiwan and the Taiwan Liver Research Foundation

* Study populations overlap.
† Study populations overlap.
‡ Study population appears to overlap with Ioannou 2018.
§ Study populations overlap.
‖ Study population appears to overlap with Backus, 2011, Butt, 2017, Cozen, 2013, Dieperink, 2014, and El-Serag, 2014.
¶ Study populations likely overlap.
# Study populations appear to overlap.
Abbreviations: AFP = alpha fetoprotein; aHR = adjusted hazard ratio; ALT = alanine aminotransferase; AST = aspartate amino transferase; BMI = body mass index; CI = confidence interval; DAA = direct acting antiviral; FIB-4 = Fibrosis 4; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HR = hazard ratio; IFN = interferon; IQR = interquartile range; IVDU = injection drug use; PCR = polymerase chain reaction; PEG-IFN = pegylated interferon; NR = not reported; RNA = ribonucleic acid; SD = standard deviation; SVR = sustained virologic response; VA = Veterans Affairs.

Appendix B Table 16. Key Question 9: Quality Assessment of Studies of the Association Between Sustained Virologic Response After Antiviral Therapy and Clinical Outcomes

Author year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to follow-up or overall high loss to follow-up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality rating
Arase 2007[204]	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Asahina 2010[217]	Yes	Unclear	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Backus 2011[69]	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Fair
Butt 2017[205]	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Carrat 2019[168]	Yes	Unclear	Yes	Unclear	Yes	Yes	No	Yes	Fair
Cozen 2013[206]	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Dieperink 2014[207]	Yes	No	Yes	No	Yes	Yes	Unclear	Yes	Fair
Dohmen 2013[218]	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
El-Serag 2014[215]	Unclear	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Fair
Ikeda 1999[219]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No	Yes	Fair
Imai 1998[220]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Fair
Imazeki 2003[208]	Yes	No	Yes	Unclear	Yes	Yes	No	Yes	Fair
Innes 2011[209]	Yes	No	Yes	Unclear	Yes	Yes	No	Yes	Fair
Ioannou 2018[221]	Yes	No	Yes	No	No	Yes	Unclear	Yes	Fair
Izumi 2005[222]	Yes	Unclear	Yes	Unclear	No	No	Unclear	Yes	Fair
Kasahara 1998[223]	Unclear	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Kasahara 2004[210]	Yes	Yes	Yes	Unclear	No	No	Unclear	Yes	Fair
Kurokawa 2009[224]	Yes	Unclear	Yes	Unclear	No	No	Unclear	Yes	Fair
Lee 2017[225]	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Maruoka 2012[211]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Okanoue 2002[226]	Yes	No	Yes	No	Yes	Yes	No	Yes	Fair
Osaki 2012[227]	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Singal 2013[212]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Sinn 2008[231]	Yes	No	Yes	Unclear	Yes	Yes	No	Yes	Fair
Tanaka 2000[228]	Yes	No	Yes	No	Yes	Yes	Unclear	Yes	Fair
Tateyama 2011[229]	Unclear	Unclear	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Tseng 2016[216]	Yes	Unclear	Yes	Unclear	Yes	Yes	No	Yes	Fair
Yoshida 1999[230]	Yes	No	Yes	No	Yes	Yes	No	Yes	Fair
Yoshida 2002[213]	Yes	No	Yes	No	Yes	No	No	Yes	Fair
Yu 2006[214]	Yes	No	Yes	No	No	Yes	Unclear	Yes	Fair