From:	CED AMCO REGS (CED sponsored)
To:	Marijuana, CED ABC (CED sponsored)
Subject:	FW: Updates
Date:	Tuesday, September 3, 2019 5:41:54 PM
Attachments:	Screenshot_20190828-065316.png hepatitis-c-screening-draft-evidence-review.pdf Childhood Cancer Among Alaska Natives.full.pdf SEA_52.pdf

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This is a general comment not on a specific open regulation project.

Jedediah R. Smith
Local Government Specialist
Alcohol and Marijuana Control Office
(907) 334-2195
https://www.commerce.alaska.gov/web/amco/

From: Cheryl Bowie <cherylbwab@gmail.com>
Sent: Thursday, August 29, 2019 5:16 AM
To: CED AMCO REGS (CED sponsored) <amco.regs@alaska.gov>; Marijuana, CED ABC (CED sponsored) <marijuana@alaska.gov>
Subject: Updates

Hi there,

I attached other links to read but it would be a nice to open our industry up to medical and research in addition to adult use.

There's been some changes recently, they're asking for input on testing recommendations for Hepatitis C. I attached the HCV Guidelines which was just updated to recommend testing for pregnant women but I recommend infectious disease testing annually for all people but for children and adults receiving healthcare for a chronic condition to help identify an infectious disease at an earlier stage to mitigate problems.

Draft Recommendation Statement
Hepatitis C Virus Infection in Adolescents and Adults: Screening - Comments Due September 23, 2019, 8:00 PM EST https://t.co/fGY5k7jRt8

Welcome to HCV GUIDELINES https://t.co/Q2M0HjrO0X

Steady Rise In Hep C Cases Among Young People Prompts U.S. Task Force To Expand Screening Recommendations https://t.co/Ja01rPdgst

Hepatitis C virus infection in children and adolescents
https://www.ncbi.nlm.nih.gov/pubmed/30982721/

FDA approves first treatment for all genotypes of hepatitis C in pediatric patients https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-all-genotypes-hepatitis-c-pediatric-patients

Prisons will add staff to screen for Hepatitis C https://t.co/k0mvzTWWT8

All Adults Should Be Tested for Hepatitis C; It Now Kills More Americans Than All Other Reportable Infectious Diseases Combined https://t.co/q3GITLT77L

Bone disorders in children and adolescents with chronic HCV infection
https://t.co/gIktJ9KWcE

Cannabinoids and the skeleton: from marijuana to reversal of bone loss.
https://t.co/3aVqRCZHbR

ICH Global Meeting on ICH E8(R1) Guideline on General Considerations for Clinical Trials - 10/31/2019 - 10/31/2019 https://t.co/159wlVjmI2

NIH will soon share genetic data with those who participated in precision medicine study https://t.co/ZmVQCJWIGR via @statnews

Finally, here's my article in the Kaiser Health News. The Battle For Uniform Excellence In Tribal Care - Cheryl Bowie, Anchorage, Alaska https://t.co/68innqgX6O

New Research Connects Atherosclerotic Cardiovascular Disease with HCV Infections https://t.co/svt5NqAZEB

The Endocannabinoid System and Heart Disease: The Role of Cannabinoid Receptor Type 2
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6020134/

Marijuana use in hepatitis C infection does not affect liver biopsy histology or treatment outcomes
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4144456/

Anti-tumoral action of cannabinoids on hepatocellular carcinoma: role of AMPK-dependent activation of autophagy https://t.co/TUrJelxIIv

Potential Use of Cannabinoids for the Treatment of Pancreatic Cancer
https://t.co/xMNoHdKfho

In Retrospect: Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain
https://t.co/V4SHqz3uOt

I was also invited to submit public testimony in the Center for Substance Abuse Treatment National Advisory Council in support of medical marijuana and research that's therapeutic in nature. I sent in all the cannabis/hemp documentation I could find, it helps people living with chronic conditions reduce the harm of procedures or dosages of approved drug therapies, each drug has a comparable risk profile if not an even higher adverse event profile comparatively and can be found on the drug pamphlet that comes with the prescription and/or doctor. Patients are using it as adjunctive therapies to help mitigate the impact of their medical treatment.

Alaska is missing a wonderful opportunity others are taking by expanded all aspects of the cannabis industry.

Notice of NCCIH Pre-Application Webinar for RFA-AT-19-008 and RFA-AT-19-009, "Exploring the Mechanisms Underlying Analgesic Properties of Minor Cannabinoids and Terpenes"
https://grants.nih.gov/grants/guide/notice-files/NOT-AT-19-023.html

Rationale for cannabis-based interventions in the opioid overdose crisis
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5563007/

Brain Damage Aside: FDA approves treatment for patients with rare bone marrow disorder

https://t.co/Sz7PQU6pNE

Anchorage Doctor Pleads Guilty for Prescribing Medically Unnecessary Opioids in Health Care Fraud Scheme
https://t.co/BdXdg1p2fr https://t.co/Ea6fNVHgWG

Cannabis use is associated with reduced prevalence of progressive stages of alcoholic liver disease
https://www.ncbi.nlm.nih.gov/pubmed/29341392/

I just wanted to give you an update and encourage you to submit a comment in support of access to HCV drugs and treatment in all age groups and to support research and access to medical marijuana for patients and doctors.

This is an area I'm interested and was inspired through my fellowship experience and meeting so many people, medical professionals, other Fellows, researchers and advocates in DC; it really added on to the medicinal plant training I completed during my role at the Viral Hepatitis Program run by Indian Health Service in the 1990s. I support safe access, medical marijuana and research, (obviously). If we can't get outside investment, medical marijuana and research I'll have to move to a different state that supports it. Have a great day.

Sincerely,

Cheryl Bowie
@dreamgbutterfly botanicals
9079036513

Risk Exposures
• Persons on long-term hemodialysis (ever)
• Persons with percutaneous/parenteral exposures in an unregulated setting
• Healthcare, emergency medical, and public safety workers after needle-stick, sharps, or mucosal exposures to HCV-infected blood
• Children born to HCV-infected women
• Prior recipients of transfusions or organ transplants, including persons who:
  • Were notified that they received blood from a donor who later tested positive for HCV
  • Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
	I, B

Evidence Synthesis

Number 188

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

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
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This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality, Rockville, MD (Contract No. HHSA-290-2015-00009-I, Task Order No. 7). The findings and conclusions in this document are those of the authors, who are responsible for its contents, and do not necessarily represent the views of Agency for Healthcare Research and Quality. Therefore, no statement in this report should be construed as an official position of Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

The final report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. Agency for Healthcare Research and Quality or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgments

The authors acknowledge Christina Bougatsos, MPH. The authors also thank AHRQ Medical Officer Iris Mabry-Hernandez, MD, MPH, as well as members of the U.S. Preventive Services Task Force.

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 and manually reviewed reference lists.

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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Appendixes

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.

- 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?
- What are the effects of different risk- or prevalence-based methods for screening for HCV infection in modeling studies?
- 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]

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).

External Review

The draft research plan was posted for public comment and modified prior to finalization. The draft report will be reviewed by content experts, USPSTF members, Agency for Healthcare Research and Quality Medical Officers, and collaborative partners, and will be posted for public comment.

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 Versus 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 an 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, 1.09 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 10 to 706 (total N=9,917), 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 versus 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 versus 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, 1.09 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 versus 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 (4 trials), 98.2 percent (95% CI, 96.4% to 99.1%; I^2=68%) for genotype 1b infection (7 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 96.7%, 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 99.7%, 95% CI, 97.6% to %, 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 99.1%, 95% CI, 94.0% to 99.9%), 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 63 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=31%)
    - 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): 8.3 percent (95% CI, 6.8% to 10.1%, I^2=58%)
    - Nausea (36 trials): 11.1 percent (95% CI, 9.1% to 13.5%, I^2=82%)
    - Diarrhea (18 trials): 8.7 percent (95% CI, 6.9% to 11.0%, I^2=70%)
    - 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 versus 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 (two 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 versus 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=31%; **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 (5 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 27.6 percent (95% CI, 24.0% to 31.5%, I^2=60%) 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 (14 trials, pooled event rate 19.6%, 95% CI, 15.5% to 24.3%) or included some patients with cirrhosis (19 trials, pooled event rate 19.1%, 95% CI, 14.9% to 24.1%; p for interaction=0.89), 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 8.3 percent (95% CI, 6.8% to 10.1%, I^2=58%;

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 13.3% (95% CI, 11.1% to 15.9%; I^2=0%) for ombitasvir / paritaprevir / ritonavir / dasabuvir with ribavirin (5 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 9.0%, 95% CI, 7.0% to 11.5%) or included some patients with cirrhosis (8 trials, pooled event rate 8.4%, 95% CI, 6.4% to 10.9%; p for interaction=0.70), and there was no interaction between prior treatment experience status and rates of insomnia (p for interaction=0.81).

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).

Eighteen trials (in 17 publications, total N=2,336) 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, 6.9% to 11.0%, I^2=70%; **Figure 32**). Stratified by antiviral regimen, rates of diarrhea ranged from 6.1 percent (95% CI, 3.4% to 10.8%, I^2=50%) for sofosbuvir / velpatasvir (2 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 (5 trials, pooled event rate 8.0%, 95% CI, 5.5% to 11.6%; p for interaction=0.33), 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 7.1%) 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 0.71, 95% CI, 0.60 to 0.86, 0.62, 95% CI, 0.44 to 0.87, and 0.51, 95% CI, 0.35 to 0.75, 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 145 to 50,886 (total N=116,821), mean age ranged from 42 to 69 years, and the proportion of female participants ranged from 1.1 to 60 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 99%), with genotype 2 the second most common (8% 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] Estimates favored SVR in all studies, and 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, and HRs ranged from 0.29 to 0.40. 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, 0.19 to 0.35). 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, direct acDAA 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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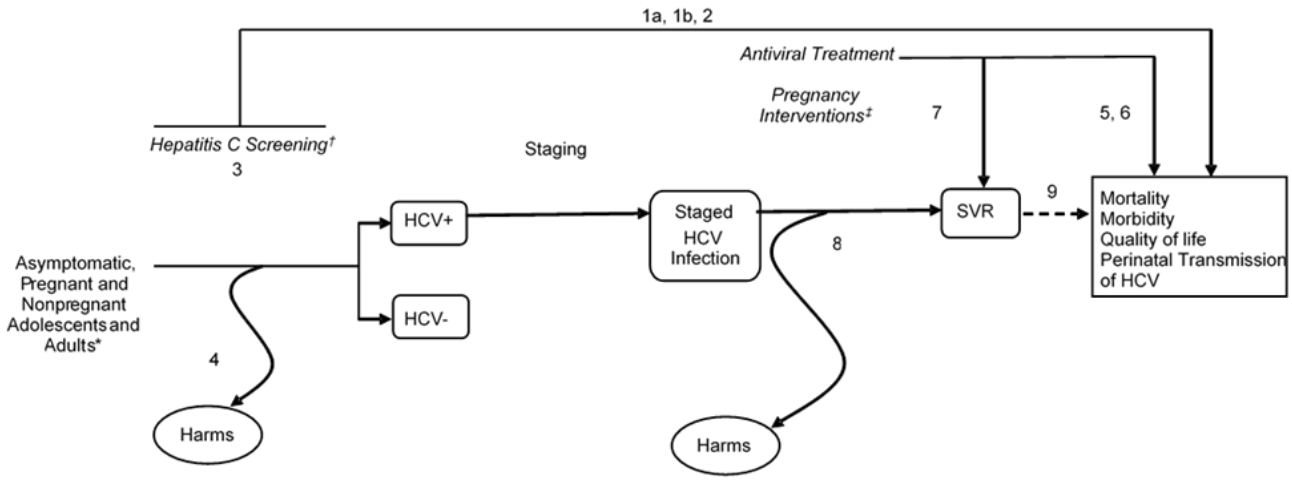
Figure 1. Analytic Framework and Key Questions



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?

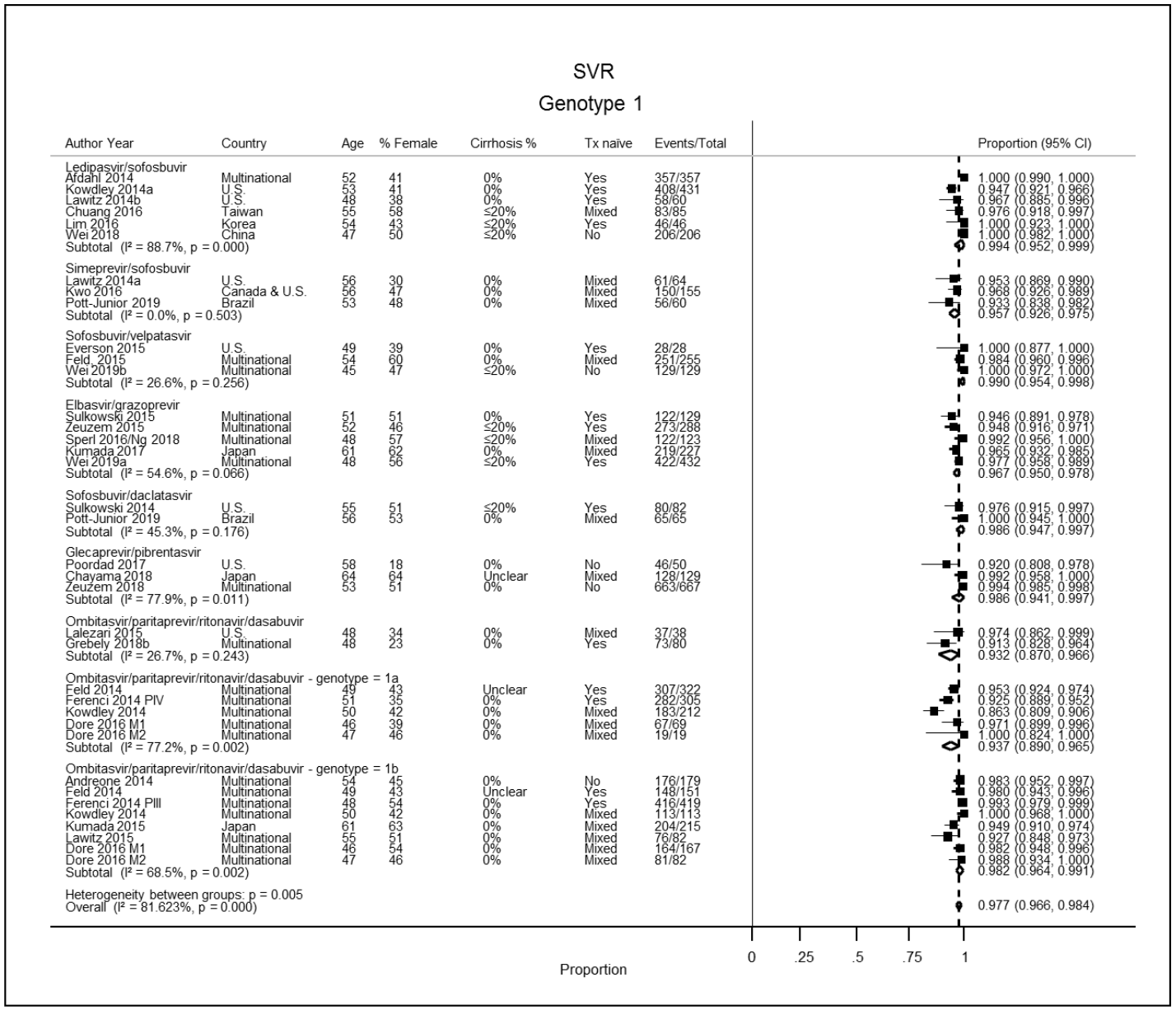
7. What is the effectiveness of currently recommended antiviral treatments in achieving a sustained virologic response in patients with HCV infection?

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?

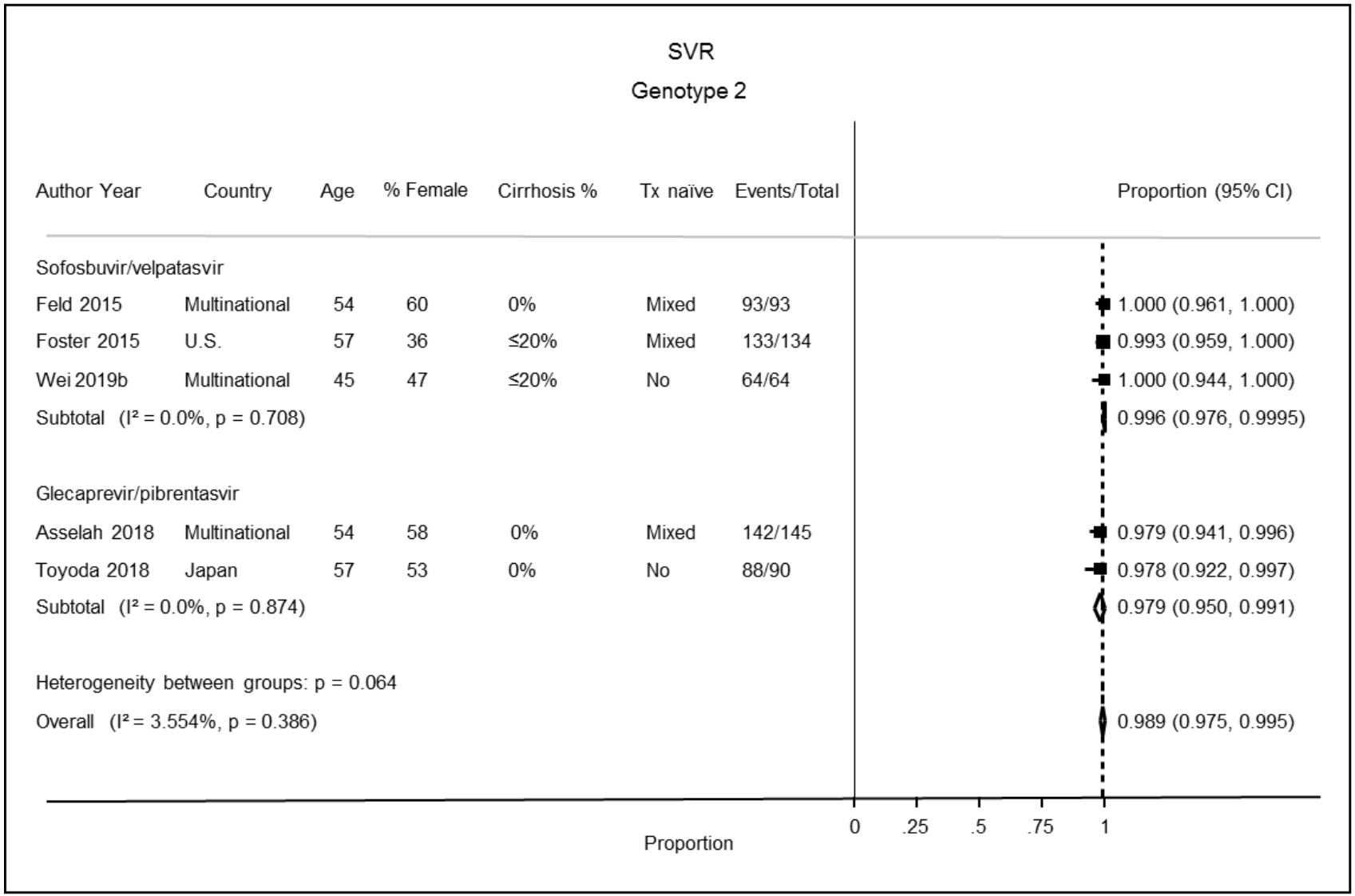
Note: The numbers in the figure correspond to the numbers of the Key Questions.
* Includes persons without abnormal laboratory values. Adolescents are defined as those ages 12 to 17 years. Excludes persons living with HIV, transplant recipients, and patients with renal failure.
† Defined as HCV antibody 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



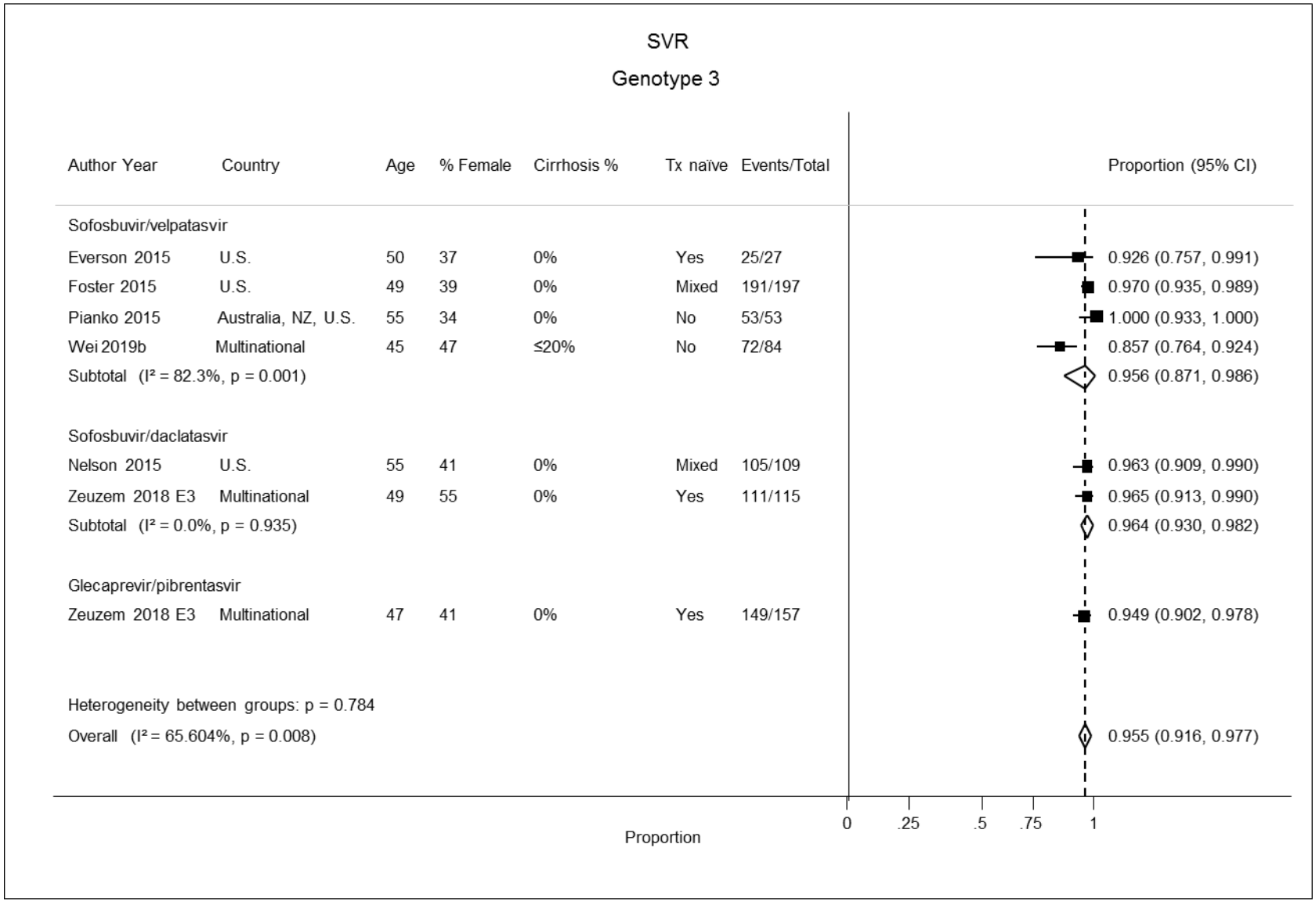
Abbreviations: CI = confidence interval; NR = not reported; SVR = sustained virologic response; Tx = treatment; U.S. = United States.

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



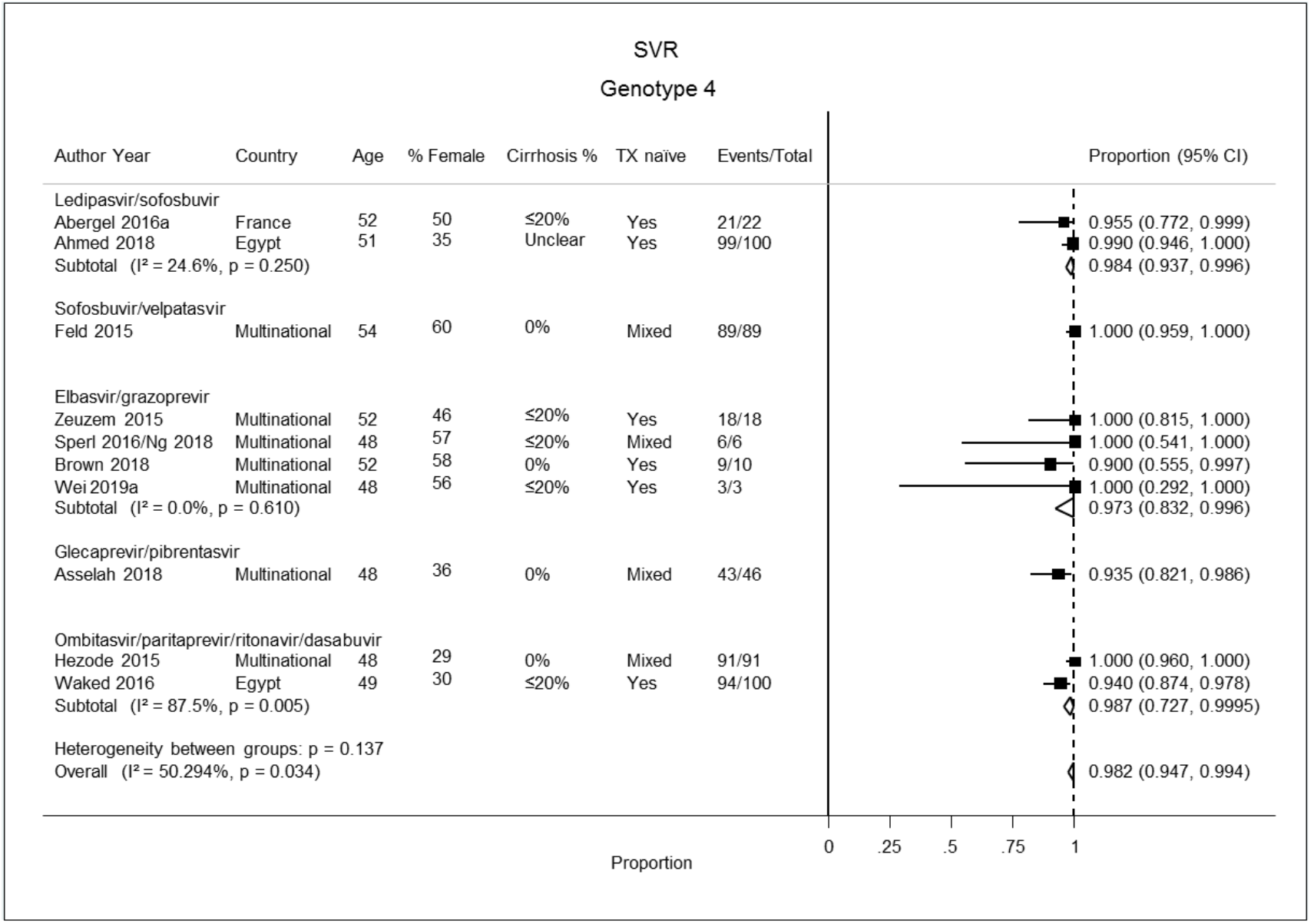
Abbreviations: CI = confidence interval; SVR = sustained virologic response; Tx = treatment; U.S. = United States.

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



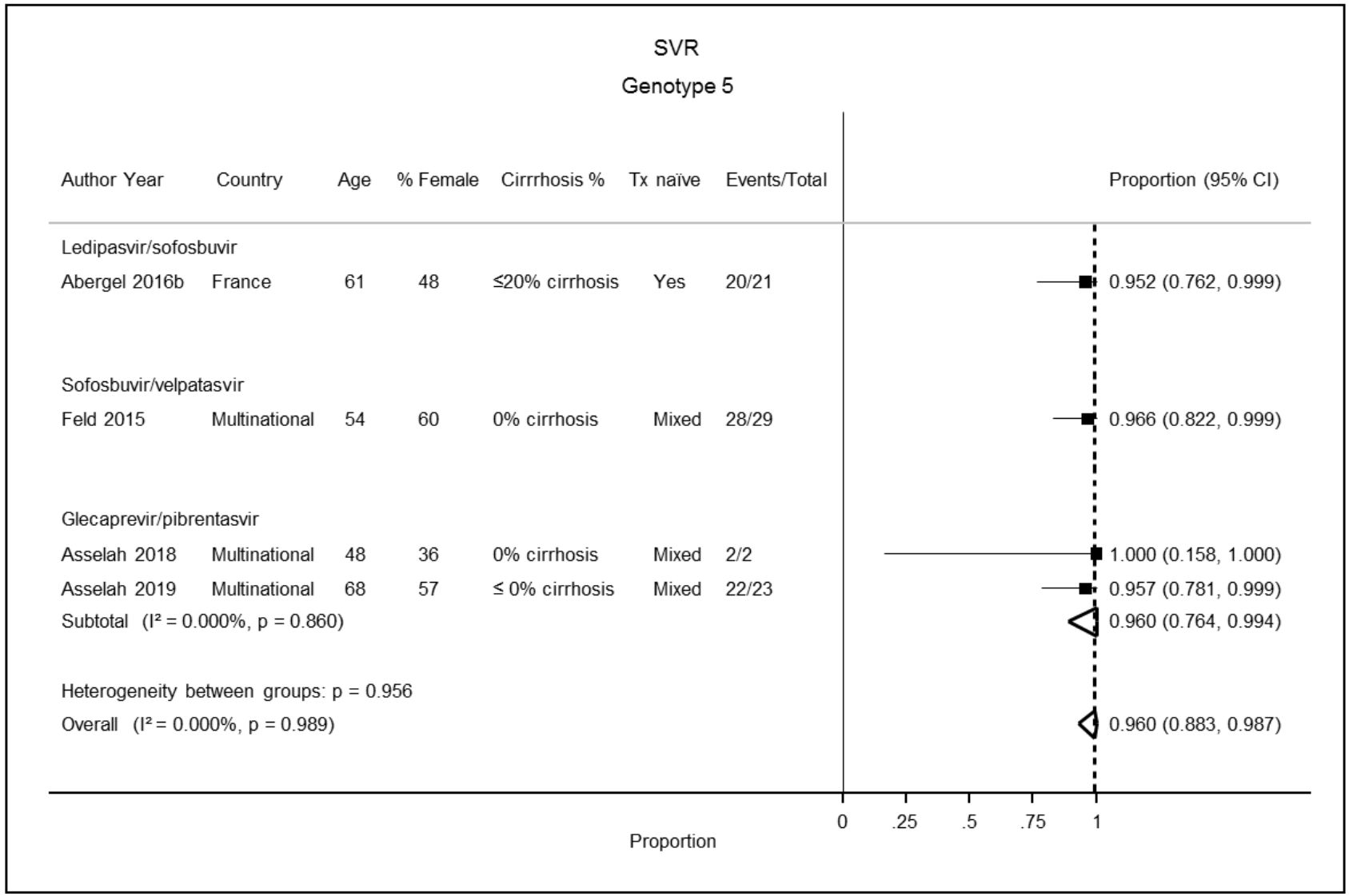
Abbreviations: CI = confidence interval; NZ = New Zealand; SVR = sustained virologic response; Tx = treatment; U.S. = United States.

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



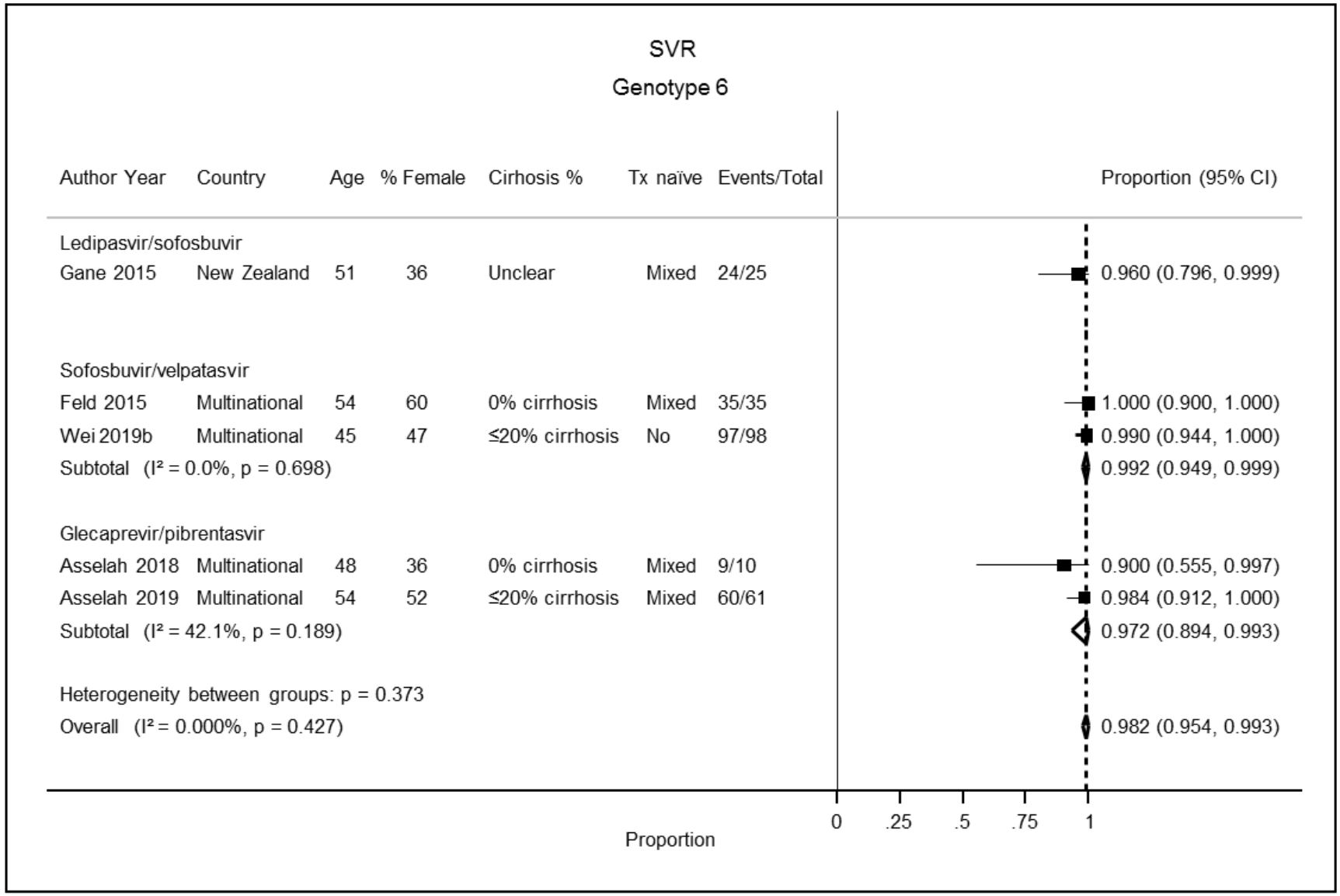
Abbreviations: CI = confidence interval; SVR = sustained virologic response; Tx = treatment.

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



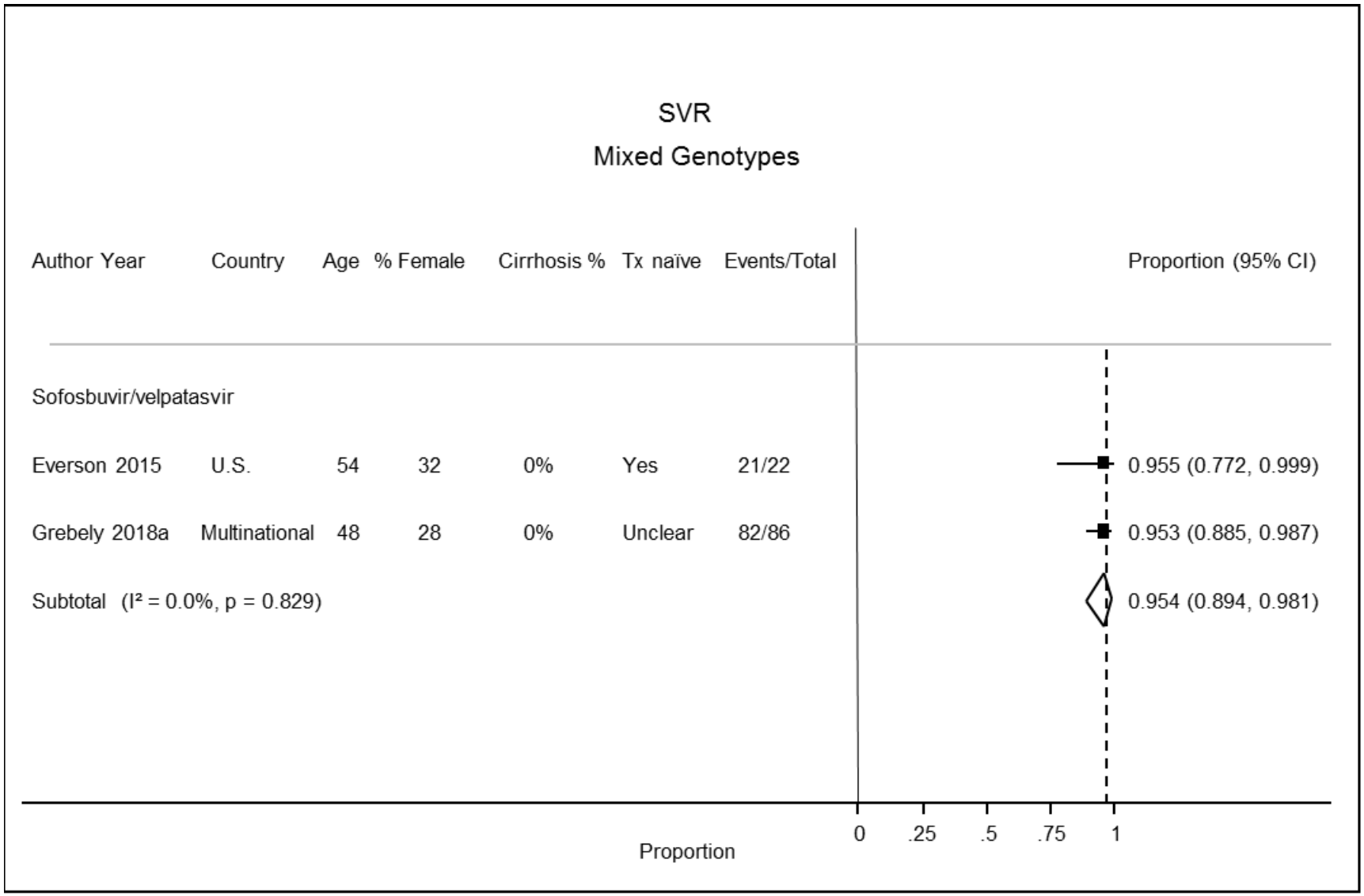
Abbreviations: CI = confidence interval; SVR = sustained virologic response; Tx = treatment.

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



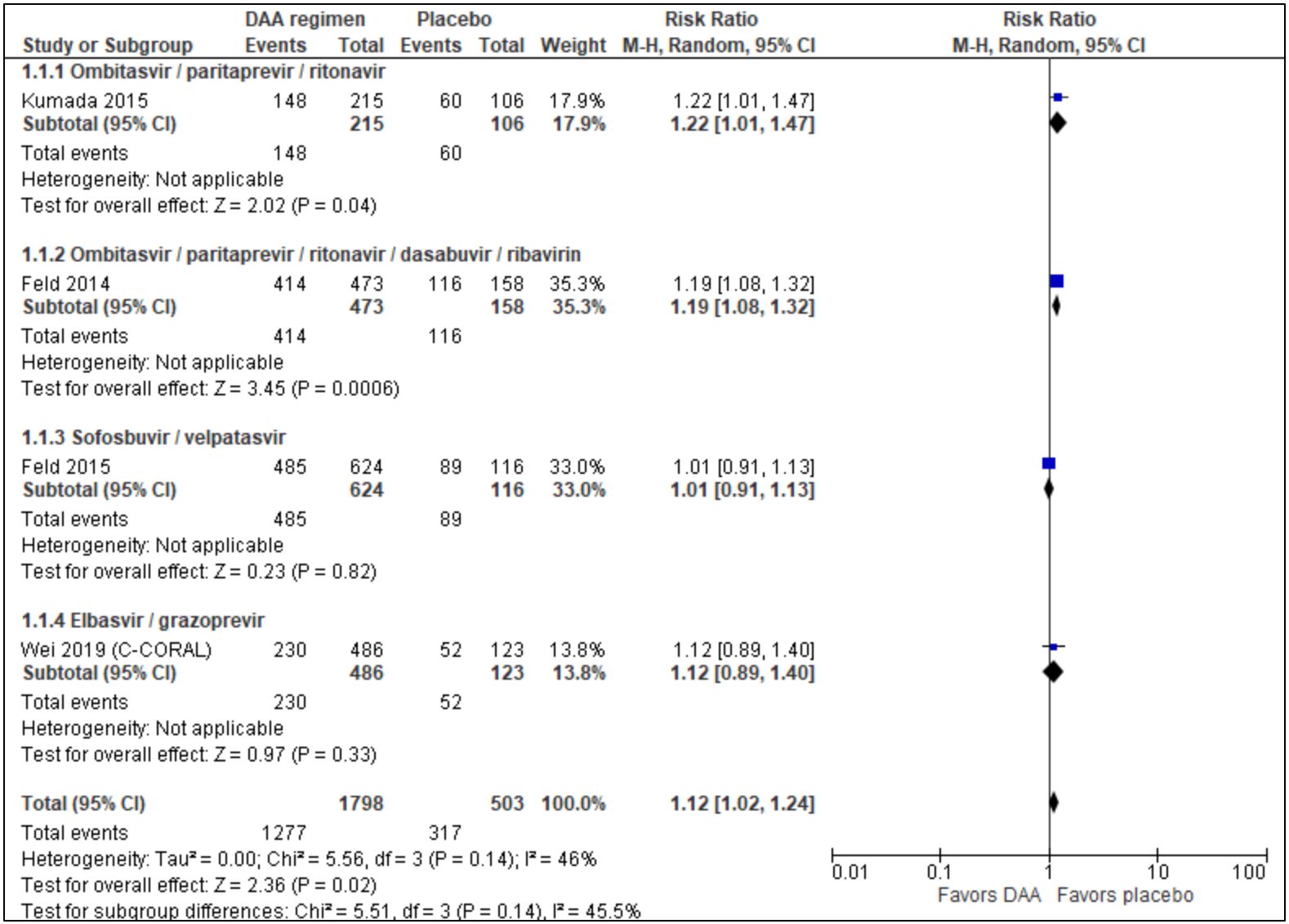
Abbreviations: CI = confidence interval; SVR = sustained virologic response; Tx = treatment.

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



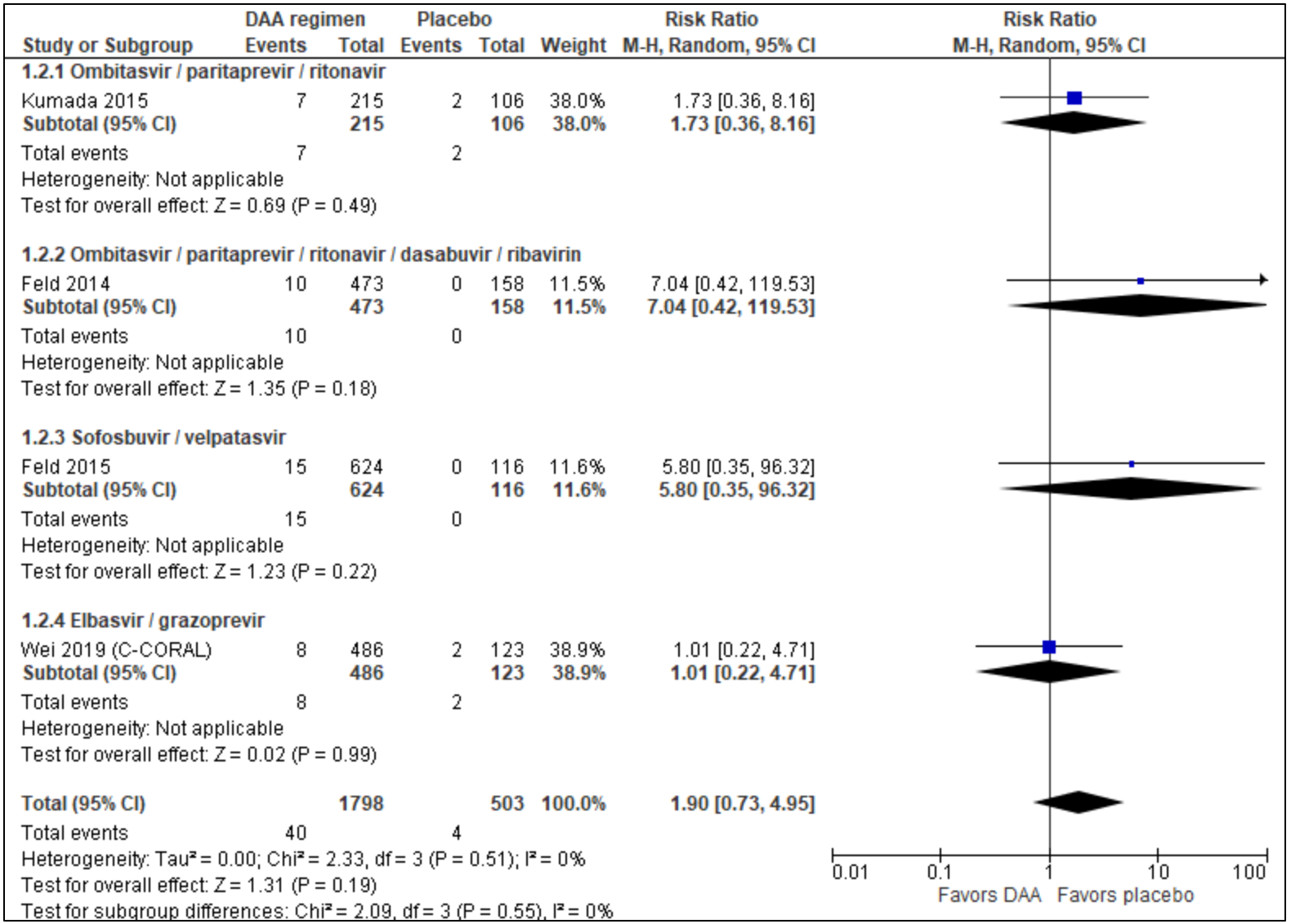
Abbreviations: CI = confidence interval; SVR = sustained virologic response; Tx = treatment; U.S. = United States.

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



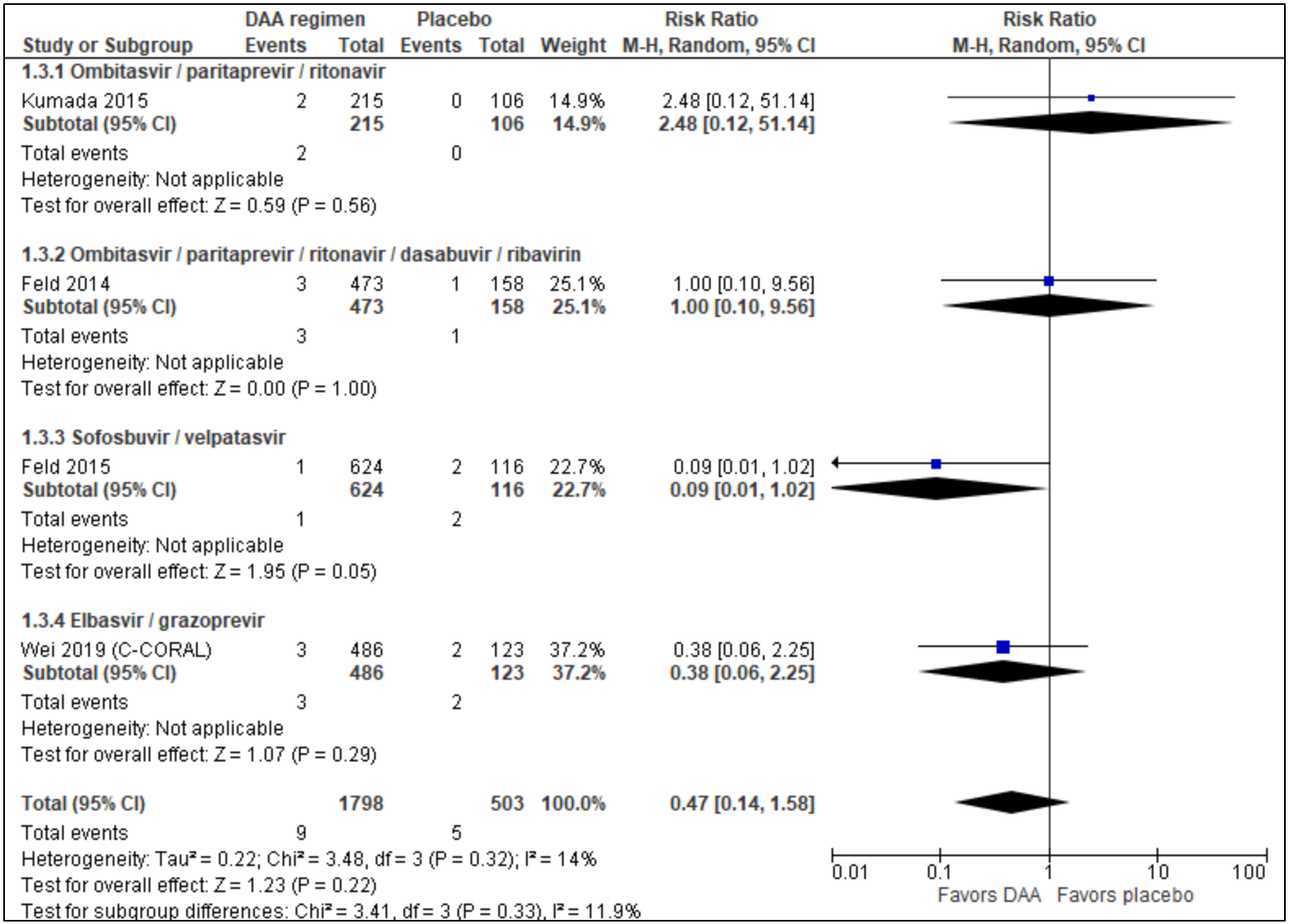
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

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



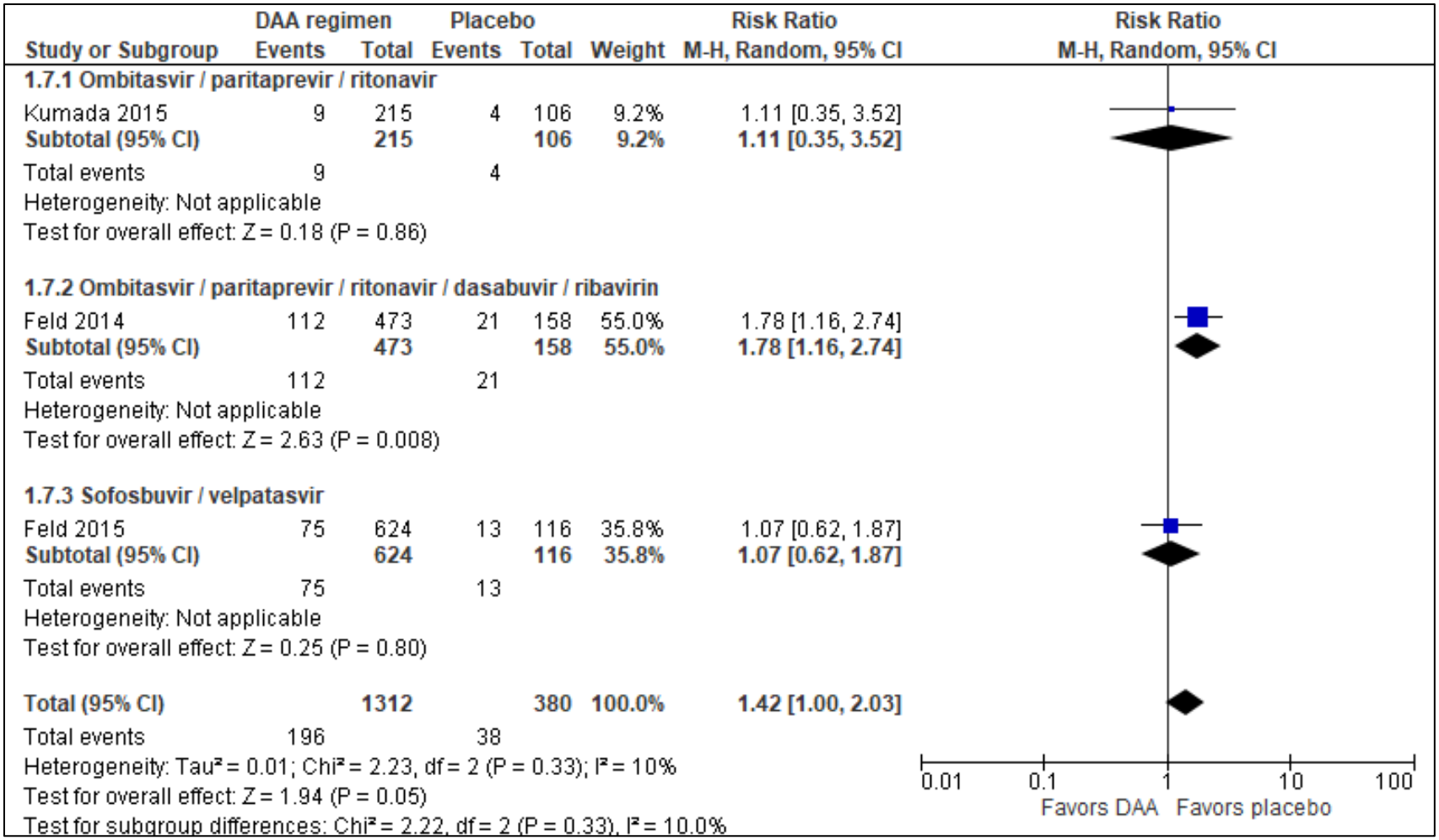
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

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



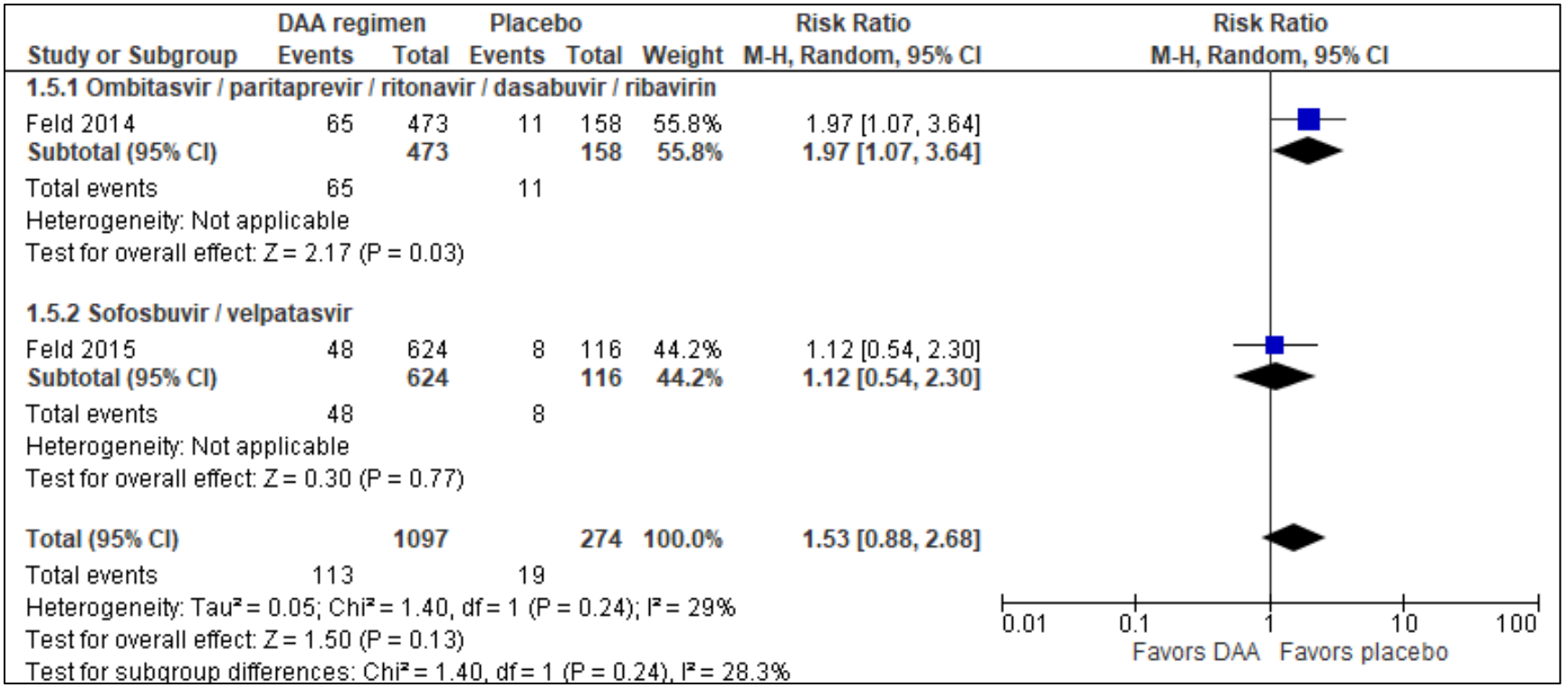
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

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



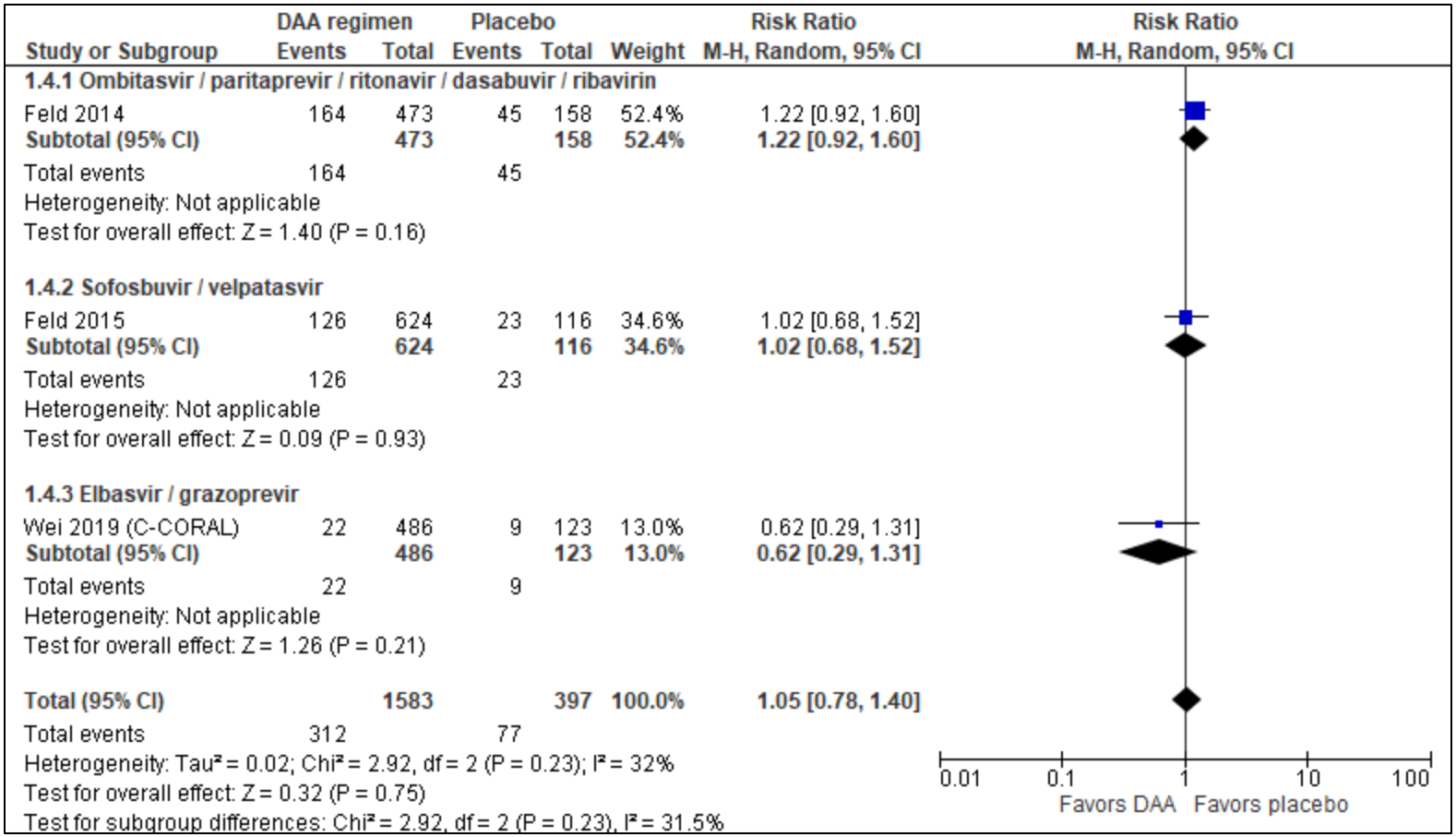
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test.

Figure 13. Key Question 8: Direct Acting Antivirals Versus Placebo, Diarrhea



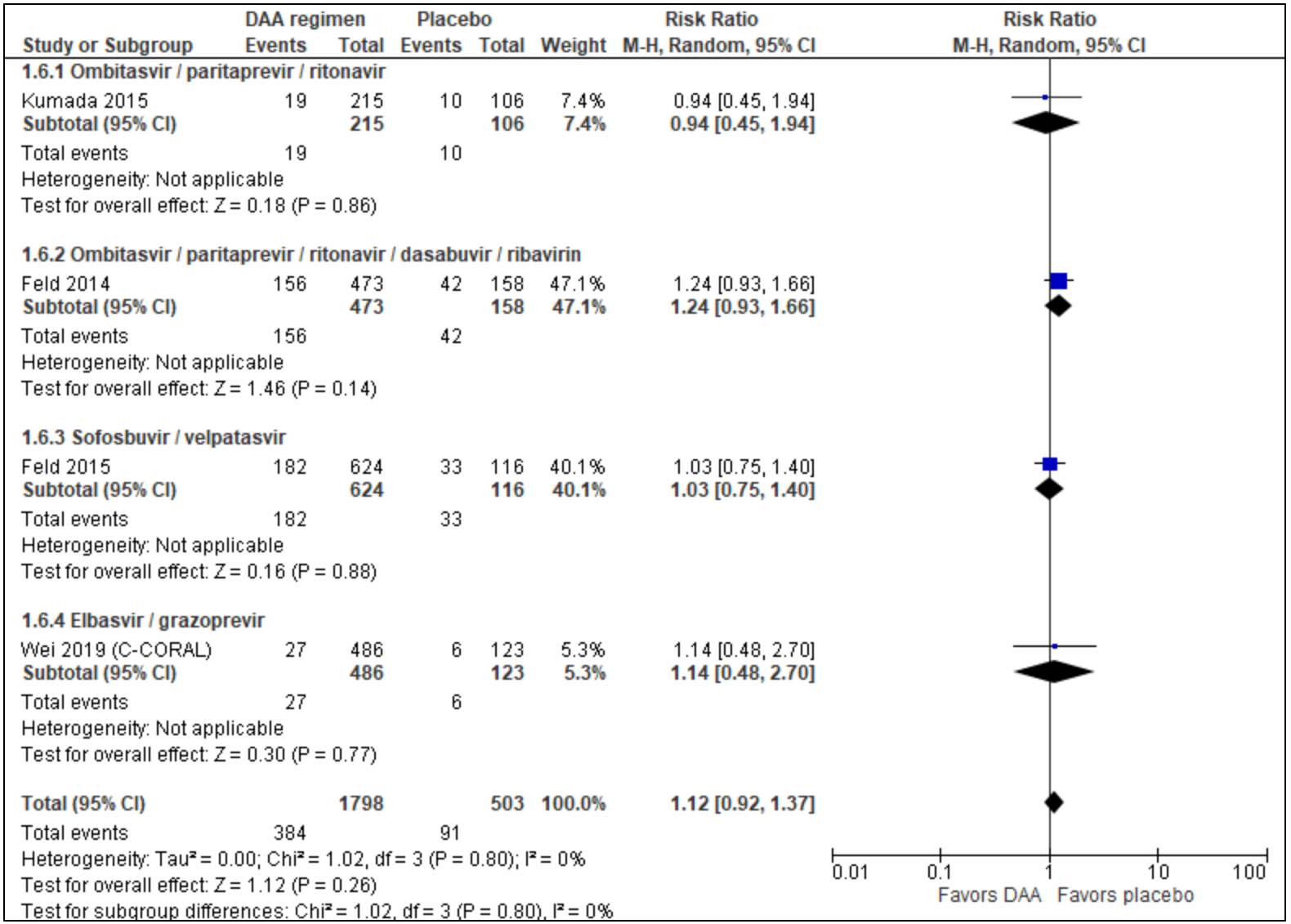
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test.

Figure 14. Key Question 8: Direct Acting Antivirals Versus Placebo, Fatigue



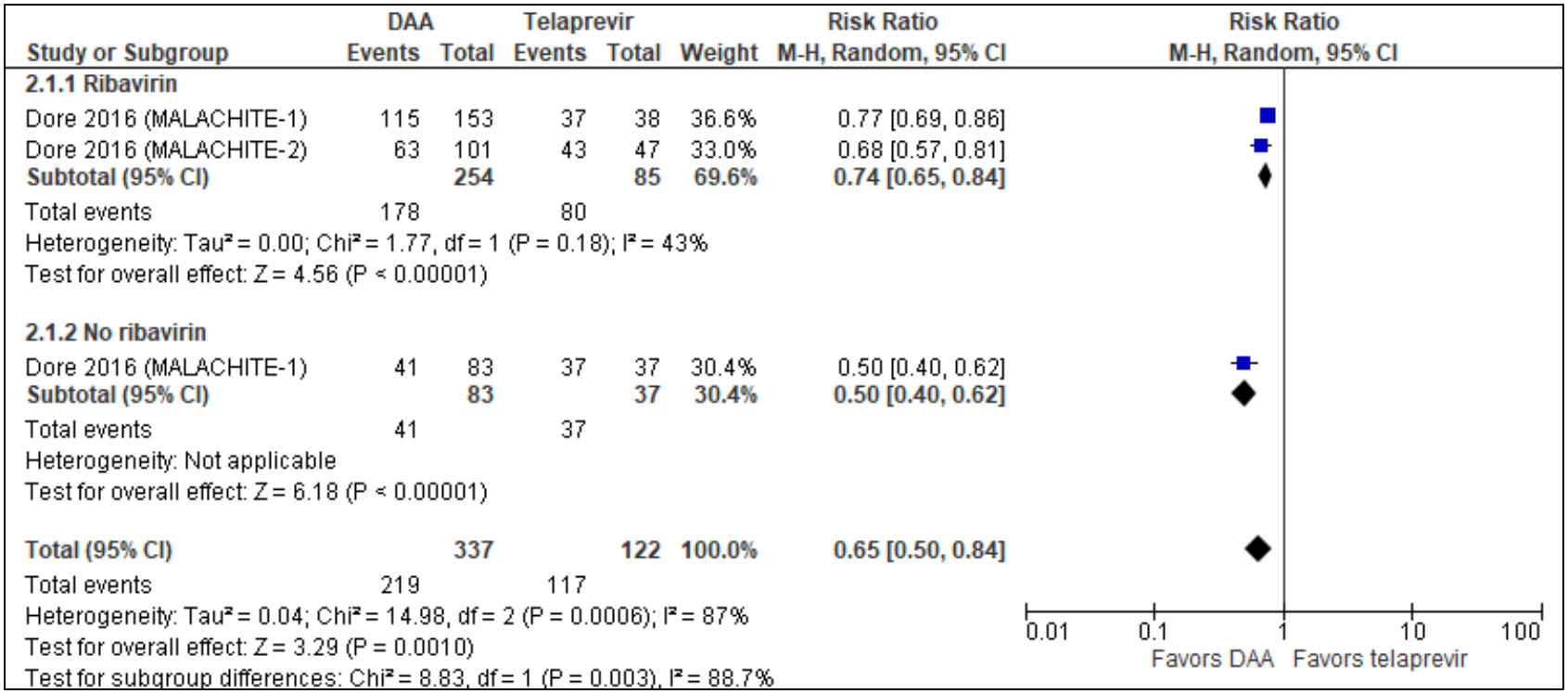
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

Figure 15. Key Question 8: Direct Acting Antivirals Versus Placebo, Headache



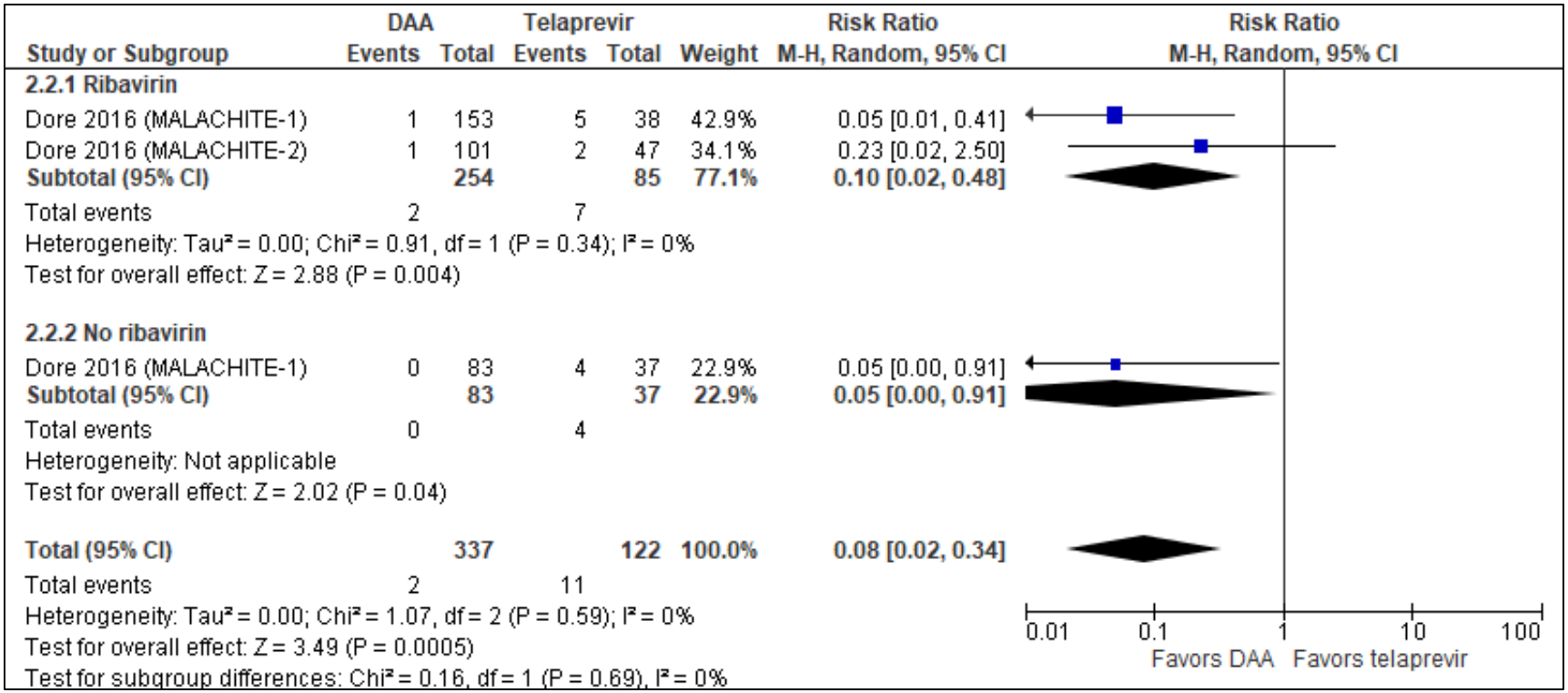
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

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



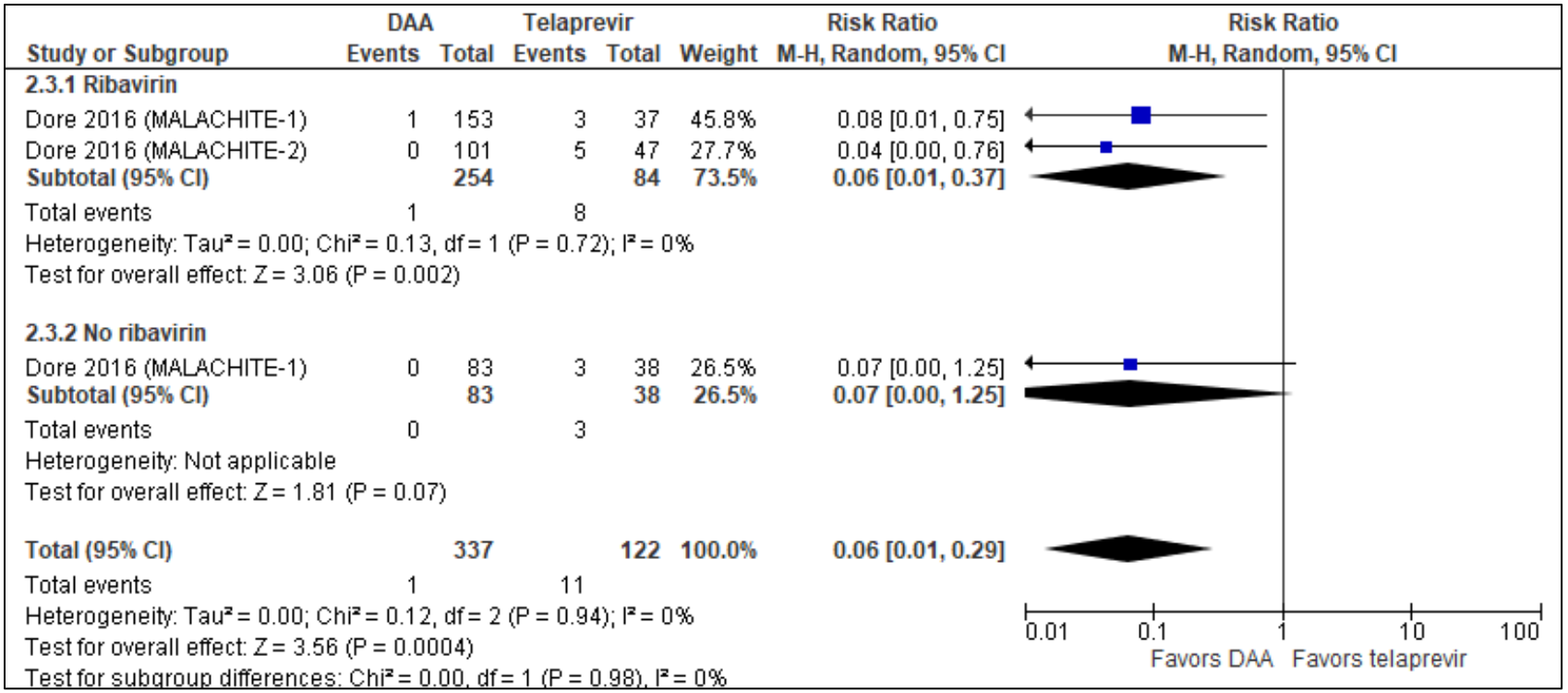
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

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



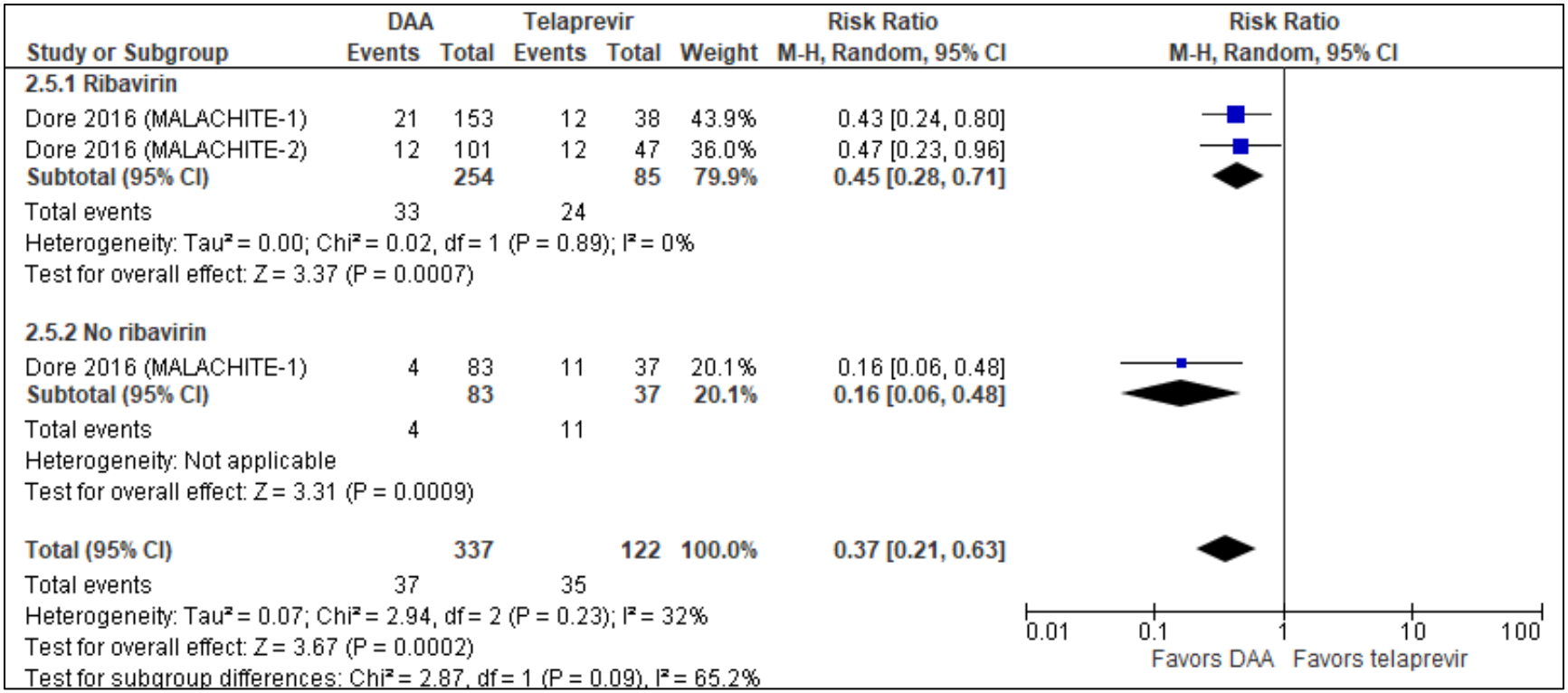
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

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



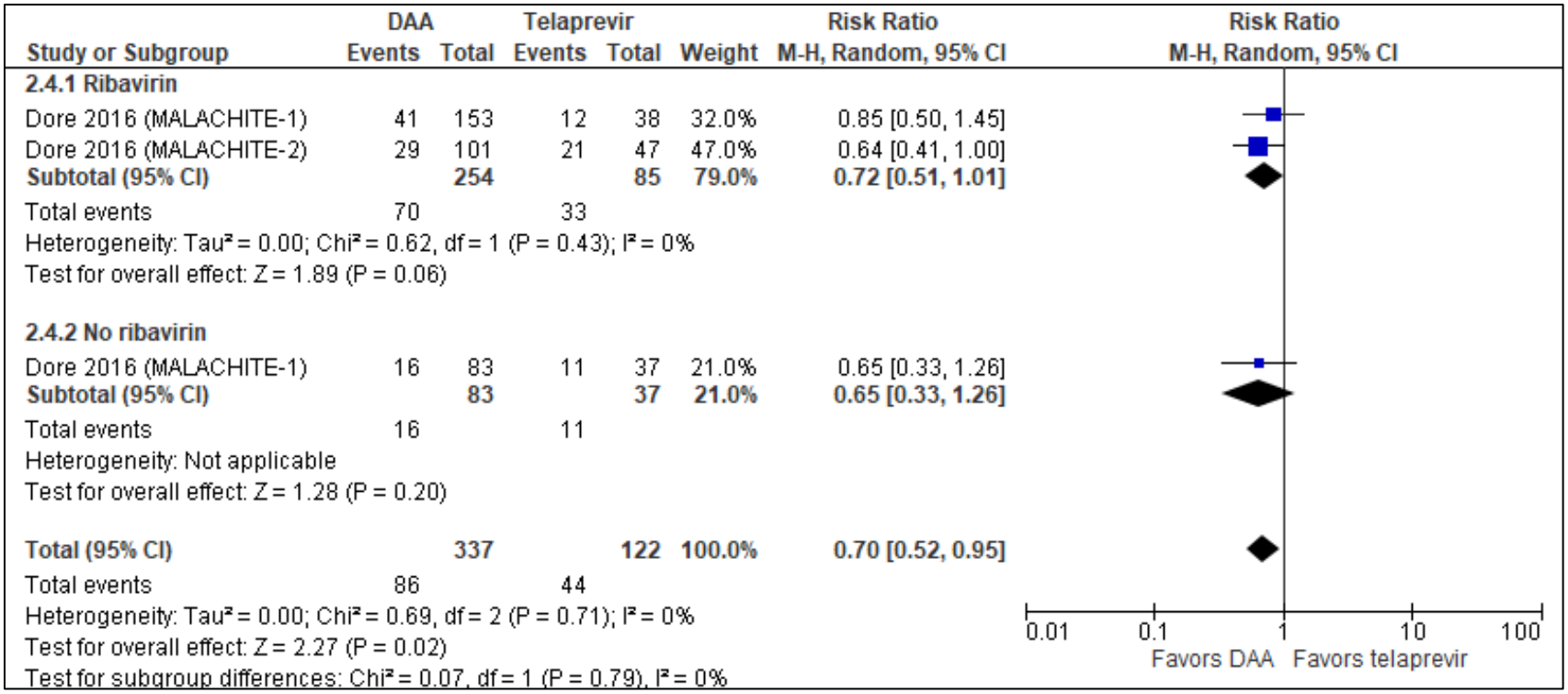
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

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



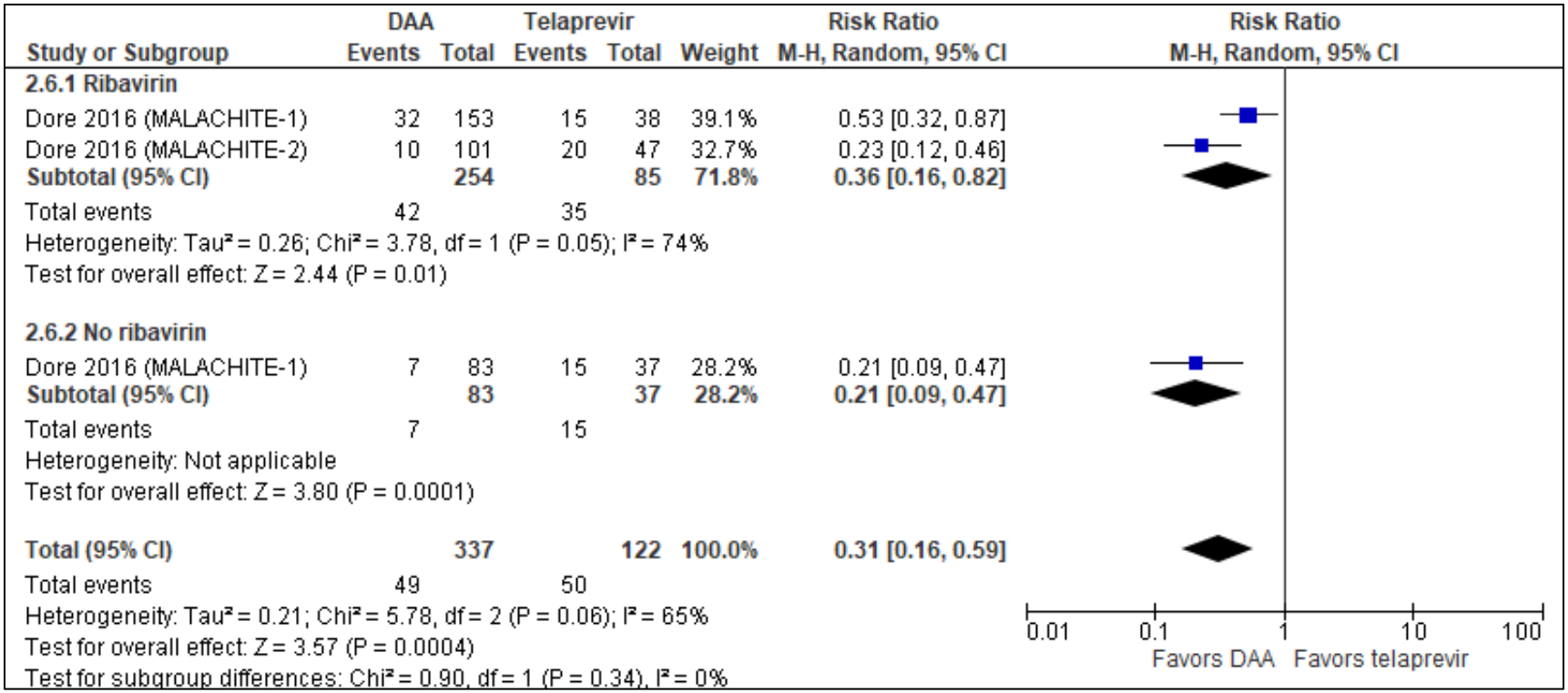
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

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



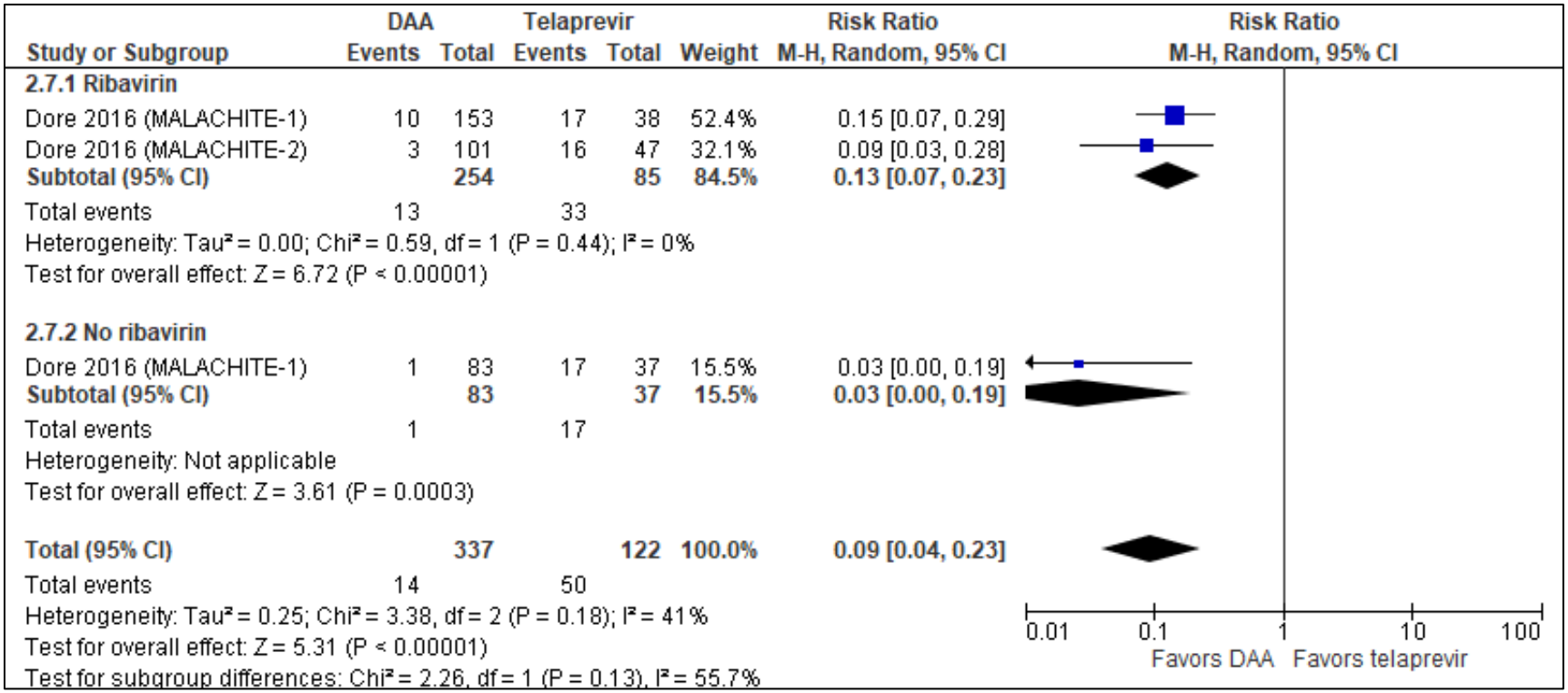
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

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



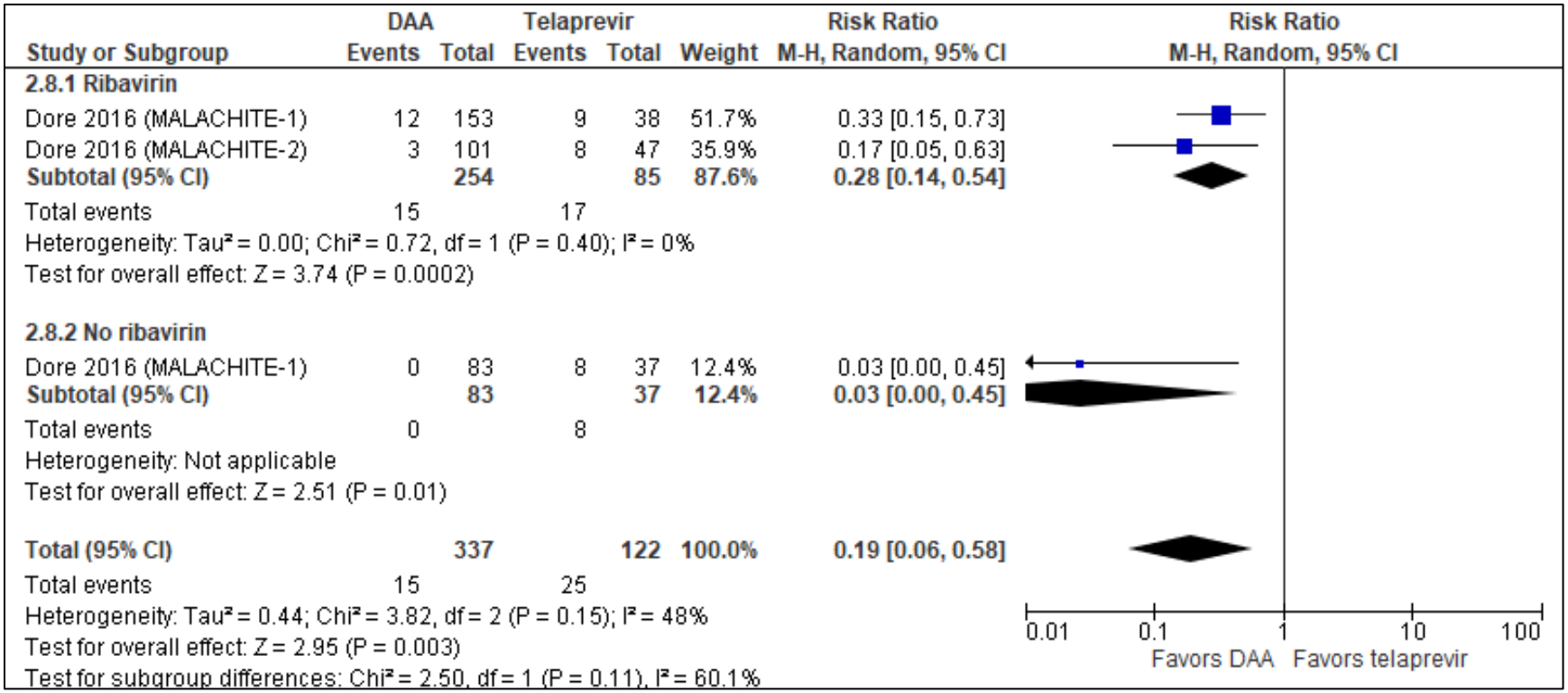
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

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



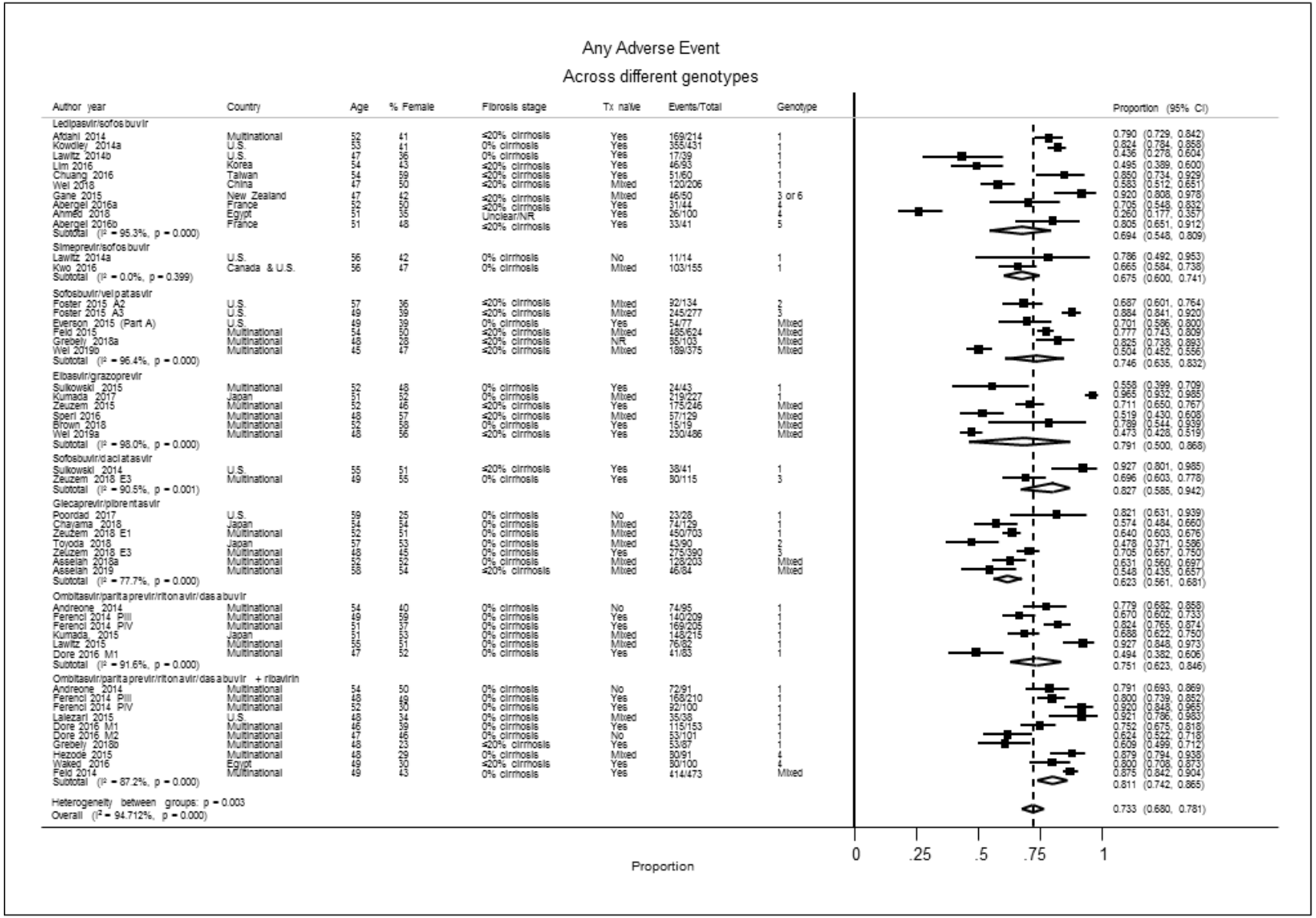
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

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



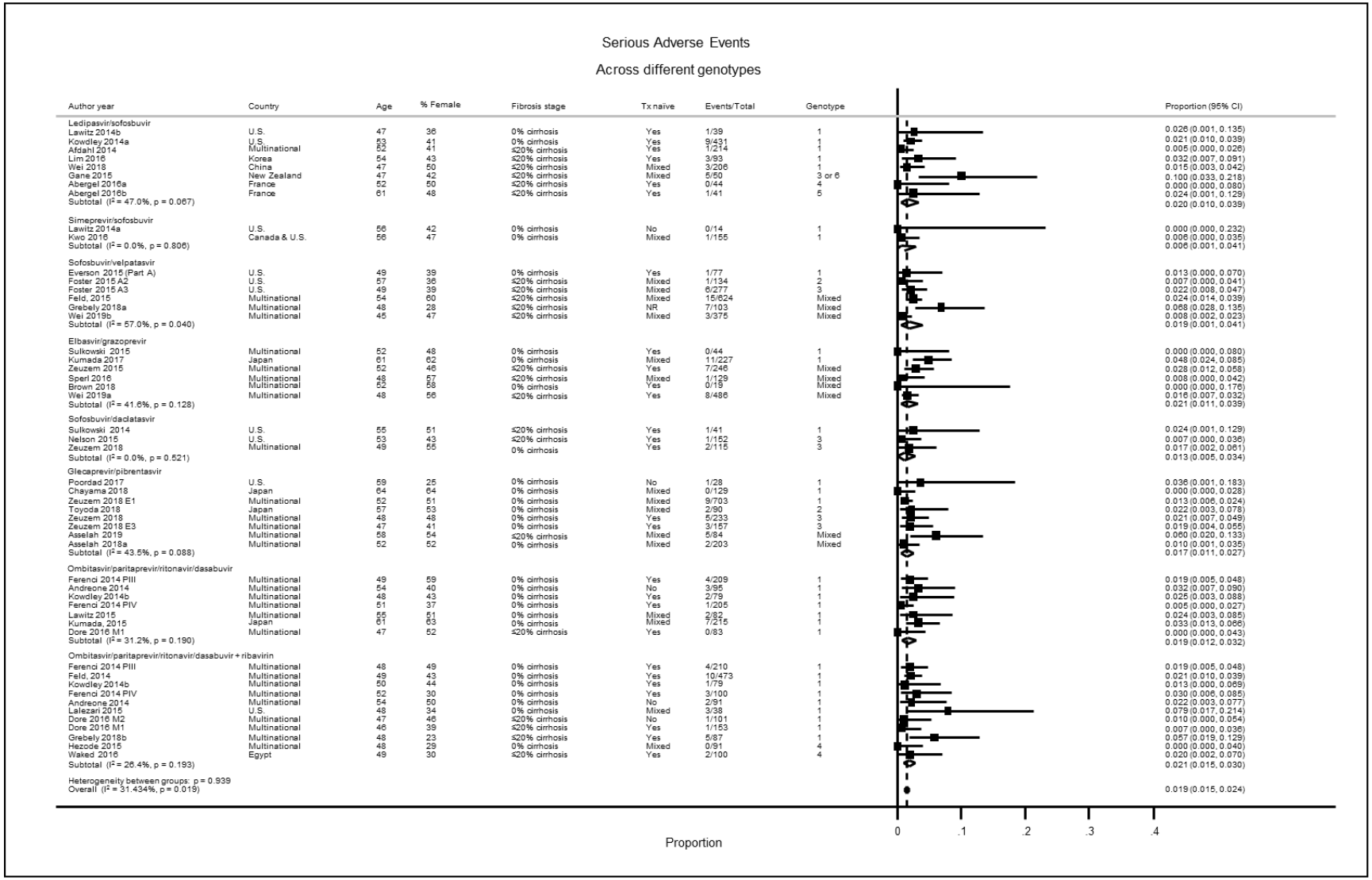
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; df = degrees of freedom; M-H = Mantel-Haenszel test. Study names are not acronyms.

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



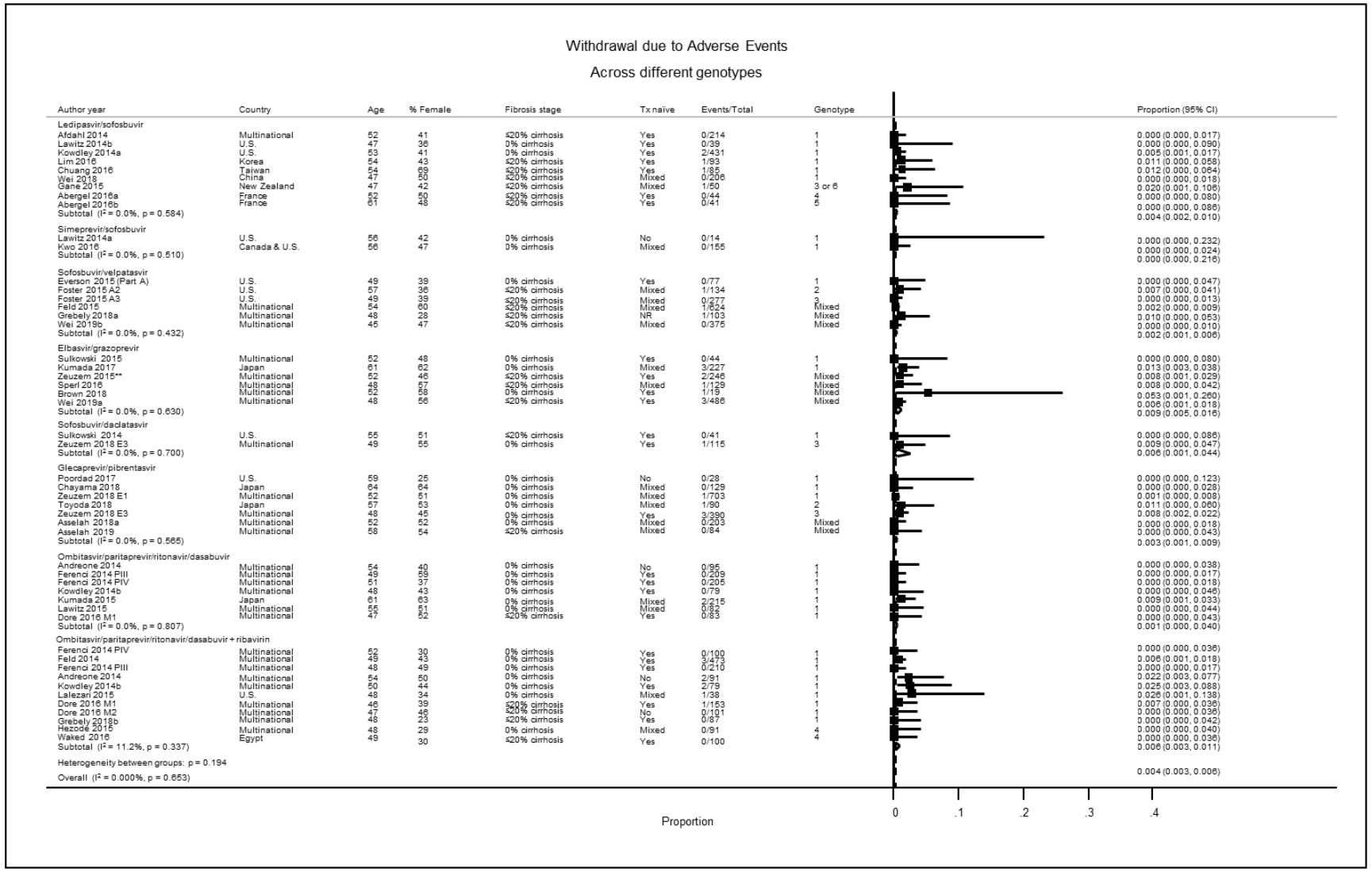
Abbreviations: CI = confidence interval; Tx = treatment; U.S. = United States.

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



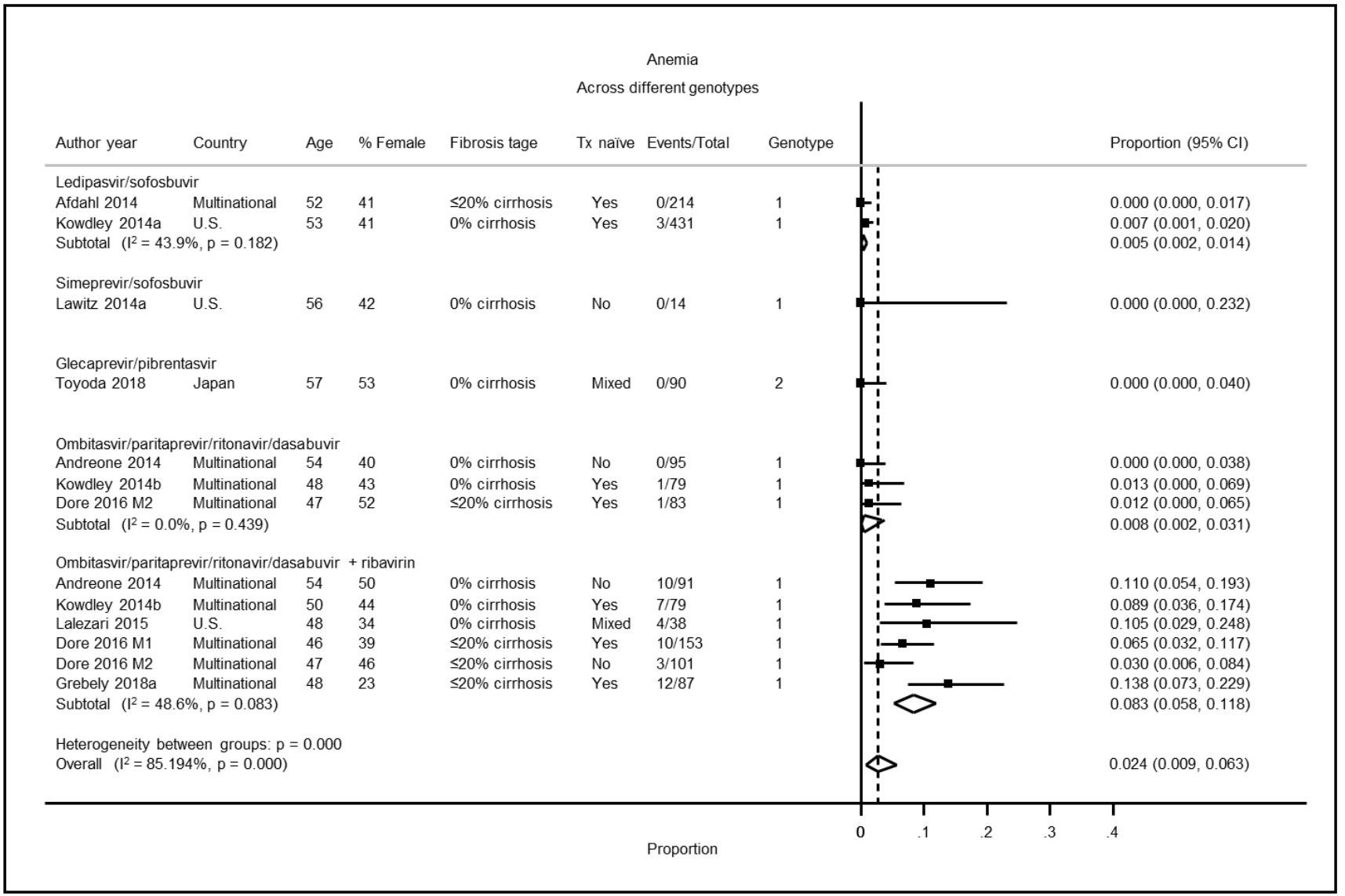
Abbreviations: CI = confidence interval; Tx = treatment; U.S. = United States

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



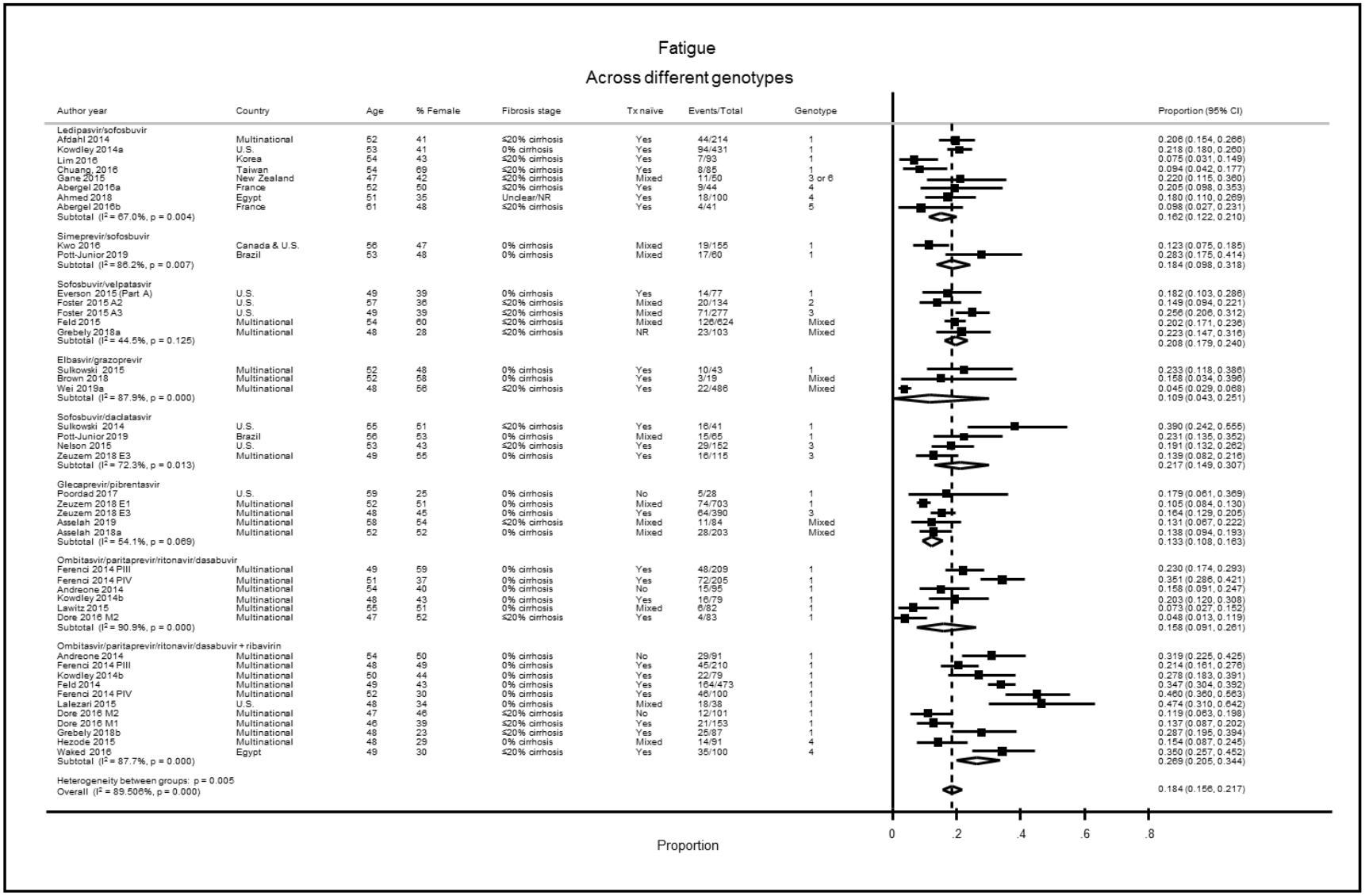
Abbreviations: CI = confidence interval; NR = not reported; Tx = treatment; U.S. = United States.

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



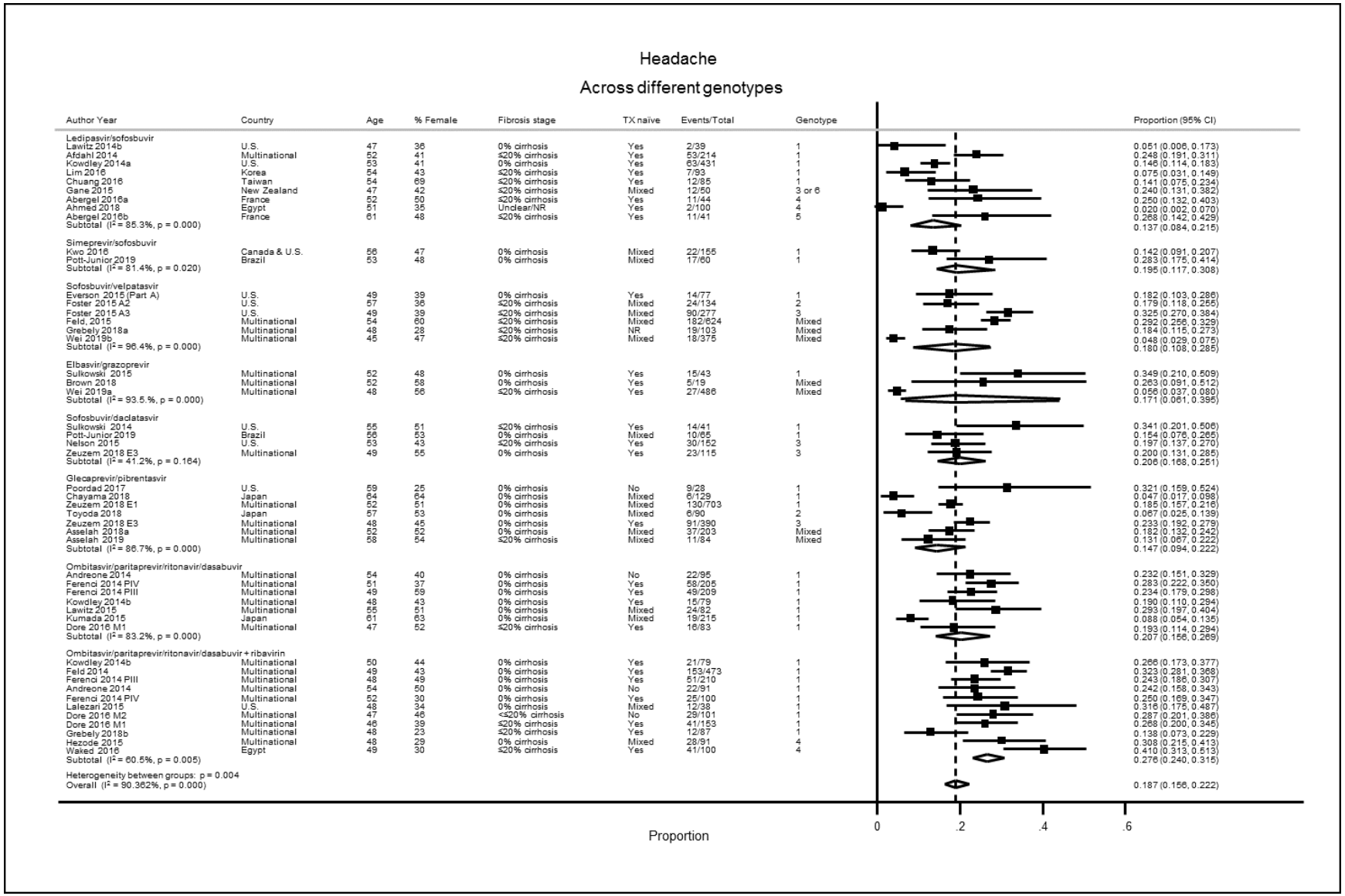
Abbreviations: CI = confidence interval; Tx = treatment; U.S. = United States.

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



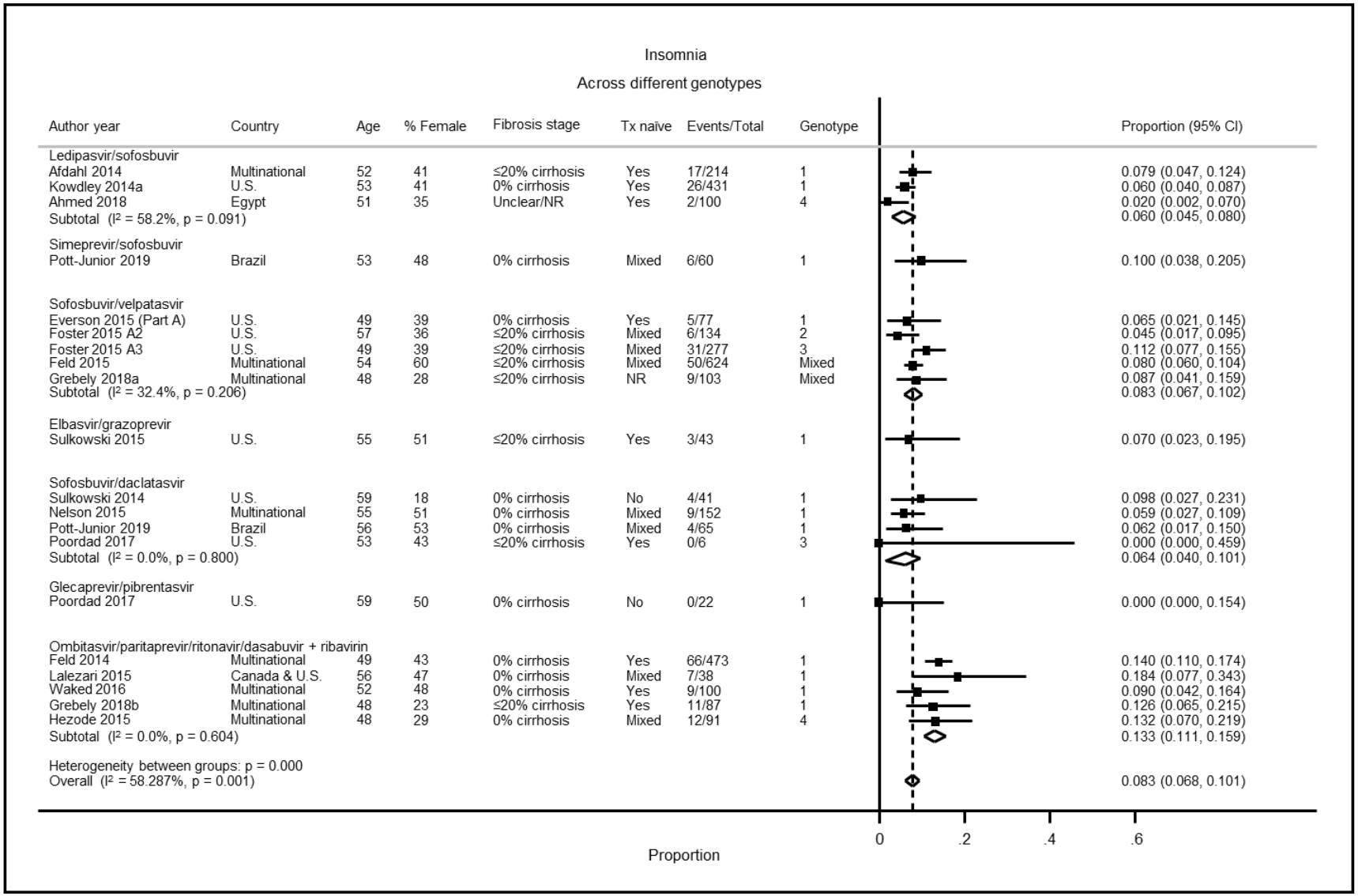
Abbreviations: CI = confidence interval; NR = not reported; Tx = treatment; U.S. = United States.

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



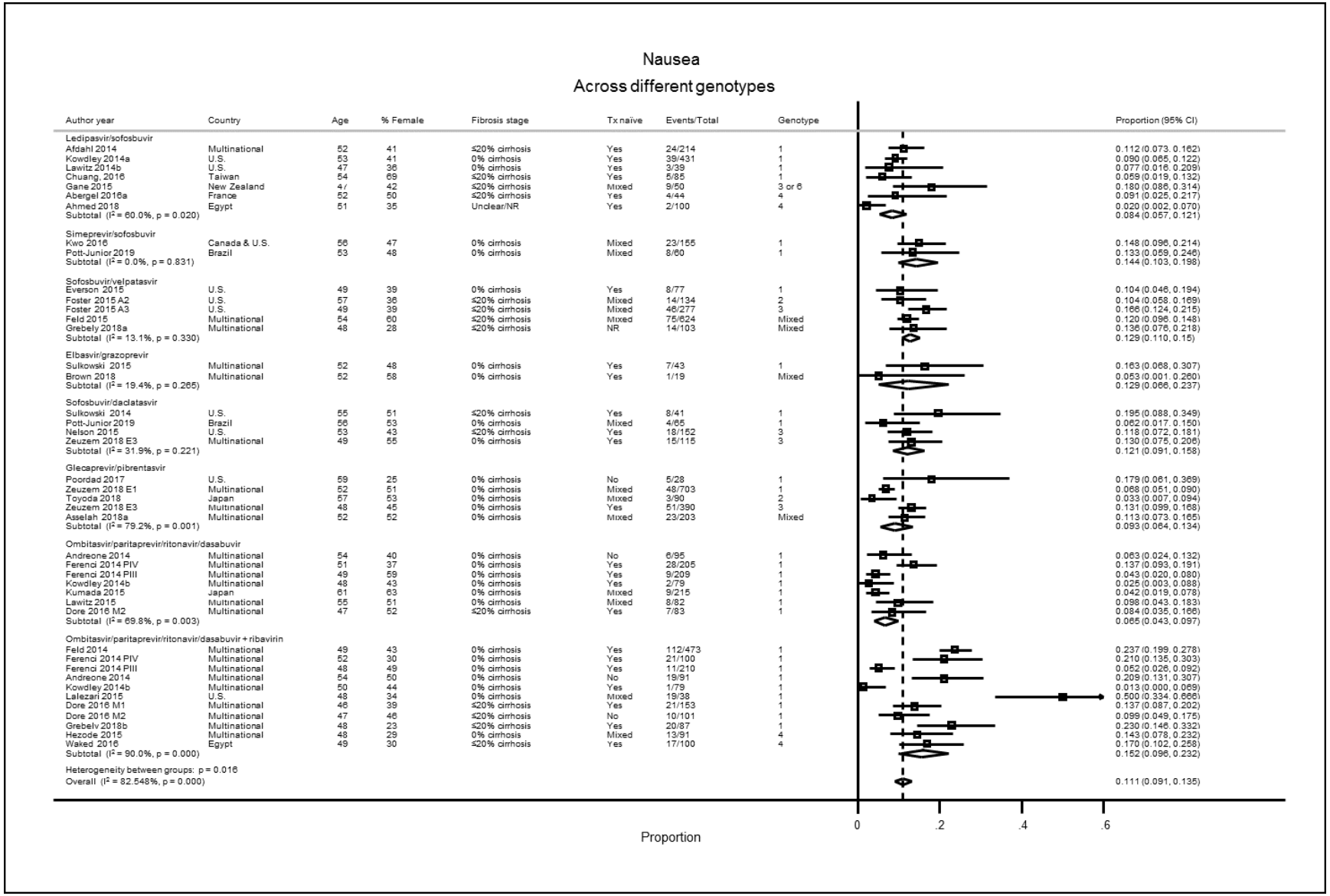
Abbreviations: CI = confidence interval; NR = not reported; Tx = Treatment; U.S. = United States.

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



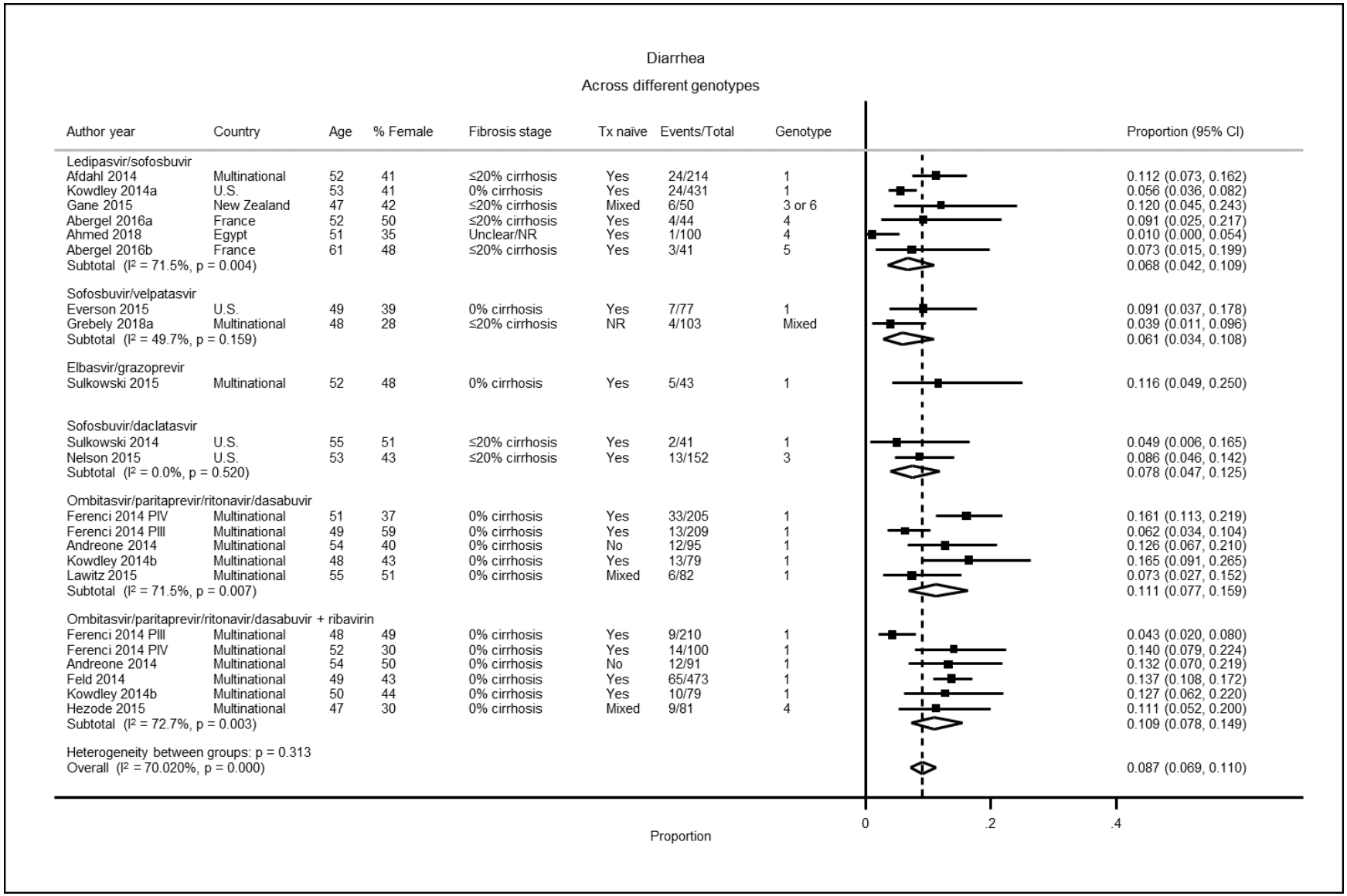
Abbreviations: CI = confidence interval; Tx = treatment; U.S. = United States.

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



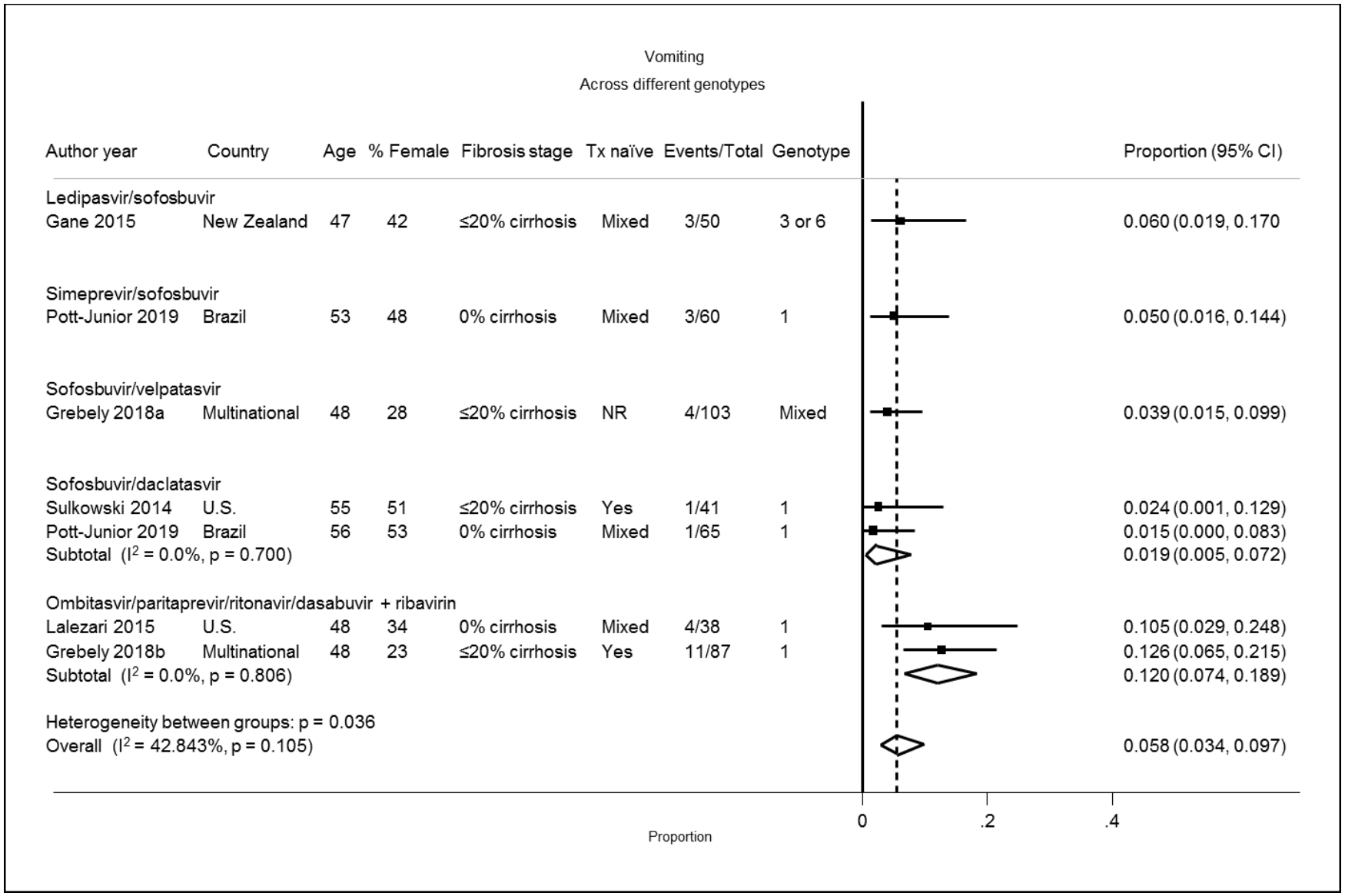
Abbreviations: CI = confidence interval; NR = not reported; Tx = Treatment; U.S. = United States.

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



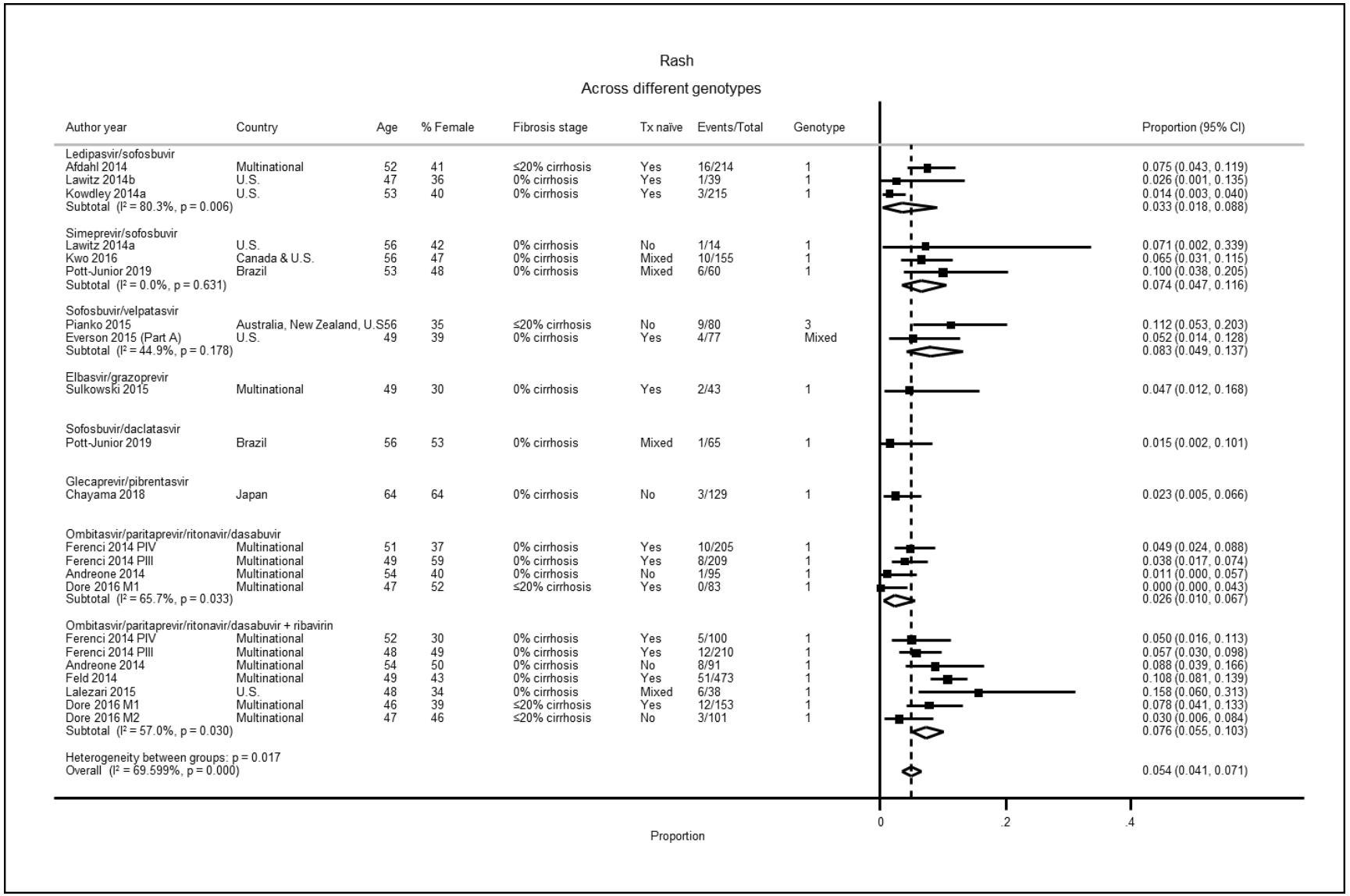
Abbreviations: CI = confidence interval; NR = not reported; Tx = treatment; U.S. = United States.

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



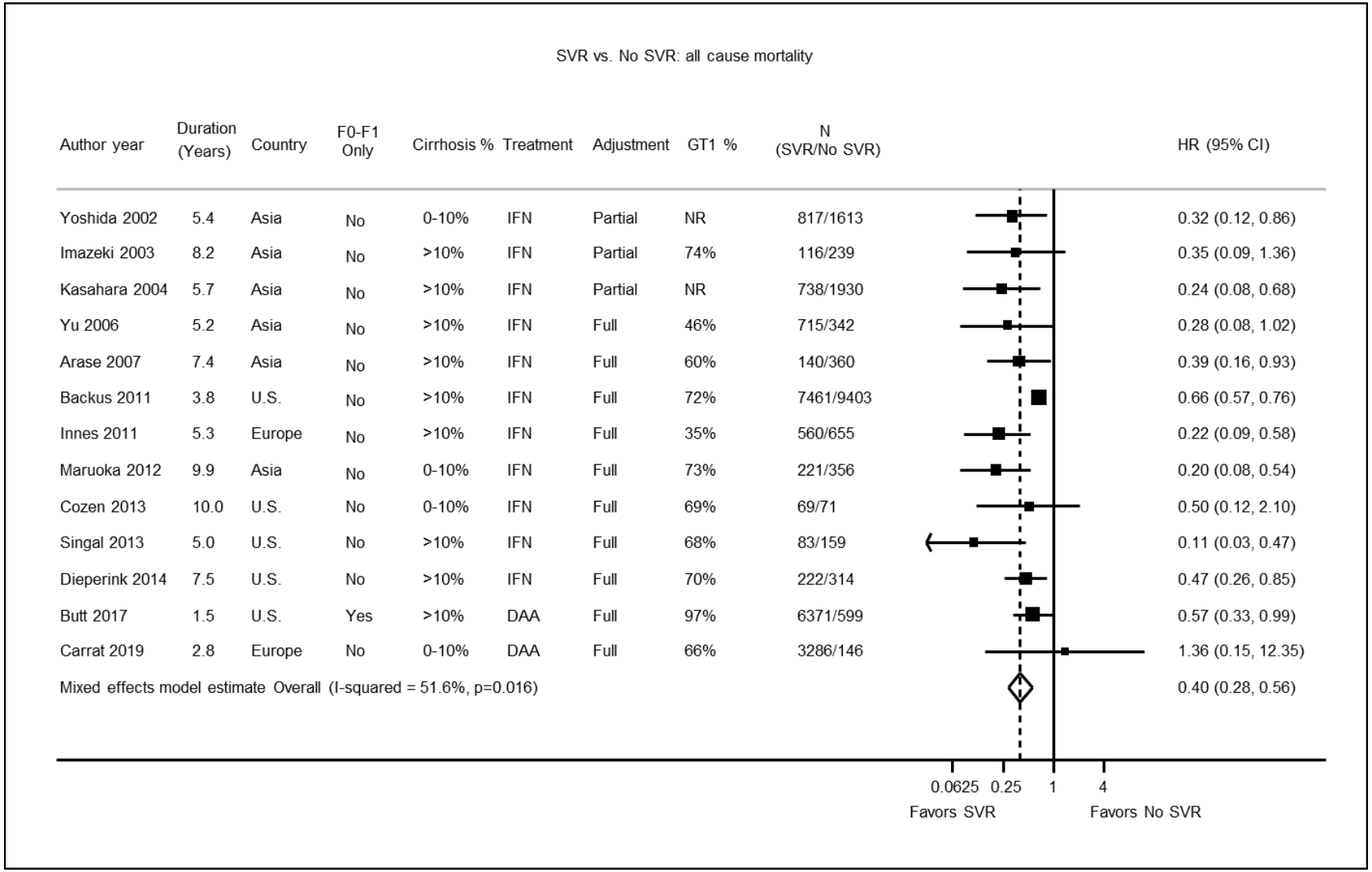
Abbreviations: CI = confidence interval; NR = not reported; Tx = treatment; U.S. = United States.

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



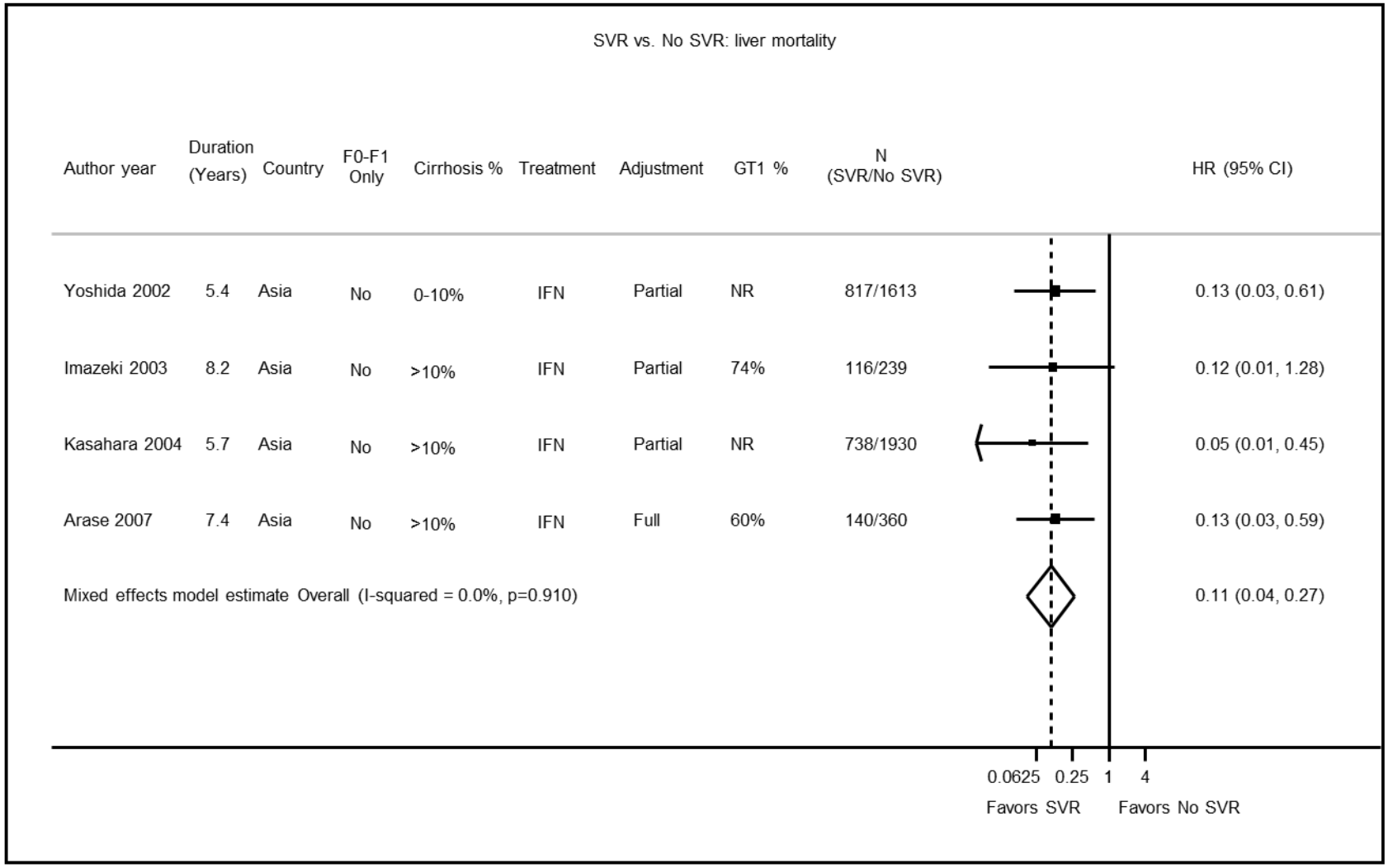
Abbreviations: CI = confidence interval; Tx = treatment; U.S. = United States.

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



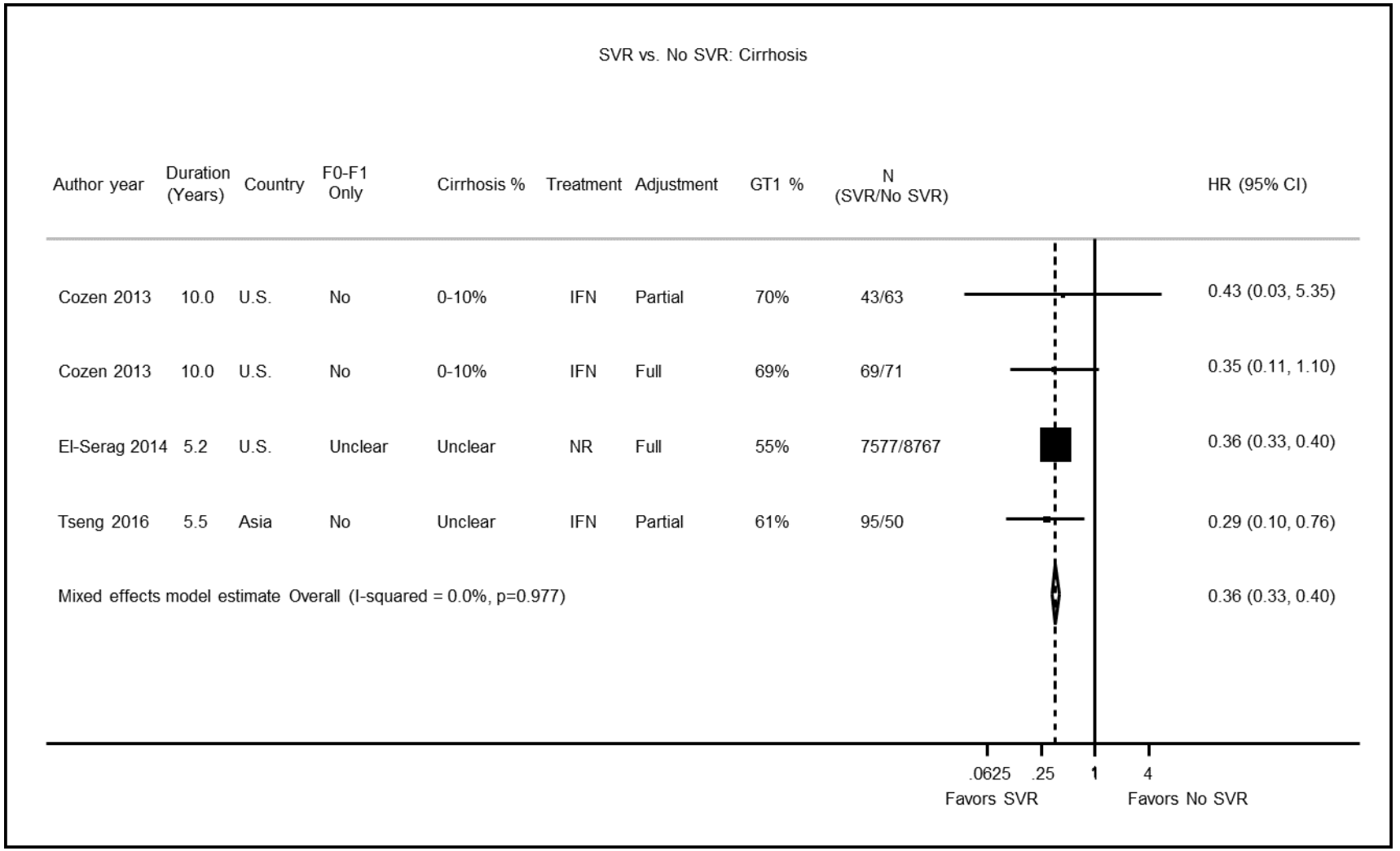
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; HR = hazard ratio; IFN = interferon; NR = not reported; SVR = sustained virologic response; U.S. = United States.

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



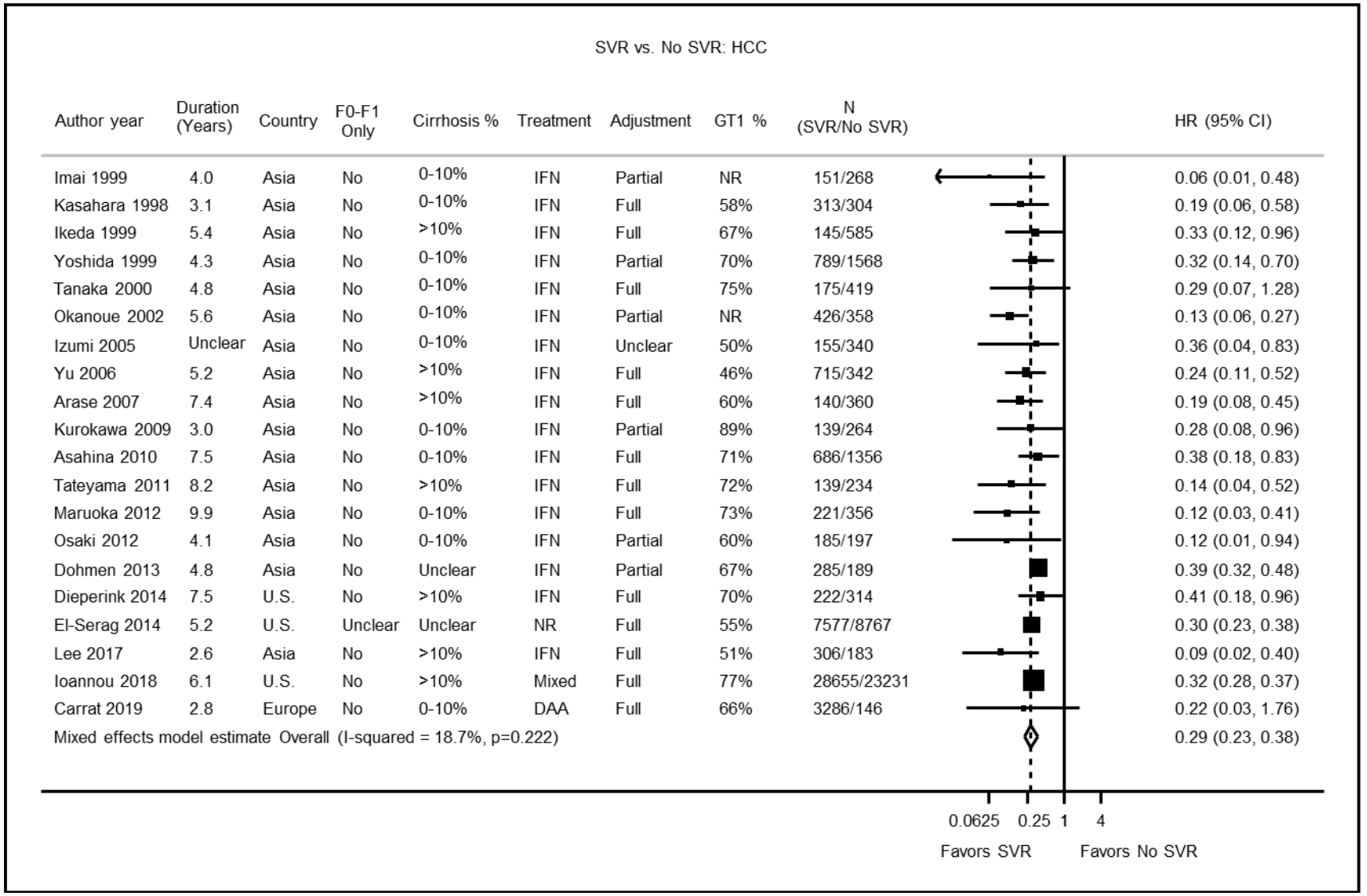
Abbreviations: CI = confidence interval; GT1 = genotype 1; HR = hazard ratio; IFN = interferon; NR = not reported; SVR = sustained virologic response.

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 ≥12 Years Old 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. U.S. 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%	0%	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	52%	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%	15%	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)
Afdahl 2014[185] ION-1	Ledipasvir + sofosbuvir	1	52	41%	0%*	100%	100% (357/357)
Chuang 2016[145]	Ledipasvir + sofosbuvir	1	55	58%	12%	100%	98% (83/85)
Lawitz 2014b[193] LONESTAR	Ledipasvir + sofosbuvir	1	48	38%	0%	100%	97% (58/60)
Lim 2016[156]	Ledipasvir + sofosbuvir	1	54	43%	9%	100%	100% (46/46)
Wei 2018[163]	Ledipasvir + sofosbuvir	1	47	50%	16%	52%	100% (206/206)
Grebely 2018[149] D3FEAT	Ombitasvir + paritaprevir + ritonavir + dasabuvir	1	48	22%	8%	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	30%	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	53%	0%	60%	100% (65/65)
Sulkowski 2014[161] A1444040 Study	Sofosbuvir + daclatasvir	1	55	51%	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	60%	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	45%	0%	0%	98% (176/179)
Feld, 2014[187] SAPPHIRE-1	Ombitasvir + paritaprevir + ritonavir + dasabuvir	1b	49	43%	0%	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	42%	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%	8%	92%	96% (24/25)
Feld 2015[139] ASTRAL-1	Sofosbuvir + velpatasvir	6	54	60%	0%*	68%	100% (35/35)
Grebely 2018[150] SIMPLIFY	Sofosbuvir + velpatasvir	1, 3	48	28%	9%	NR	94% (97/103)
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)	4[137,187,188,191]	93.7% (89.0% to 96.5%)	77%	--
• Ombitasvir / paritaprevir / ritonavir / dasabuvir‡ (genotype 1b)	7[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]	96.7% (93.1% to 98.4%)	82%	0.48 (geographic setting)
• Multinational	12†	97.7% (96.4% to 98.6%)	89%	--
• Other geographic setting	4	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]	99.7% (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[146,147,157,158,164,167]	95.2% (91.4% to 97.3%)	0%	--
• Treatment-naïve	4[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)	6[139,142,162,164,166,198]	99.1% (91.2% to 99.9%)	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
Afdahl 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 2018[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 2018c[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%	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%	27% (11/41)	10% (4/41)	Diarrhea: 7% (3/41)	NR	NR	NR
Afdahl 2014[185] ION-1	Ledipasvir + sofosbuvir	NA	79% (169/214)	0.5% (1/214)	0%	25% (53/214)	21% (44/214)	Nausea: 11% (24/214) Diarrhea: 11% (24/214)	0%	8% (17/214)	7% (16/214)

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
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
Andreone 2014[186] PEARL II	Ombitasvir + paritaprevir + ritonavir + dasabuvir	NA	77.9% (74/95)	3% (3/95)	0%	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%	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%	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%	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%	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%	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%	25% (25/100)	46% (46/100)	Nausea: 21% (21/100) Diarrhea: 14% (14/100)	NR	NR	5% (5/100)

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
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
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 2018[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 2018c[149] D3FEAT	Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	NA	61% (53/87)	6% (5/87)	0%	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%	31% (28/91)	15% (14/91)	Nausea: 14% (13/91) Diarrhea: 14% (6/42)	NR	13% (12/91)	NR
Kowdley 2014b[191] AVIATOR	Ombitasvir + paritaprevir + ritonavir + dasabuvir	NA	NR	3% (2/79)	0%	19% (15/79)	20% (16/79)	Nausea: 3% (2/79) Diarrhea: 16% (13/79)	1% (1/79)	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 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
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%	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%	NR	NR	NR	0%	NR	7% (1/14)
Lawitz 2014b[193] LONESTAR	Ledipasvir + sofosbuvir	NA	45% (17/39)	3% (1/39)	0%	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%	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

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
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%	32% (9/28)	18% (5/28)	Nausea: 18% (5/28)	NR	0%	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)
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%	NR	NR	NR	NR	NR	NR
Sulkowski 2014[161] A1444040 Study	Sofosbuvir + daclatasvir	NA	93% (38/41)	2% (1/41)	0%	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%	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%	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
Waked 2016[162] AGATE-II	Ombitasvir + paritaprevir + ritonavir + ribavirin	NA	80% (80/100)	2% (2/100)	0%	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%	NR	NR	NR	NR	NR	NR
Wei 2019b[165]	Sofosbuvir + velpatasvir	NA	50% (189/375)	1% (3/375)	0%	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% (7/390)	0.8% (3/390)	23% (91/390)	16% (64/390)	Nausea: 13% (51/390)	NR	NR	NR
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=31%; k=42[137,139,141-144,146-157,160-167,185-194,196-199]	0.4% (0.3% to 0.6%); I^2=0%; k=41[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%); 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% (1.1% to 2.7%); I^2=44%; 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=19%; k=24[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=93.4%; k=16[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=9%; 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]	8.3% (6.8% to 10.1%); I^2=58%; 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 30.1%); 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]	6.4% (4.0% to 10.1%); I^2=0%; k=4[157,159,161,194]
• 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 15.4%); 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]	27.6% (24.0% to 31.5%); I^2=61%; k=11[137,149,162,187-189,191,192]	13.3% (11.1% to 15.9%); I^2=0%; k=5[149,162,187,189,192]
• Patients with cirrhosis excluded	2.1% (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% (15.5% to 24.3%); I^2=87%; k=22[144,146,151,153,155,159,160,167,186-194,196,197,199]	9.0% (7.0% to 11.5%); I^2=68%; 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]	8.4% (6.4% to 10.9%); I^2=12%; 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 26.1%); I^2=91%; k=24[137,141,142,144-146,148,149,156,157,160,162,164,167,185,187-191,193,195]	7.9% (5.9% to 10.7%); I^2=68%; k=10[146,149,160,162,185,187,189,190,194,195]
• 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]	10.0% (5.2% to 18.5%); I^2=68%; k=3[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.

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]	8.7% (6.9% to 11.0%); I^2=70%; k=18[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]	6.1% (3.4% to 10.8%); I^2=50%; k=2[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 7.1%); I^2=69%; 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% (5.5% to 11.6%); I^2=8%; k=7[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]	8.9% (6.9% to 11.4%); I^2=77%; k=15[141,142,146,148,157,160,161,185,187-191,195]	9.6% (5.3% to 16.9%); 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]	10.0% (5.0% to 18.9%); 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=87%; k=12[139,147,148,151,153,155,159,167,192,196,199]	10.1% (4.5% to 21.1%); I^2=39%; k=2[148,155]	4.3% (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)
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 Versus 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: 7,461 No SVR: 9,403	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: 145 No SVR: 585	0%	67%	Yes
Imai 1999[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%	35%	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%	89%	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: 426	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 Versus 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 Versus 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	0.48 (0.30 to 0.79)	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%	0.33 (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 0.50)	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 (0.19 to 0.35)	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=5 (3 trials [n=230] and 2 post-hoc observational studies [n=152])	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=9,917; 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=9,917)	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=31% • 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): 8.3%, 95% CI, 6.8% to 10.1%; I^2=58% • Nausea (36 trials): 11.1%; 95% CI, 9.1% to 13.5%, I^2=82% • Diarrhea (18 trials): 8.7%, 95% CI, 6.9% to 11.0%; I^2=70% • 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	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 – 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=116,821 [n=27,367 from studies included in the prior report + n=89,454 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

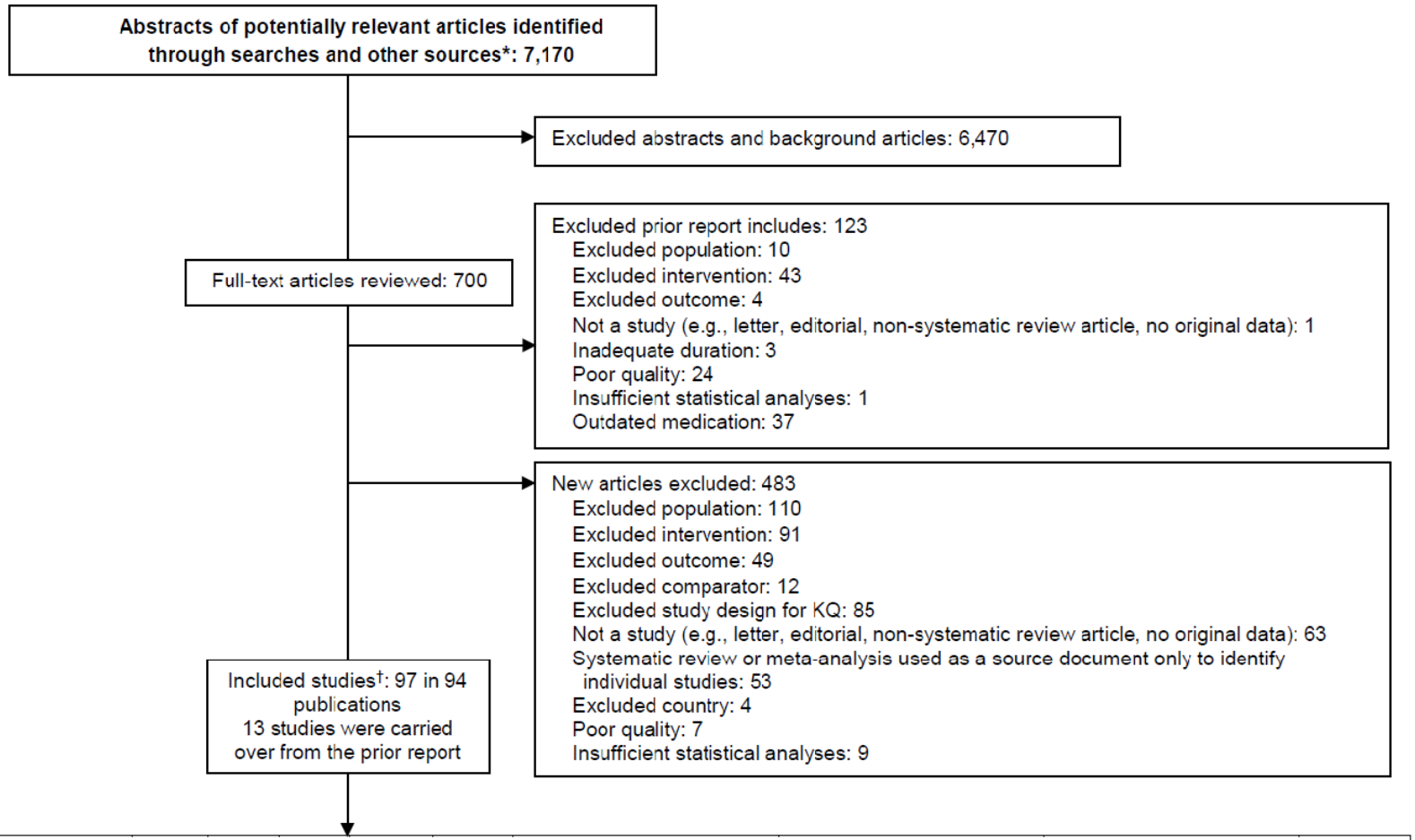
Appendix A2. Inclusion and Exclusion Criteria

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.

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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.

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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.

Ng X, Nwankwo C, Arduino JM, et al. Patient-reported outcomes in individuals with hepatitis C virus infection treated with elbasvir/grazoprevir. Patient Prefer Adherence. 2018;12:2631-8. doi: 10.2147/PPA.S172732. PMID: 30587935.

Okanoue T, Itoh Y, Kirishima T, et al. Transient biochemical response in interferon therapy decreases the development of hepatocellular carcinoma for five years and improves the long-term survival of chronic hepatitis C patients. Hepatol Res. 2002;23(1):62-77. PMID: 12084557.

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Pianko S, Flamm SL, Shiffman ML, et al. Sofosbuvir plus velpatasvir combination therapy for treatment-experienced patients with genotype 1 or 3 hepatitis C virus infection: a randomized trial. Ann Intern Med. 2015;163(11):809-17. doi: 10.7326/M15-1014. PMID: 26551263.

Poordad F, Felizarta F, Asatryan A, et al. Glecaprevir and pibrentasvir for 12 weeks for hepatitis C virus genotype 1 infection and prior direct-acting antiviral treatment. Hepatology. 2017;66(2):389-97. doi: 10.1002/hep.29081. PMID: 28128852.

Pott-Junior H, Bricks G, Grandi G, et al. Sofosbuvir in combination with daclatasvir or simeprevir for 12 weeks in noncirrhotic subjects chronically infected with hepatitis C virus genotype 1: a randomized clinical trial. Clin Microbiol Infect. 2019;25(3):365-71. doi: 10.1016/j.cmi.2018.06.007. PMID: 29906601.

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Sulkowski M, Hezode C, Gerstoft J, et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015;385(9973):1087-97. doi: 10.1016/s0140-6736(14)61793-1. PMID: 25467560.

Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014;370(3):211-21. doi: 10.1056/NEJMoa1306218. PMID: 24428467.

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Toyoda H, Chayama K, Suzuki F, et al. Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 2 hepatitis C virus infection. Hepatology. 2018;67(2):505-13. PMID: 28865152.

Tseng CW, Chang TT, Tzeng SJ, et al. Association of sustained virologic response with reduced progression to liver cirrhosis in elderly patients with chronic hepatitis C. Clin Interv Aging. 2016;11:327-34. doi: 10.2147/CIA.S97242. PMID: 27051280.

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.

Wei L, Jia JD, Wang FS, et al. Efficacy and safety of elbasvir/grazoprevir in participants with hepatitis C virus genotype 1, 4, or 6 infection from the Asia-Pacific region and Russia: final results from the randomized C-CORAL study. J Gastroenterol Hepatol. 2019a;34(1):12-21. doi: 10.1111/jgh.14509. PMID: 30311701.

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.

Wei L, Xie Q, Hou JL, et al. Ledipasvir/sofosbuvir for treatment-naive and treatment-experienced Chinese patients with genotype 1 HCV: an open-label, phase 3b study. Hepatol Int. 2018;12(2):126-32. doi: 10.1007/s12072-018-9856-z. PMID: 29637511.

Wirth S, Rosenthal P, Gonzalez-Peralta RP, et al. Sofosbuvir and ribavirin in adolescents 12-17 years old with hepatitis C virus genotype 2 or 3 infection. Hepatology. 2017;66(4):1102-10. doi: 10.1002/hep.29278. PMID: 28543053.

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Yoshida H, Arakawa Y, Sata M, et al. Interferon therapy prolonged life expectancy among chronic hepatitis C patients. Gastroenterology. 2002;123(2):483-91. PMID: 12145802.

Yoshida H, Shiratori Y, Moriyama M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of hepatocarcinogenesis by Interferon Therapy. Ann Intern Med. 1999;131(3):174-81. PMID: 10428733.

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Younossi ZM, Stepanova M, Feld J, et al. Sofosbuvir and velpatasvir combination improves patient-reported outcomes for patients with HCV infection, without or with compensated or decompensated cirrhosis. Clin Gastroenterol Hepatol. 2017;15(3):421-30.e6. doi: 10.1016/j.cgh.2016.10.037. PMID: 27847279.

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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 wrong 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 wrong 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 wrong population.

Abdel-Moneim A, Abood A, Abdel-Gabaar M, et al. Effectiveness of sofosbuvir/pegylated-interferon plus ribavirin in treatment of hepatitis C virus genotype 4 patients. Clin Exp Hepatol. 2018;4(3):191-6. doi: 10.5114/ceh.2018.78123. PMID: 30324144. Excluded for wrong intervention.

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 wrong 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 wrong intervention.

Abergel A, Hezode C, Leroy V, et al. Peginterferon alpha-2b plus ribavirin for treatment of chronic hepatitis C with severe fibrosis: a multicentre randomized controlled trial comparing two doses of peginterferon alpha-2b. J Viral Hepat. 2006;13(12):811-20. doi: 10.1111/j.1365-2893.2006.00768.x. PMID: 17109680. Excluded for outdated medication.

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 wrong intervention.

Adler H, Lambert JS. Daclatasvir for the treatment of hepatitis C virus infection. Expert Rev Gastroenterol Hepatol. 2014;8(7):725-38. doi: 10.1586/17474124.2014.925798. PMID: 24882552. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

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 wrong population.

Aghemo A, Prati GM, Rumi MG, et al. Sustained virological response prevents the development of insulin resistance in patients with chronic hepatitis C. Hepatology. 2012;56(5):1681-7. doi: 10.1002/hep.25867. PMID: 22619107. Excluded for wrong population.

Ahmed OA, Elsebaey MA, Fouad MHA, et al. Outcomes and predictors of treatment response with sofosbuvir plus daclatasvir with or without ribavirin in Egyptian patients with genotype 4 hepatitis C virus infection. Infect Drug Resist. 2018;11:441-5. doi: 10.2147/IDR.S160593. PMID: 29628768. Excluded for wrong population.

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 wrong intervention.

Airoldi J, Berghella V. Hepatitis C and pregnancy. Obstet Gynecol Surv. 2006;61(10):666-72. doi: 10.1097/01.ogx.0000238671.13495.33. PMID: 16978426. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

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 wrong intervention.

Akiyama MJ, Kaba F, Rosner Z, et al. Hepatitis C screening of the "Birth Cohort" (born 1945-1965) and younger inmates of New York City jails. Am J Public Health. 2016;106(7):1276-7. doi: 10.2105/AJPH.2016.303163. PMID: 27196656. Excluded for wrong study design for Key Question.

Akiyama MJ, Kaba F, Rosner Z, et al. Correlates of hepatitis C virus infection in the targeted testing program of the New York City jail system. Public Health Rep. 2017;132(1):41-7. doi: 10.1177/0033354916679367. PMID: 28005477. Excluded for wrong study design for Key Question.

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 wrong 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 wrong 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 wrong 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 wrong 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.

Anderson EM, Mandeville RP, Hutchinson SJ, et al. Evaluation of a general practice based hepatitis C virus screening intervention. Scott Med J. 2009;54(3):3-7. doi: 10.1258/rsmsmj.54.3.3. PMID: 19728405. Excluded for poor quality.

Anderson ES, Galbraith JW, Deering LJ, et al. Continuum of care for hepatitis C virus among patients diagnosed in the emergency department setting. Clin Infect Dis. 2017;64(11):1540-6. doi: 10.1093/cid/cix163. PMID: 28207069. Excluded for wrong outcome.

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong intervention.

Bini EJ, Mehandru S. Sustained virological response rates and health-related quality of life after interferon and ribavirin therapy in patients with chronic hepatitis C virus infection and persistently normal alanine aminotransferase levels. Aliment Pharmacol Ther. 2006;23(6):777-85. doi: 10.1111/j.1365-2036.2006.02819.x. PMID: 16556180. Excluded for wrong outcome.

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong study design for Key Question.

Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology. 2007;45(3):579-87. doi: 10.1002/hep.21492. PMID: 17326216. Excluded for wrong population.

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong population.

Dal Molin G, D'Agaro P, Ansaldi F, et al. Mother-to-infant transmission of hepatitis C virus: rate of infection and assessment of viral load and IgM anti-HCV as risk factors. J Med Virol. 2002;67(2):137-42. doi: 10.1002/jmv.2202. PMID: 11992574. Excluded for insufficient statistical analysis.

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong intervention.

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 wrong population.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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.

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 wrong 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 wrong intervention.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong intervention.

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 wrong study design for Key Question.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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.

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 wrong population.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong population.

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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 wrong 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 wrong 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.

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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 wrong 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.

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 wrong 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 wrong outcome.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong study design for Key Question.

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 wrong 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 wrong population.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong outcome.

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 wrong 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 wrong intervention.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong intervention.

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 wrong 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 wrong population.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong intervention.

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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.

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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 wrong intervention.

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.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong study design for Key Question.

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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 wrong 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 wrong outcome.

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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 wrong population.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong outcome.

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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 wrong intervention.

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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 wrong 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 wrong 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 wrong 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 wrong intervention.

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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 wrong intervention.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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.

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 wrong 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 wrong study design for Key Question.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong intervention.

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 wrong 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 wrong population.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong intervention.

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 wrong 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.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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.

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 wrong 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.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong study design for Key Question.

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 wrong 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 wrong study design for Key Question.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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.

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 wrong 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 wrong outcome.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong intervention.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong study design for Key Question.

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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 wrong intervention.

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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 wrong population.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong population.

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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 wrong outcome.

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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 wrong population.

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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 wrong 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 wrong intervention.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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.

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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 wrong population.

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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 wrong population.

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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 wrong 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 wrong intervention.

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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 wrong 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 wrong 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 wrong population.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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.

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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 wrong 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 wrong 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 wrong outcome.

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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 wrong 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 wrong 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 wrong intervention.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong study design for Key Question.

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 wrong 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 wrong 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.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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.

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 wrong 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 wrong 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 wrong intervention.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong 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 wrong intervention.

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 wrong 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 wrong intervention.

Appendix A5. List of Excluded Studies With Reasons For Exclusion

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 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%)
European Pediatric Hep C Virus Network 2005 (Tovo)[106]	Multicenter prospective cohort study	Children considered infected if they had ≥2 positive HCV RNA PCR	Account for differences between centers in the HCV RNA	Children received clinical examination at birth, 6	HCV infected mothers and their singleton infants or first-born infants	Second-born twins and second- and third-born triplets were	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)	Maternal HIV infection (n=1391) Yes: 208 (15%) No: 1183 (85%)

Appendix B Table 1. Key Question 5: Evidence Table 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
Italy, Spain, Germany, Ireland, U.K., Norway, Sweden *Good*		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.	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	weeks, and 3, 6, 9, 12, 18, and 24 months; and thereafter every 6 months if infected or every year if uninfected	from multiple pregnancies with confirmed HCV infection status.	excluded. Mother-infant pairs with infants of indeterminate infection status were excluded.		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%)	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%)
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	Variables with p<.1 from the univariate analysis and maternal demographic characteristics included in	Infants born to HCV+ mothers followed from birth to ≥12 months, HCV-infected	Women presenting for prenatal care (and in Houston, those who did not receive prenatal care who	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%)

Appendix B Table 1. Key Question 5: Evidence Table 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
		(qualitative and quantitative), and genotyping.	multivariate analysis	infants followed annually until age 5	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).				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: <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 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 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 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 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 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 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)	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 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)	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	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
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	NR	NR	NR	U.K. Department of Health

Appendix B Table 3. Key Question 5: Evidence Table 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)	Transmission by other risk factors (child)	Subgroup analyses	Adverse events	Funding source
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)	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
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)	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**
Afdahl 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
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

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**
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: 100%	0% (0/85)	HCV RNA <25 IU/mL
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

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-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
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 60% 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 2018[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 2018[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
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

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
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
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

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 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
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

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 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
Afdahl 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)

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
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
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

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
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
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
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

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
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
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)
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)	*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)

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* (cont'd)					-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

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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
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 2018[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)

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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
Grebely 2018[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)

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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
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)

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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
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)

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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
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

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
Afdahl 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 <u>12-week intervention group</u> 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) <u>24-week intervention group</u> 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

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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

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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 2018[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 2018[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
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

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
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
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

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
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
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

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
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
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

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
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
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%	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

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Author year Country *Quality*	Treatment Regimen (1x/day unless otherwise noted)	Clinical Outcomes	Adverse Events	Funding Source
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
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 wrong 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
Feld 2015[139]	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
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 2018[150] SIMPLIFY	Single	Unclear	NA	NA	NA	Yes	Yes	NA	No	No	Yes	No	Yes	Fair
Grebely 2018[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
Lawitz 2014a[154]	Multi	NA	Yes	No (open label)	No	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 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
Zeuzem 2018[167] ENDURANCE-1	Multi	NA	Yes	No	Yes	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
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
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

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
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
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

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
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.
‖ 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: 0.71 (0.60 to 0.86), 6.7% No SVR: Reference, 14% <u>Genotype 2</u> SVR: 0.62 (0.44 to 0.87), 7.3% No SVR: Reference, 16% <u>Genotype 3</u> SVR: 0.51 (0.35 to 0.75), 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=358 SVR: n=69 Nonresponder: n=49 Relapser: n=22 Early treatment discontinuation/unknown: n=19 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
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

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Author year *Quality*	Treatment duration Followup	Intervention(s)	Population	Variables accounted for in analyses	Outcomes	Funding source
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: 89% 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

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
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: 60% 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

Childhood Cancer Among Alaska Natives

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ABSTRACT. *Objective.* **The primary purpose of this study was to examine the occurrence of cancer in Alaska Native (AN) children (under age 20). Although several studies have compared differences in cancer incidence between white and black children, few have examined cancer among Alaska Natives/American Indians. We know of no published article describing cancer incidence in AN children. We compared our findings with those of American Indian children of New Mexico and of Alaska white children. Data on mortality, survival, and prevalence are also included. Alaska Native is the term used collectively for the inhabitants whose ancestors occupied the area before European contact of what is now the state of Alaska. Alaska Natives include Eskimo, Indian, and Aleut groups. Although the 3 major groups differ in culture, language, and probably genetics, there are similarities in numerous social and economic indicators. The Northern Eskimo of Alaska (Inupiat) are related to Canadian and Greenland Inuit. Indians in Alaska include Athabaskan (in the interior of the state), who share commonalities with Canadian Athabaskan as well as with Navajo and Apache in the southwestern United States. Tlingit, Haida, and Tsimshian groups reside primarily in the southeast panhandle of the state. The panhandle Indian groups are similar to those of British Columbia.**

Methods. **Data on cancer incidence are from the Alaska Native Tumor Registry, 1969–1996. We studied children under age 20 to make our results comparable to national data as presented in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Pediatric Monograph. Population data for AN are based on census data and Indian Health Service intercensal estimates. Data for US whites and New Mexico Indians are from the National Cancer Institute's SEER program. Calculations were made using SEERStat software. Data for Alaska whites are for the years 1996–2000. (The Alaska Cancer Registry has collected data for all Alaskans only since 1996). Odds ratios (ORs) of rates with 95% confidence intervals (CIs) were calculated.**

Results. **The rate among all AN children (both sexes) for all cancers combined is similar to that of US whites (OR: 1.0; 95% CI: 0.8–1.1). Examination of childhood cancer rates by ethnicity, however, reveal that rates are significantly lower for Indian (OR: 0.6; 95% CI: 0.4–0.8) but not significantly different for Eskimo or Aleut children. For most International Classification of Childhood Cancers groups, incidence rates for AN children are also similar to those of US whites. However, AN children are at significantly higher risk for hepatic tumors (OR: 13.1; 95% CI: 7.9–20.5), particularly hepatocellular carcinoma (OR: 43.8; 95% CI:24.4–75.1) and retinoblastoma (OR: 2.8; 95% CI: 1.3–5.3). By ethnic group, rates for hepatocellular carcinoma are significantly high only for Eskimo. Rates for all AN children are lower for neuroblastoma (OR: 0.1; 95% CI: 0.1–0.6) and lymphoma (OR: 0.5; 95% CI: 0.3–0.9), particularly Hodgkin's disease (OR: 0.2; 95% CI: 0.0–0.5). On the basis of 5 years of data, rates for Alaska white children do not seem to differ from those of US white children. Because of our findings of differences between AN and US whites, we reviewed data of other relevant populations, specifically American Indian data from the New Mexico SEER registry. Using SEER data and SEER software, we calculated rates for New Mexican American Indians (NMAI) and compared them with US white rates. Rates for all cancers combined among NMAI are significantly lower than for US white (OR: 0.8). However, similar to AN children, the rate among NMAI for retinoblastoma is higher compared with US whites (OR: 2.5; 95% CI:1.4–4.5). Similar to AN, NMAI also seem to be at low risk for neuroblastoma (OR: 0.2; 95% CI: 0.1–0.7), lymphoma as a group (OR: 0.1; 95% CI: 0.0–0.3), and, specifically, Hodgkin's disease (OR: 0.1; 95% CI: 0.0–0.4). Rates among NMAI children are low for central nervous system tumors (OR: 0.5; 95% CI: 0.3–0.7). The average annual age-adjusted cancer mortality rate among AN children is lower but not significantly lower than that of US white children (28.6 vs 37.3 per million).**

Conclusions. **Comparison of AN rates for all cancers combined are similar to those of US and Alaska white children but seem higher than those of NMAI. Differences between AN and US whites exist for select International Classification of Childhood Cancers groups. The most striking rate differences are found in hepatic tumors, largely because of elevated rates of hepatitis B-associated hepatocellular carcinoma. All children in our study with hepatocellular carcinoma were hepatitis B antigen positive. A statewide hepatitis B virus immunization program was begun in late 1982. Although 16 children who were born before 1983 developed hepatocellular carcinoma, no children who were born in the 20 years since hepatitis B immunization was instituted among infants have received a diagnosis of hepatocellular carcinoma, a significant difference. Comparing AN and US white childhood cancer rates after removing hepatocellular carcinoma cases from both populations results in an OR of 0.8 (95% CI: 0.7–1.0). Thus, if no increase in other childhood cancers occurs in the coming generations, then rates for childhood cancer may soon be significantly lower than those in US white children. Rates are low for all lymphomas, largely because of very low rates of Hodgkin's disease. Rates are also low for neuroblastoma. It is reassuring that rates for AN children are not in excess and do not seem to be increasing. There is concern among the population regarding environmental**

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exposure, including ionizing radiation. Our data do not show excess childhood leukemia or thyroid cancers, malignancies for which radiation is known to increase risk. *Pediatrics* **2003;112:e396–e403. URL: http://www.pediatrics.org/cgi/content/full/112/5/e396;** ***neoplasm, Alaska Native, pediatric, hepatitis.***

ABBREVIATIONS. AN, Alaska Native(s); NMAI, New Mexican American Indians; SEER, Surveillance, Epidemiology, and End Results; ICCC, International Classification of Childhood Cancers; OR, odds ratio; CI, confidence interval; CNS, central nervous system; HBV, hepatitis B virus; NHL, non-Hodgkin's lymphoma; SNS, sympathetic nervous system; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; EBV, Epstein-Barr virus.

Compared with cancers that occur in adults, childhood cancers are rare, comprising only 1.0% of all cancers in the United States. However, cancer is the number 1 cause of disease-related deaths in children.[1,2] Childhood cancer comprises a variety of malignancies with incidence varying worldwide by age, sex, ethnicity, and geography.[3] These variations in the incidence of cancer, particularly those among racial/ethnic groups and/or geography, have provided important insights into cancer etiology. Although several studies have compared differences in cancer incidence between white and black children, few have examined cancer among Alaska Natives/American Indians.[1,4] We know of no published article describing cancer incidence in Alaskan Native (AN) children.

Alaska Native is the term used collectively for the inhabitants whose ancestors occupied the area before European contact of what is now the state of Alaska. AN include Eskimo, Indian, and Aleut groups. Although the 3 major groups differ in culture, language, and probably genetics, there are similarities in numerous social and economic indicators. The Eskimo of Alaska are composed of 2 main groups, the Inupiat and the Yup'ik. The Inupiat are related to Canadian and Greenland Inuit. Indians in Alaska include Athabaskan (in the interior of the state), and Tlingit, Haida, and Tsimshian groups, who reside primarily in the southeast panhandle of the state. Alaskan Athabaskan have commonalities with Canadian Athabaskan as well as with Navajo and Apache in the southwestern United States. The southeast panhandle Indians are similar to the Indians of British Columbia.[5]

Cancer incidence among AN of all ages was first reported in 1976[6] and has been reported subsequently in numerous publications.[7–11] Cancer, once thought to be a rare disease among AN, has increased, and rates for all cancers combined now exceed those of US whites. In addition, there are many differences in site-specific cancer incidence rates among AN compared with US whites.[10]

This study examined cancer in AN children (under age 20), comparing incidence rates in AN children with those of US whites by sex, age group (0–4, 5–9, 10–14, and 15–19), and ethnicity (Indian, Aleut, and Eskimo). We also compared our data with that of New Mexican American Indians (NMAI) and with Alaska whites. Data on AN cancer survival, prevalence, and mortality are also included.

METHODS

Incidence data in this report are for AN patients under age 20 in the Alaska Native Tumor Registry. This registry includes all AN patients statewide who received a diagnosis of invasive cancer while a resident of Alaska. Data for the years 1969–1996 were examined for this study. However, to confirm a finding of the study, the registry was searched at a later date to identify liver cancers diagnosed through 2002. Data collection methods have been previously described.[6–11] Data were collected in accordance with the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program.[12] To make our results most easily comparable to national data, our analysis was designed to mirror that used in the National Cancer Institute's SEER Pediatric Monograph.[1] Classification of ethnicity (Indian, Aleut, and Eskimo) is based on self-classification by the parents of the patient at the time of registration to the hospital/clinic. Classification of tumors followed the International Classification of Childhood Cancers (ICCC).[13] The ICCC divides cancers into 12 major groups each with up to 6 subgroups. Data for US whites and NMAI aged 0 to 19 years from the SEER program for 1973–1996 were used for comparison. We also analyzed data for Alaska white children provided by the State of Alaska for the years 1996–2000 (the only years available). All incidence rates were adjusted to the 1970 US standard population under age 20. AN rates for all cancers and for each group and subgroup of cancer (classified by the ICCC) were calculated using 1969–1996 data.

Death data for AN were obtained from the State of Alaska Bureau of Vital Statistics and were available for 1979 to 1996. Deaths among US whites for the same time period were obtained from the National Center for Health Statistics.

Population estimates for AN were based on census data and Indian Health Service population estimates for 1970–1996. The ethnic composition of AN children in the 1990 census was 11% Aleut, 34% Indian, and 54% Eskimo and was similar for 1970 and 1980 censuses. Age distribution among the population of AN under 20 years of age has fluctuated somewhat during this period. Interpolations of population estimates for intercensal years were estimated using cubic splines.[14] Odds ratios (ORs; and associated 95% confidence intervals[CIs]) for comparisons were calculated using exact methods. Poisson regression was used to model trends over time. Kaplan Meier curves and log-rank tests were used for examination and comparison of relative survival data. All analyses were performed using S-Plus 2000, StatExact 4.0.1, and Epi Info 2000 software.

RESULTS

From 1969 to 1996, a total of 131 cases of cancer were diagnosed among AN under age 20. One patient had 2 different cancers (central nervous system [CNS], germ cell) diagnosed 6 years apart. Of the 131, more were male (78) than female (53). Cancer in AN children was most frequently diagnosed within the first year of life. Children of ages 0 to 4 and 15 to 19 accounted for more cases than those ages 5 to 9 and 10 to 14. The distribution by ethnicity was 26 Indians, 24 Aleut, and 81 Eskimo.

Distribution of Cancers

Table 1 compares rank order of cancers by ICCC classification of AN to US whites. The 5 most frequently diagnosed cancers, in rank order among AN children, are leukemia, hepatic tumors, CNS tumors, lymphoma, and germ cell tumors. Together, these cancers compose >70% of all AN childhood cancers. Four of these cancer groups—leukemia, CNS, lymphoma, and germ cell tumors—are among the 5 most frequent in US white children. Rank order is similar, except in the US whites, carcinoma ranks fourth after

TABLE 1. Childhood Cancers by ICCC Major Group

Alaska Native			US White		
ICCC	Count	%	ICCC	Count	%
Male and female					
I Leukemia	35	27	I Leukemia	4888	24
VII Hepatic tumors	19	15	III CNS	3490	17
III CNS	18	14	II Lymphoma	3399	17
II Lymphoma	11	8	XI Carcinoma	1974	10
X Germ cell	9	7	XI Germ cell	1383	7
VII Retinoblastoma	8	6	IX Soft tissue	1382	7
IX Soft tissue	8	6	VIII Bone	1121	6
VI Renal tumors	8	6	IV(a) Neuroblastoma	1101	5
VIII Bone	7	5	VI Renal tumors	850	4
XI Carcinoma	7	5	V Retinoblastoma	374	2
IV(a) Neuroblastoma	1	1	VII Hepatic tumors	196	1
XII Unknown	0	0	XII Unknown	99	0
Total	131	100		20 257	100
Male					
I Leukemia	24	31	I Leukemia	2782	25
VII Hepatic tumors	14	18	II Lymphoma	1981	18
II Lymphoma	9	12	III CNS	1922	18
III CNS	9	12	X Germ cell	815	7
IX Soft tissue	6	8	IX Soft tissue	753	7
X Germ cell	4	5	XI Carcinoma	659	6
XI Carcinoma	4	5	VIII Bone	649	6
VIII Bone	3	4	IV(a) Neuroblastoma	598	5
VI Renal tumors	2	3	VI Renal tumors	414	4
V Retinoblastoma	2	3	V Retinoblastoma	186	2
IV(a) Neuroblastoma	1	1	VII Hepatic tumors	111	1
XII Unknown	0	0	XII Unknown	47	0
Total	78	100		10 917	100
Female					
I Leukemia	11	21	I Leukemia	2106	23
III CNS	9	17	III CNS	1568	17
V Retinoblastoma	6	11	II Lymphoma	1418	15
VI Renal tumors	6	11	XI Carcinoma	1315	14
VII Hepatic tumors	5	9	IX Soft tissue	629	7
X Germ cell	5	9	XI Germ cell	568	6
VIII Bone	4	8	IV(a) Neuroblastoma	503	5
XI Carcinoma	3	6	VIII Bone	472	5
II Lymphoma	2	4	VI Renal tumors	436	5
IX Soft tissue	2	4	V Retinoblastoma	188	2
IV(a) Neuroblastoma	0	0	VII Hepatic tumors	85	1
XII Unknown	0	0	XII Unknown	52	1
Total	53	100		9340	100

lymphoma. Among AN, hepatic tumors rank second and compose 15% of childhood cancers, whereas among US whites, hepatic tumors rank 11th and account for only 1%. Although lymphoma ranked among the top 5 cancers in both AN and US white children, it ranked fourth in AN, composing 8%, and third in US white children (17%). The category carcinoma accounts for 10% of cancers among US white children (and ranks fourth) but accounts for only 5% of cancers among AN children (and ranks 10th). Neuroblastomas ranked lower (11th) among AN than US whites (eighth). Distribution of cancer by sex was remarkable for the higher ranking of hepatic tumors in both AN boys (second) and girls (fifth) and higher ranking of retinoblastoma and renal tumors in AN girls.

Rank order of AN childhood cancers was examined by ethnic group: Indian, Aleut, and Eskimo (data not shown). Leukemia ranked first in all ethnic groups. Distribution was similar between ethnic groups, with the exception of hepatic tumors. Hepatic tumors were the second most common cancer among Eskimo children but ranked fifth and seventh among Indians and Aleuts, respectively.

Within nearly all major ICCC groups, the distributions of cancers by subgroup seem to be similar for AN and US whites. An exception again is hepatic tumors. Among AN children, 16 (84%) of 19 cases of hepatic tumors were hepatocellular carcinoma, and only 3 were hepatoblastoma. Among US whites, hepatoblastoma occurs much more frequently in children than hepatocellular carcinoma. Only 56 (28%) of 199 cases of hepatic tumors among US whites were hepatocellular carcinoma.

There may also be differences in distribution in the ICCC group "carcinoma." Among US white children, the majority of the carcinomas were thyroid (36%), malignant melanoma (35%), and "other and unspecified carcinomas" (25%). Of the 7 AN children who had a diagnosis of carcinoma, only 1 cancer was thyroid carcinoma and none was melanoma. The remaining 6 were "other and unspecified carcinomas" (colon, rectum, cervix, stomach, brain, and 1 unknown site).

The distribution of cancers by 5-year age group was reviewed. The age distributions of AN and US white children with cancer by ICCC group are similar, again with the exception of hepatic tumors.

Among US white children, most hepatic tumors (primarily hepatoblastoma) occur under age 5, whereas among AN children, the highest percentage of hepatic tumors occurs in the 15 to 19 age group (hepatocellular carcinoma).

In the US, childhood cancer occurs most frequently in the first year of life. AN children are similar. Thirteen AN infants received a diagnosis of cancer, the largest number with cancer in any year of age in our study. These 13 include leukemia (5); retinoblastoma (3); and 1 infant each with neuroblastoma, lymphoma, soft tissue, renal, and CNS tumors. Rank order among infants with cancer in the US is generally neuroblastoma, CNS tumors, leukemia, retinoblastoma, and renal tumors.[14]

In US whites, cancers occur more often in male than female children. Among AN children in this study, there were also more cancers in boys (78) than in girls (53). The ratio of boys to girls seems to be higher in AN but is not significantly different.

Incidence Rates

Table 2 shows average annual age-adjusted incidence rates of childhood cancer and ORs for AN compared with US whites. Rates among AN children for all cancers combined are similar to those of US whites (OR: 1.0; 95% CI: 0.8–1.1). Rates by age and sex were also calculated (data not shown). ORs of AN to US whites for all cancers combined were 1.1 and 0.9 for boys and girls and did not differ significantly. Age-specific rates of all cancers combined among AN children display a pattern by age similar to that observed among US whites. Specifically, rates are high among young AN children (160 per million among age 0–4), decline somewhat in age groups 5 to 9 and 10 to 14 (116 and 119 per million, respectively), and then increase again in older children (188 per million in age group 15–19).

For most ICCC cancer groups, incidence rates for AN children are similar to those of US whites. However, AN children are at significantly higher risk for all hepatic tumors (OR: 13.1; 95% CI: 8.0–20.5) and especially for hepatocellular carcinoma (OR: 43.8; 95% CI: 24.4–75.1). AN risk of hepatocellular carcinoma is also significantly increased for each sex separately. The rate for hepatoblastoma for both sexes combined was not significantly high; however, on the basis of the 3 cases (all male), AN boys seem to be at higher risk for hepatoblastoma compared with US white boys (OR: 4.80; 95% CI: 1.20–13.45).

All children in our study with hepatocellular carcinoma were hepatitis B antigen positive. We therefore evaluated the impact of a statewide hepatitis B virus (HBV) immunization program begun in late

TABLE 2. Numbers and Rates* for AN Childhood Cancers, 1969–1996, Compared with US Whites, 1973–1996, Boys and Girls Combined

ICCC Groups		Count	Rate per Million		OR AK:US	Exact 95% CI	
		AN	AN	US White SEER			
All Cancer		131	147.3	153.9	1.0	0.8	1.1
I	Leukemia	35	38.6	37.0	1.0	0.7	1.4
Ia	ALL	24	26.5	27.7	0.9	0.6	1.3
Ib	AML	6	6.6	6.2	1.1	0.4	2.2
Ic	CML	3	3.3	1.1	3.3	0.8	9.0
Id	Other specified	0	0.0	0.3	0.0	0.0	13.5
Ie	Unspecified	2	2.2	1.8	1.2	0.2	3.9
II	Lymphoma	11	13.2	26.2	0.5	0.3	0.9
IIa	Hodgkin's disease	2	2.4	15.4	0.2	0.0	0.5
IIb	NHL	4	4.8	7.2	0.7	0.2	1.6
IIc	Burkitt's	1	1.3	2.1	0.6	0.0	2.8
IId	Miscellaneous	1	1.3	0.4	2.6	0.1	13.1
IIe	Unspecified	3	3.4	1.1	3.3	0.7	9.7
III	CNS tumors	18	20.3	27.0	0.7	0.4	1.1
IIIa	Ependymoma	2	2.4	2.2	0.9	0.2	3.1
IIIb	Astrocytoma	7	8.2	14.3	0.6	0.3	1.1
IIIc	Primitive neural ectodermal	4	4.0	5.3	0.8	0.3	1.9
IIId	Other gliomas	5	5.7	4.4	1.3	0.5	2.8
IV	SNS tumors	1	0.9	7.9	0.1	0.1	0.6
IVa	Neuroblastoma	1	0.9	7.9	0.1	0.1	0.6
V	Retinoblastoma	8	7.4	2.7	2.8	1.3	5.3
VI	Renal tumors	8	8.2	6.3	1.2	0.6	2.4
VIa	Wilm's tumor	7	6.9	6.1	1.1	0.5	2.2
VIb	Renal carcinoma	1	1.3	0.2	5.9	0.3	31.0
VII	Liver tumors	19	22.6	1.5	13.1	7.9	20.5
VIIa	Hepatoblastoma	3	2.7	1.0	2.8	0.7	7.7
VIIb	Hepatocellular carcinoma	16	19.9	0.4	43.8	24.4	75.1
VIII	Bone tumors	7	8.4	8.8	1.0	0.4	1.9
VIIIa	Osteosarcoma	4	4.9	4.4	1.1	0.4	2.7
VIIIc	Ewing's sarcoma	2	2.5	3.5	0.7	0.1	2.3
VIIIe	Unspecified	1	0.9	0.1	11.1	0.5	62.9
IX	Soft tissue tumors	8	8.5	10.6	0.9	0.4	1.6
X	Germ cell tumors	9	10.4	10.3	1.0	0.6	2.1
XI	Carcinoma	7	8.8	14.9	0.6	0.3	1.2
XII	Unknown	0	0.0	0.7	0.0		

* Rates age-adjusted to US 1970 standard million.

1982 on the occurrence of hepatic tumors among AN children. Although 16 children who were born before 1983 developed hepatocellular carcinoma, no children who were born in the 20 years since HBV immunization was instituted among infants have received a diagnosis of hepatocellular carcinoma. The difference in hepatocellular carcinoma rates between these 2 birth cohorts, 1950–1982 and 1983–2002, is significant at $P < .05$.

The only other category for which AN rates are increased is retinoblastoma (OR: 2.8; 95% CI: 1.3–5.3). Eight children received a diagnosis of retinoblastoma in this population, 6 female and 2 male. All but 1 was diagnosed under age 2, and 3 patients had synchronous bilateral disease. Review of medical records did not indicate that any of the children were related, although detailed family pedigrees have not been done. Tumor registry information does not include information on genetic testing, and many of the patients' cancers were diagnosed before genetic testing became available.

Lower rates were found for AN children compared with US whites for lymphoma and for neuroblastoma. The rate for the lymphoma category is significantly low for both sexes combined (OR: 0.5; 95% CI: 0.3–0.9) and for girls separately. The low rate for this cancer is largely attributable to low rates for Hodgkin's disease (OR: 0.2; 95% CI: 0.0–0.5). Only 2 patients with Hodgkin's disease, both male, were identified in the 18-year period. The rate for non-Hodgkin's lymphoma (NHL) also seems low but not significantly different from the US white rate.

Only 1 AN patient received a diagnosis of cancer in the sympathetic nervous system (SNS) category, specifically neuroblastoma. On the basis of this 1 case, the rate for neuroblastoma in AN seems to be significantly lower than in US whites (OR: 0.1; 95% CI: 0.1–0.6).

The rate of leukemia was similar in AN and US white children (OR: 1.0; 95% CI: 0.7–1.4), and distribution by subcategory also seemed to be similar. Of the 35 cases of leukemia diagnosed among AN children, 24 (66%) were acute lymphoblastic leukemia (ALL), 6 (17%) were acute myeloid leukemia (AML), 3 (9%) were chronic myeloid leukemia (CML), and 2 (6%) were unspecified. Data for AN leukemia were also similar to US whites in that boys have higher incidence and leukemia occurs most frequently in the 0- to 4-year age group.

Ethnic Comparisons

We calculated overall age-adjusted childhood cancer rates for each of the 3 major ethnic groups among AN (data not shown). Compared with US whites, rates were significantly lower for Indians (OR: 0.6; 95% CI: 0.4–0.8) and not significantly different for Eskimo (OR: 1.1; 95% CI: 0.9–1.3) or Aleut (OR: 1.4; 95% CI: 0.9–2.1). Comparisons of AN rates with US whites by ethnic group for separate ICCC groups are difficult because of limited numbers of cases. Our data indicate that rates for hepatic cancer are significantly higher only among Eskimo (OR: 23.9; 95% CI: 13.9–38.8). Retinoblastoma may be higher in all 3 ethnic groups, but none was significantly higher.

Rates for AN for all lymphomas are significantly low relative to US whites. Numbers of cases (11) were too small for analysis by ethnic group. Patients from all 4 ethnic groups were among the 11 patients who had a diagnosis of lymphoma.

Mortality

Cancer-specific mortality rates were calculated using death data for AN and all US whites, 1979–1996. Twenty-three AN children died from cancer during the period studied. The average annual age-adjusted cancer mortality rate among AN children was lower but not significantly lower than that of US white children (28.6 vs 37.3 per million). US white cancer mortality decreased in children during this period, but no similar trend was evident among AN cancer mortality rates.

Survival and Prevalence

For all childhood cancers, relative 5-year survival for AN is lower than for US whites (60% vs 70%; $P < .05$). The numbers of cases were too small to calculate survival by ICCC group or subgroup. Of all AN children who received a diagnosis of cancer from 1969 through 1996, 58 had died by January 1, 1997, 43 (74%) from cancer, 7 from other causes, and 8 from unknown causes. The 72 survivors originally had a diagnosis of leukemia (14); germ cell (10) and hepatic tumors (10); retinoblastoma (8); renal (7) and CNS (6) tumors; lymphoma (6), soft tissue (5), bone (3), and SNS (1) tumors; and carcinoma (2). All children who had a diagnosis of retinoblastoma, germ cell tumors, and neuroblastoma and all but 1 of 8 who had a diagnosis of renal tumor were known to be alive on January 1, 1997.

Because of our findings of differences between AN and US whites, we reviewed data of other relevant populations, specifically, American Indian data from the New Mexico SEER registry. Using SEER data and SEER software, we calculated rates for NMAI and compared them with US whites (Table 3). Rates for all cancers combined among NMAI were significantly lower than for US white (OR: 0.8). Rates are similar between NMAI and US white children for most ICCC groups, with a few exceptions. Similar to AN children, the rate among NMAI for retinoblastoma was higher compared with US whites (OR: 2.5; 95% CI: 1.4–4.5). The rate for osteosarcoma among NMAI seems to be higher (OR: 1.8; 95% CI: 1.0–3.4), although the rate for bone tumors as a group was not significantly higher. Similar to AN, NMAI also seem to be at low risk for neuroblastoma (OR: 0.2; 95% CI: 0.1–0.7), lymphoma as a group (OR: 0.1; 95% CI: 0.0–0.3), and, specifically, Hodgkin's disease (OR: 0.1; 95% CI: 0.0–0.4). In addition, rates among NMAI children are low for CNS tumors (OR: 0.5; 95% CI: 0.3–0.7).

We also examined statewide incidence data for Alaska whites. Data for this population have been collected only since 1996. However, the Alaska white population is nearly 5 times that of Natives in Alaska. During the period 1996–2000 (data not shown), 92 resident white children of Alaska under age 20 at diagnosis were identified. We found no

TABLE 3. Numbers and Rates* for NMAI Childhood Cancers Compared with US Whites, 1973–1996, Boys and Girls Combined

ICCC Groups		Count	Rate per Million		OR NM:US	Exact 95% CI	
		NMAI	NMAI	US White SEER			
All Cancer		148	108.7	153.9	0.7	0.6	0.8
I	Leukemia	49	35.1	37.0	0.9	0.7	1.2
Ia	ALL	36	25.0	27.7	0.9	0.6	1.2
Ib	AML	10	7.6	6.2	1.2	0.6	2.2
Ic	CML	2	1.6	1.1	1.4	0.4	5.7
II	Lymphoma	3	2.4	26.2	0.1	0.0	0.3
IIa	Hodgkin's disease	1	0.8	15.4	0.1	0.0	0.4
IIb	NHL	2	1.6	7.2	0.2	0.1	0.9
III	CNS tumors	17	12.3	27.0	0.5	0.3	0.7
IIIa	Ependymoma	1	0.6	2.2	0.3	0.0	2.2
IIIb	Astrocytoma	3	2.5	14.3	0.2	0.1	0.5
IIIc	Primitive neural ectodermal	6	4.0	5.3	0.8	0.4	1.8
IIId	Other gliomas	4	3.2	4.4	0.7	0.2	1.8
IVa	Neuroblastoma	3	1.9	7.9	0.2	0.1	0.7
V	Retinoblastoma	11	6.8	2.7	2.5	1.4	4.5
VI	Renal tumors	5	3.5	6.3	0.5	0.2	1.2
VIa	Wilm's tumor	4	2.7	6.1	0.4	0.2	1.1
Vib	Renal carcinoma	1	0.8	0.2	3.8	0.5	28.1
VII	Liver tumors	3	1.8	1.5	1.3	0.4	4.1
VIIa	Hepatoblastoma	3	1.8	1.0	1.8	0.6	5.7
VIIb	Hepatocellular carcinoma	0	0.0	0.4	—		
VIII	Bone tumors	13	10.6	8.8	1.2	0.7	2.1
VIIIa	Osteosarcoma	10	8.2	4.4	1.8	1.0	3.4
VIIIc	Ewing's sarcoma	3	2.4	3.5	0.7	0.2	2.1
IX	Soft tissue tumors	15	11.1	10.6	1.0	0.6	1.8
X	Germ cell tumors	17	13.5	10.3	1.3	0.8	2.1
XI	Carcinoma	12	9.5	14.9	0.7	0.4	1.1
XII	Unknown	0	0.0	0.7	—		

* Rates age-adjusted to U.S. 1970 standard million.

evidence that Alaska whites were at increased risk for hepatic tumors or retinoblastoma or that particularly low rates occur for the lymphomas, Hodgkin's disease in particular, or neuroblastoma among Alaska whites. Alaska white childhood cancer rates seem to be similar to those of US whites.

DISCUSSION

Cancer incidence patterns for AN of all ages have been well described.[7–11] These reports indicate that the rate of all cancers combined among AN of all ages and both sexes currently exceed the rates for US whites. Compared with US whites, rates are similar for AN men but 18% higher among AN women.[11] In addition, many site-specific rates differ. For many sites, rates in AN exceed those of US whites, whereas other cancer sites occur less frequently.

This is the first study to focus on cancer in AN children (under age 20). The incidence rate for all cancers and both sexes of AN under age 20 is similar to that of US whites.

Mortality rates from all cancers for all ages were much higher (30%) in AN compared with US whites during the 1990s.[15] Data on cancer deaths for children for 1979–1996 result in a cancer mortality rate for AN children that is lower (28.6 per million), although not significantly lower, than the rate for US white children (37.3 per million).

Comparison of rates of AN childhood cancers by ICCC groups and subgroups with US whites shows more similarities than differences, with some marked exceptions. In comparison with US whites, AN children have excess hepatic tumors (OR: 13.1) and retinoblastoma (OR: 2.8). Conversely, AN have significantly lower rates of SNS tumors (OR: 0.1) and lymphoma (OR: 0.5).

The most striking differences between AN and US white childhood cancers are found in the hepatic tumor category, specifically hepatocellular carcinoma (OR: 43.8). Most childhood hepatic cancer in the US is hepatoblastoma, but among AN children, the incidence of hepatocellular carcinoma is much higher than that of hepatoblastoma. Although the number of male children with hepatocellular carcinoma was nearly 3 times greater than for female, the rate of hepatocellular carcinoma is significantly increased over US whites for both AN boys and girls.

Chronic infection with HBV has been implicated as the leading cause of hepatocellular carcinoma in this population.[16] All children in our study with hepatocellular carcinoma were hepatitis B antigen positive. A hepatitis B program was instituted in Alaska in the early 1980s, including universal immunization of AN infants at birth and immunization of all serosusceptible AN. More than 90% of the AN population was tested for HBV in the mid-1980s and immunized as needed.[17] The region of Alaska with the highest infection rate of HBV experienced an immediate decrease in annual incidence of acute asymptomatic HBV infection from 215 to 14 per 100 000 after the immunization campaign. A screening program for hepatocellular carcinoma using α-fetoprotein has resulted in improvement in survival rates for patients with hepatocellular carcinoma.[18]

For this study, we evaluated the impact of the program on the occurrence of hepatic tumors among

AN children. The statewide HBV immunization program began in late 1982. Although 16 children who were born before 1983 developed hepatocellular carcinoma, no children who were born in the 20 years since HBV immunization was instituted among infants have received a diagnosis hepatocellular carcinoma. In contrast, hepatoblastoma has occurred since 1983. There is no known association between hepatoblastoma and hepatitis B, so a protective effect would not be expected.

Because hepatocellular carcinoma occurs in such excess among AN children and is the second leading cancer, we calculated a rate for all cancers in AN children excluding hepatocellular carcinoma. Comparing AN and US white childhood cancer rates after removing hepatocellular carcinoma cases from both populations resulted in an OR of 0.8 (95% CI: 0.7–1.0). Thus, if no increase in other childhood cancers occurs in the coming generations, then rates for childhood cancer may soon be significantly lower than those in US white children.

The only other cancer for which AN children seemed to be at increased risk was for retinoblastoma. Retinoblastoma has not been found to have any race or sex predilection.[19] A retinoblastoma gene was identified and reported in 1986 and is transmitted in a dominant manner. The gene Rb1 functions as a tumor suppressor. Hereditary cases are thought to compose 40% of cases in the United States. Hereditary cases tend to occur in younger (mean age: 1) than sporadic cases (mean age: 2) and are more often bilateral. Although a review of records did not indicate that any of the children in this study were related, the occurrence of bilateral disease and diagnosis at young age suggests that heredity may play a role in some of these patients.

Lymphoma occurs in AN children at half the rate of that in US white children (OR: 0.5). Among both AN and US white children, the incidence is lower among girls than boys. The lymphoma category is composed of Hodgkin's disease and NHL. The low overall OR of lymphoma among AN children is primarily attributable to the very low occurrence of Hodgkin's disease (OR: 0.2). Only 2 cases (both male) of Hodgkin's disease occurred among AN children, classified as nodular sclerosis and lymphocyte depletion.

Although Hodgkin's disease was described >200 years ago, the cause of the disease and the origin of the malignant cell remain unknown. The epidemiology and pathology of the disease have strongly implicated an infectious cause, especially viral. A variety of infectious agents have been suggested to play a role in Hodgkin's disease; the case for Epstein-Barr virus (EBV) seems to be strongest.[20] Risk varies worldwide, and occurrence of disease is greater among people with higher socioeconomic status. The role of infectious agent(s) may be associated with the finding of higher rates among those of higher socioeconomic status. Genetic predisposition is implicated because positive family history of Hodgkin's disease increases risk. Seroprevalence surveys of AN in the 1980s found that AN children were all EBV antibody positive by age 4 (AP Lanier, unpublished observations). If EBV is confirmed to play a role in the development of Hodgkin's disease or other lymphomas, then the fact that AN children are known to be infected early in life (and infectious mononucleosis occurs rarely) may be relevant.

NHL generally comprises approximately 60% of lymphoma in children and adolescents.[21] In our study, NHL was diagnosed in 9 of 11 lymphoma patients. Rates of NHL are higher in whites than in blacks in the United States. The frequency and relative proportion of NHL subtypes differ worldwide. In parts of Africa, Burkitt's lymphoma accounts for a large percentage of lymphomas in childhood. In our study, only 1 patient was classified as having Burkitt's lymphoma. The relatively low rates of lymphoma in AN children parallels our findings in previous studies of AN of all ages.[7–11,22] Compared with US whites, rates for AN of all ages are low for all lymphomas combined, especially for Hodgkin's disease (OR: 0.58 and 0.16, respectively). Comparison of age-specific rates for AN with US whites for the period 1973–1996 shows lower rates for all AN age groups for lymphoma and Hodgkin's disease.

The findings of our study were also remarkable in the relative absence of SNS tumors in AN children (OR: 0.1). In US whites, these tumors are the most common malignancies in infants and compose 5% of all childhood cancers. SNS tumors are predominantly neuroblastomas.[23] Only 1 AN child had a diagnosis of SNS tumor, specifically, neuroblastoma. In the United States, this tumor occurs at similar rates in whites and blacks. The cause is unknown. However, it has been noted that microscopic neuroblastoma nodules are observed in most fetuses and in infants under age 3 who die of causes other than cancer.[23] It has been hypothesized that these lesions may be neuroblastoma precursors and may spontaneously regress. If this hypothesis is valid, then the finding of infrequent occurrence of this neoplasm in this population would suggest an absence of a factor(s) that promotes neuroblastoma or the presence of a factor(s) that enhances regression.

Because AN are heterogeneous, including multiple ethnic, linguistic, and cultural groups, we reviewed the occurrence of childhood cancer by the 3 major ethnic groups: Eskimo, Indian, and Aleut. The rate for Alaska Indian children was lower than US white rates for cancer overall and for most of the common childhood tumors. The low rate among Alaska Indians agrees with the only previous report on childhood cancer in American Indian/AN. Among NMAI children under age 15 for the years 1970–1982, NMAI rates per million were significantly lower (75.5 for boys and 78.0 for girls) than non-Hispanic whites in the state.[4] On the basis of SEER data 1990–1995, NMAI had the lowest childhood cancer rate (79.6 per million) of 4 ethnic groups analyzed; blacks had 124.6, Asian Pacific Islanders had 136.8, and whites had 161.7 per million.[1]

We compared NMAI childhood cancer incidence data with that of US whites for 1973–1996. As would be expected from the studies cited above, we found the rate for all cancers combined among NMAI to be significantly lower than the US white rate (OR: 0.7).

Leukemia, especially ALL, was the leading cancer in children of all groups—AN, NMAI, and US whites—and rates were similar. NMAI do not experience an excess of hepatic tumors. In fact, no NMAI children received a diagnosis of hepatocellular carcinoma; all were hepatoblastoma. Of interest is that elimination of hepatic tumors from calculations of rates for AN children results in rates similar to NMAI. Similar to AN children, the rate among NMAI for retinoblastoma was also higher than US white rates. The rate for osteosarcoma among NMAI seems to be higher than US whites, although the rate for bone tumors as a group was not significantly higher. Among all 3 populations, osteosarcomas are the most frequently diagnosed bone tumors. Because the overall rates for childhood cancer in NMAI are low, it is not surprising that rates are low for various ICCC groups. Similar to AN, NMAI also seem to be at low risk for neuroblastoma, lymphoma as a group, and Hodgkin's disease. In addition, rates are low among NMAI children for CNS tumors.

Our report indicates that rates of all childhood cancers combined among AN are similar to US whites, although rates differ for select ICCC groups. Age-adjusted rates for AN for all ages have increased 38% during the past 30 years and now exceed those of US whites. It is reassuring that rates for AN children are not in excess and do not seem to be increasing. There is concern among the population regarding environmental exposure, including ionizing radiation. Our data do not show excess childhood leukemia or thyroid cancers, malignancies for which radiation is known to increase risk. Our data suggest that the HBV immunization program has already resulted in a decrease in hepatic cancers in children. Hepatic tumors rank second and compose 15% of AN childhood cancers in our study. In the future, elimination of most hepatic tumors should result in even lower rates of childhood cancer than we report in this study. The reasons for very low rates of Hodgkin's disease and neuroblastoma are not known.

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Childhood Cancer Among Alaska Natives

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Sentinel Event Alert

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Preventing infection from the misuse of vials

Published for Joint Commission accredited organizations and interested health care professionals, *Sentinel Event Alert* identifies specific types of sentinel and adverse events and high risk conditions, describes their common underlying causes, and recommends steps to reduce risk and prevent future occurrences.

Accredited organizations should consider information in a *Sentinel Event Alert* when designing or redesigning processes and consider implementing relevant suggestions contained in the alert or reasonable alternatives.

Thousands of patients have been adversely affected by the misuse of single-dose/single-use and multiple-dose vials. The misuse of these vials has caused harm to individual patients through occurrences and outbreaks of bloodborne pathogens and associated infections, including hepatitis B and C virus,[1,2] meningitis, and epidural abscesses.[3] Adverse events caused by this misuse have occurred in both inpatient and outpatient settings, according to the Centers for Disease Control and Prevention (CDC).

The misuse of vials primarily involves the reuse of single-dose vials,[3] which are intended to be used once for a single patient. Single-dose vials typically lack preservatives; therefore, using these vials more than once carries substantial risks for bacterial contamination, growth and infection.

Since 2001, at least 49 outbreaks have occurred due to the mishandling of injectable medical products, according to the CDC. Twenty-one of these outbreaks involved transmission of hepatitis B or C; the other 28 were outbreaks of bacterial infections, primarily invasive bloodstream infections. While many of these outbreaks occurred in inpatient settings, a high percentage occurred in pain management clinics, where injections often are administered into the spine and other sterile spaces using preservative-free medications, and in cancer clinics, which typically provide chemotherapy or other infusion services to patients who may be immuno-compromised. In addition, more than 150,000 patients required notification during this time frame to undergo bloodborne pathogen testing after their potential exposure to unsafe injections.[4]

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The CDC is aware of at least 19 bloodborne or bacterial infection outbreaks since 2007 associated with the misuse of single-dose/single-use vials. Seven involved bloodborne pathogen infections, and 12 were bacterial infections. All of these outbreaks occurred in the outpatient setting, with eight occurring in pain remediation clinics.[3] According to CDC officials, these examples likely underestimate the harm resulting from the misuse of single-dose/single-use vials. Due to the difficulty of tracing the misuse of vials to infections, the adverse impact of misusing a vial is typically not seen immediately.[5] Adverse events related to unsafe injection practices and lapses in infection control practices are underreported, and it remains a challenge to measure the true frequency of such occurrences.

While the misuse of disposable parenteral syringes and pen injectors also contribute to adverse events and outbreaks, this Alert will focus on the safe use of vials.

Causes and documentation of misuse

A significant contributing factor to the misuse of vials is the lack of adherence to safe infection control practices and to aseptic techniques within health care organizations. For example, a survey of 5,446 health care practitioners found lapses in basic infection control practices relating to vial use. The results included:

- For single-dose/single-use vials, 6 percent admitted to sometimes or always using vials for multiple patients.
- For multiple-dose vials, 15 percent reported using the same syringe to re-enter a vial numerous times for the same patient; of that 15 percent, 6.5 percent reported saving vials for use on another patient.
- Of the 51 professionals who reported reusing a syringe to obtain an additional dose from a multiple-dose vial and then leaving it for use on another patient, about half (52.0%) were from the hospital setting.[6]

A study by the CDC and the Centers for Medicare & Medicaid Services (CMS) published in the *Journal of the American Medical Association (JAMA*) found that two-thirds of inspected CMS-certified ambulatory surgical centers had lapses in basic infection control practices. Twenty-eight percent of these facilities used medications in single-dose vials for multiple patients.[7]

In addition, some providers compromise safe infection control practices in attempts to prevent waste.[5,6,8] The compulsion to prevent waste is sometimes exacerbated by medication shortages or costs.[3,5,9] However, any cost savings achieved by preventing waste can quickly be offset by one or more adverse clinical outcomes. The medical literature contains many examples of individuals who acquired preventable bloodborne and bacterial infections.[10-20] Some patients died from these infections, and many others required prolonged, sometimes life-long, treatment and follow-up care as a result. In other instances, underlying health conditions may have been exacerbated. In addition, there can be tremendous financial costs associated with treating infected patients or containing an outbreak, and providers causing harm face significant legal ramifications or disciplinary action.[3]

Recommendations and potential strategies for improvement

While organizations are required by Joint Commission standards to safely dispense and administer medications (see next section for all related Joint Commission requirements), the accomplishment of these goals depends on preventative action taken by clinical staff who administer injections. Staff should always follow safe injection and infection control practices – including correct aseptic technique, hand hygiene and the one-time-only use of needles and syringes – along with the specific recommendations for single-dose/single-use vials and multiple-dose vials in this alert. Safe infection control practices always apply when transporting, storing, preparing and administering medications, solutions and related supplies. See the CDC's comprehensive injection safety resource: http://www.cdc.gov/injectionsafety.

The following recommendations and potential strategies can be used to help prevent the misuse of vials, thereby preventing the spread of infection.

Effective processes and procedures

1. Develop and implement effective evidence-based organization-wide standardized policy and procedures for the prevention of the misuse of vials. The policy should apply to all staff who administer injections to patients, and should address the following:

Single-dose/single-use vials

- Use a single-dose/single-use vial for a single patient during the course of a single procedure. Discard the vial after this single use; used vials should *never* be returned to stock on clinical units, drug carts, anesthesia carts, etc. The One & Only Campaign from the CDC and Safe Injection Practices Coalition emphasizes ONE needle, ONE syringe, ONLY ONE time. Medications in single-dose/single-use vials lack antimicrobial preservatives and are therefore at greater risk to become contaminated and serve as a source of infection when used inappropriately. See campaign resources, including video.
- If a single-dose/single-use vial must be entered more than once during a single procedure for a single patient to achieve safe and accurate titration of dosage, use a new needle and new syringe for each entry.[21] Note: USP 797 states that single-dose/single-use vials opened in less than ISO Class 5 air quality be used within one hour, with any remaining contents discarded. Single-dose/single-use vials opened in ISO Class 5 air quality can be used up to six hours.[22]
- Do not combine or pool leftover contents of single-dose/single-use vials. Do not store used single-dose/single-use vials for later use, no matter what the size of the vial.[3]
- Unopened single-dose/single-use vials may be repackaged into multiple single-dose/single-use containers (e.g. syringes), which should be properly labeled, including the expiration date and a beyond-use date (which is different from the manufacturer assigned expiration date). This repackaging should be performed only by qualified personnel in ISO Class 5 air conditions in accordance with standards in the United States Pharmacopeia General Chapter 797, Pharmaceutical Compounding - Sterile Preparations. Also, follow the manufacturer's recommendations pertaining to safe storage of that medication outside of its original container.[3,22]

Multiple-dose vials

- Only vials clearly labeled by the manufacturer for multiple dose use can be used more than once.
- Limit the use of a multiple-dose vial to only a single patient, whenever possible, to reduce the risk of contamination.[23,24,25]
- When multiple-dose vials are used more than once, use a new needle and new syringe for each entry.[23] Do not leave needles or other objects in vial entry diaphragms between uses, as this may contaminate the vial's contents.[23]
- Disinfect the vial's rubber septum before piercing by wiping (and using friction) with a sterile 70 percent isopropyl alcohol,[22] ethyl/ethanol alcohol, iodophor,[26] or other approved antiseptic swab. Allow the septum to dry before inserting a needle or other device into the vial.[24]
- Once a multiple-dose vial is punctured, it should be assigned a "beyond-use" date. The beyond-use date for an opened or entered (e.g., needle-punctured) multiple-dose container with antimicrobial preservatives is 28 days, unless otherwise specified by the manufacturer.
- Store multiple-dose vials outside the immediate patient treatment area; observe the manufacturer's storage recommendations.[24]

All vials (single-dose/single-use and multiple-dose)

- Discard any vial if its sterility has been compromised or is questionable, including those having been placed on a used procedure tray or used during an emergency procedure – even if the vial is unopened/unused.[24]
- Select the smallest vial necessary when making purchasing and treatment decisions to reduce waste.[3]
- Urge manufacturers to produce vials in appropriate sizes to reduce waste.[27]

2. Conduct regular quality checks on clinical units to look for open vials.

Training and education

3. Provide annual education on injection safety and on preventing the misuse of vials for all staff who administer injections, including new or temporary staff. Education should include how to recognize and report known breaches of safe injection and infection control practices with vials, such as the use of a single-dose/single-use vial on more than one patient either accidentally (human error) or due to a mistaken belief that the breach was not significant or was justified (at-risk behavior). Staff education should aim to reduce gaps in knowledge regarding safe injection and infection control practices, and to reduce staff tolerance of behavioral choices that may place patients or others at risk of harm, such as using a single-dose vial of medication for multiple patients.

4. Before discharge, provide injection safety education to patients and caregivers who will use injectable medical products as part of a home health regimen. Use teach-back methods to assure understanding.

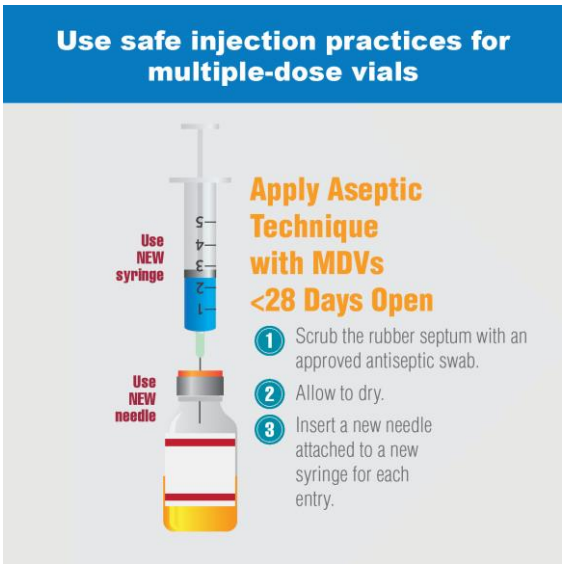
Safety culture

5. Emphasize that all staff are responsible for reporting risks, errors (including near misses), and adverse events. Create a culture within which the reporting of unsafe injection and infection control practices or near misses is viewed as a necessary step to improve safety.

6. Report clusters of infections or other adverse events to the appropriate local and state public health authorities. While reporting of adverse events is usually voluntary, outbreak reporting is typically required by state public health departments. Failure to report illness clusters to public health authorities can result in delays in recognition of disease outbreaks and in implementation of control measures. Incidents of adverse events associated with the misuse of vials can be reported to:

- The Joint Commission, in accordance with its Sentinel Event policy
- FDA Adverse Event Reporting System (FAERS)
- Appropriate state agencies (reporting may be mandatory in some states). See reportable conditions by state
- State health departments, if multiple patients are involved.
- Appropriate patient safety organizations (PSOs), such as ECRI Institute's or the Institute for Safe Medication Practices' (ISMP) National Medication Errors Reporting Program

7. When unsafe injection and infection control practices are identified, assess potential harm to patients and, if warranted, notify patients and test for bloodborne pathogens. Actions for notifying patients should be discussed with local and state public health authorities.



Related Joint Commission requirements

Reference the Standards FAQ for MM.03.01.01, Element of Performance (EP) 7, which requires organizations to re-label multiple-dose vials with a revised expiration date (that is, a beyond-use date) once staff opens or punctures a multiple-dose vial. Therefore, The Joint Commission requires a 28-day expiration date for multiple-dose vials from the date of opening or puncture, unless the manufacturer specifies otherwise (shorter or longer). In any case, the original expiration date printed on the vial cannot be extended. If the manufacturer's original expiration date is earlier than the revised expiration date, the earlier date must be used. *Note: Storage time limits for single-dose/single-use vials are defined by USP 797 (depending on the environment in which they are punctured) or the manufacturer – whichever is shorter.*[22]

See other relevant Joint Commission requirements: HR.01.05.03 (staff education and training), IC.01.04.01 (setting goals to minimize infection), IC.01.05.01 (infection prevention and control plan), IC.02.01.01 (infection prevention and control plan implementation), LD.04.04.05 (organizational patient safety program), MM.03.01.01, EP 10 (providing medications in the most ready-to-administer form)*, MM.05.01.11 (safe medication dispensing)*, MM.06.01.01 (safe medication administration), and MM.08.01.01 (medication management system evaluation).

* These requirements do not apply to some accreditation programs. MM.03.01.01 EP 10 does not apply to the Ambulatory Care or Nursing Care Center programs. However, MM.05.01.15 EP 1 does apply to the Nursing Care Center program, and it covers providing medications in the most ready-to-administer form. In addition, while MM.05.01.11 does not apply to most centers accredited under the Nursing Care Center program, it does apply to Veterans Affairs Community Living Centers (CLC), which are accredited under the Nursing Care Center program.

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From: Lacy Wilcox
To: Marijuana, CED ABC (CED sponsored)
Subject: Remediation Symbol and AMCO overreach
Date: Tuesday, September 10, 2019 10:13:09 AM
Attachments: Remediation Symbol and AMCO overreach 9-11-19.pdf

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Please see attached concern. I understand that this is too late to make it in the packet for the September meeting, however this will be given as verbal testimony so that you hear the concern sooner!

Thank you,
Lacy Wilcox

photo

Lacy Wilcox
Legislative Liaison, THC Alaska
907-302-3535 ext 105 | 907-302-3531 | lacy@thcalaska.com
www.THCalaska.com

To: Alaska Marijuana Control Board
From: THC Alaska, License #'s 10270 & 10271
Re: Remediation Symbol and AMCO overreach
Date: September 11, 2019

This is a written comment for a non-agenda item for the September 11-13, 2019 Marijuana Control Board Meeting, this is to support our verbal testimony given at said meeting.

Synopsis:

THC Alaska LLC strongly objects to AMCO authorizing METRC to add a Remediation Symbol to all subsequent and retested product packages associated with remediated trim, therefore AMCO using METRC to effectively change operations and business practices without going through the public process.

Detail:

Regulation reads-
3 AAC 306.660(b) Failed materials; retests
(b) If a sample of marijuana fails a required test, any marijuana plant trim, leaf, and other usable material from the same plants automatically fail the required test. The board or director may approve a written request, on a form prescribed by the board, to allow a batch of marijuana that fails a required test to be used to make a carbon dioxide- or solvent-based extract. After processing, the carbon dioxide- or solvent-based extract must pass all required tests.

What we thought this meant:

When we, a concentrate manufacturer, purchases failed vegetable matter to process into concentrates, the cultivator must first obtain approval from the director to transfer this material, which is understandable, however slow a process.

Once approved they can transfer "failed trim" and we can manufacture a concentrate. As long as the new product is tested and passes, it can then be sold as any concentrate product would be. This is good and has been happening with some degree of success.

What changed:

At some point recently, we believe in early August, METRC began adding a symbol  next to each package of concentrate that contained approved remediated trim. That symbol stays with the package all the way through to sale at the retail. When you hover over the symbol a pop up says, "Package contains remediated product".

This seems to have been done without public board discussion where the industry could weigh in on the effects of such a thing. We will nickname this symbol the "scarlet letter".

Why we are concerned:

First, it should have been discussed with industry and with the board, so that we don't have to resort to this sort of public outcry. It is well past time for foolery, as we should at this point be able to work together.

Second, we will at best hesitate to purchase remediated trim because a retailer may not understand that the process used to create the concentrate eliminated the failure issue. This is proven by a new test. A retailer may then reject the product, ask for discounts, or falsely assume that it is substandard quality. We agree that perhaps a discussion with a retailer can be had, but again this was not vetted through the public process where industry could weigh in.

Important for the board to understand and for the bottom line:

So if we (and presumably other manufacturers) no longer purchase trim that requires remediation a cultivator will have fewer options except to destroy the trim, decreasing the state's tax collection potential, creating more waste and unfortunately opportunity for diversion to the unregulated market.

Trying to track down justification:

When we inquired with AMCO about the Scarlet Letter we were asked to put the concern in writing. Before doing that, we reached out to METRC to see what could be learned. Below is a capture of METRC's response, citing that the change was "approved by the State" and "will be used in an ongoing basis from now on". See below.

From: *Alaska Metrc <support-ak@metrc.com>*
Sent: *Wednesday, August 28, 2019 3:56 PM*
Subject: *Fwd: Packages showing they were remediated*

Hi [redacted],

Regarding your question about the Remediation symbol, the remediation symbol is global functionality that was approved by the State to identify product that needs or has been remediated. It will be used in an ongoing basis from now on.

If you have any further questions, please contact support

Thanks,
Metrc Testing Team

We then offered our concerns to AMCO in writing and have yet to receive a response. See below.

From: [redacted]
Sent: *Wednesday, August 28, 2019 4:09 PM*
To: *CED AMCO Enforcement (CED sponsored) <amco.enforcement@alaska.gov>; marijuana.licensing@alaska.gov <marijuana.licensing@alaska.gov>*
Subject: *Fw: Packages showing they were remediated*

Hi AMCO,

I am curious what reasoning or discussion was had regarding adding the remediation symbol to all child packages from source packages with new lab results when the product was made with remediated trim.

If this is going to be a practice going forward our company and I imagine other manufacturers who purchase remediated trim, will cease to do so. As the perception at the point of wholesale is that it is substandard, even though our extraction method and subsequent new lab test prove that it is safe. Customers will ask for a reduced price, or reject it all together. There would then be more waste and less tax dollars.

Maybe this was discussed at a board meeting and I missed it, but this is certainly going to change the way we do business and I would hope that when AMCO makes changes that effect a business, it would be run through the board process.

Please let me know if this is something that was discussed in detail and if my specific concerns are understood or if I need to prepare something more substantive to present to the board.

Thank you,

[redacted]

Wrap up:

Understanding that AMCO is busy and that it is hard to get back to folks, we are curious why an overburdened office seems to have time to make these changes along with other impactful tweaks, but no time to explain their rational to the board or the industry which they regulate.

We respectfully request that the director and staff no longer be allowed to change regulatory practice unilaterally and instead by required to strictly follow the Administrative Procedure Act.

Thank you for your service and consideration.

Sincerely,

Lacy Wilcox, Manager
On behalf of THC Alaska LLC

From: Lacy Wilcox
To: Marijuana, CED ABC (CED sponsored)
Subject: AMCO Using Metrc Bulletins as Regulation Changes
Date: Tuesday, September 10, 2019 10:14:21 AM
Attachments: METRC Bulletins as Regulation Changes 9-11-19.pdf

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Please see attached concern. I understand that this is too late to make it in the packet for the September meeting, but am sending for future board consideration.

Thank you,
Lacy Wilcox

photo

Lacy Wilcox
Legislative Liaison, THC Alaska
907-302-3535 ext 105 | 907-302-3531 | lacy@thcalaska.com
www.THCalaska.com

To: Alaska Marijuana Control Board
From: THC Alaska, License #'s 10270 & 10271
Re: AMCO Using Metrc Bulletins as Regulation Changes
Date: September 11, 2019

Alaska Marijuana Control Office (AMCO) has directed Metrc staff to change the "required fields" for users (licensees). The addition of required fields in Metrc compels licensees to change their operating plan without Marijuana Control Board (MCB) approval. Thus, AMCO is making changes that are effectively changes to the regulations. AMCO does not have the authority to make regulation changes.

Changes to Metrc that require changes to operating plans should go through the MCB process and the Administrative Procedure Act (public comment, MCB discussion/evaluation, etc.) to ensure the changes are following state regulations and, in the public and industries best interest.

Two recent changes to Metrc (as directed by AMCO) require operation changes for licensees but were not approved by the MCB:

1) Requiring Gross Weight for product transfers (Bulletin #020)

2) Requiring that an entire harvest batch always remain in the same location ("Change Rooms in Harvest", Bulletin #021)

3) A third change was made regarding a remediation symbol on child packages, though it came with no notice or bulletin. We have addressed that issue in a separate cover.

Background:

Bulletin #020 (distributed 5.17.19) described a change to Metrc that effectively altered operating procedures for licensees by requiring the addition of gross weight for transfers.

Bulletin #021 (distributed on 8.23.19) described a change to Metrc that effectively altered operating procedures for licensees by requiring that "the entire harvest batch should be in the same location".

The Big Picture:

Metrc is being used as a back door to change regulation that requires licensees to change their operating plans without involving the Marijuana Control Board or public comment. If these Metrc changes are effectively regulation changes, then changes via Metrc are in violation of AS 44.62 (Administrative Procedure Act).

Furthermore, the Board is not the party which is authorizing these changes, and under AS 17.38 it does not appear that any other agency has the authority to change regulation. For reference below is the states definition for duties of the Director:

“Sec. 17.38.150. Duties of director. The director shall enforce this chapter and regulations adopted by the board. The director shall issue, renew, transfer, suspend, or revoke all licenses and permits and issue product approvals at the direction of the board. The board may delegate to the director the authority to temporarily grant or deny the issuance, renewal, or transfer of licenses and permits. The director's temporary grant or denial of the issuance, renewal, or transfer of a license or permit is not binding on the board. The board may delegate to the director any duty imposed by this chapter except its power to propose and adopt regulations.”

Metrc is regulation. Licensees are mandated to use and satisfy the parameters of the inventory tracking system. If this type of backdoor regulation change is not addressed, the state could authorize Metrc to make any kind of changes without following AS 44.62. This backdoor access to regulation change is dangerous and is not in the spirit of the Regulation of Marijuana that the State authorized.

The Specifics:
The “Gross Weight” and “Change Rooms in Harvest” changes made by AMCO were made without MCB approval. Thus, these changes implemented by AMCO did not receive the benefits of the process of the MCB (i.e., public comment, MCB discussion and input, etc.) which is designed to improve and refine proposed changes. Because of this, these changes are ineffective in achieving their goal (and may in fact increase risks), and causes undue burden on the industry.

Why adding the “Gross Weight” field (#020 Bulletin) does not increase public safety or help prevent diversion:

A single concentrate container can vary by as much as 4g per container. These are used for packaging 0.5g of Marijuana product. With this variance of packaging all that the gross weight addition to Metrc has done was to put an additional burden on licensees. This did not reduce the chance of diversion.

Why “Change Rooms in Harvest” Metrc feature is poorly designed.

1. More cannabis will be moved and handled more frequently than necessary. This creates more opportunity for diversion as well as health and safety issues.

Harvest Batches in Metrc often consist of the entirety of one variety that was grown under the same treatment regimes and with the same planting and harvest date as per 3 AAC 306.990 (B)(3). This is strategic in order to minimize the cost of testing. According to bulletin #021, the entirety of the Harvest Batch must be kept in the same location. Therefore, if trimmers need to move product from the drying rooms or secured storage in order to trim the product, than the entirety of the Harvest Batch must be moved out to the trim rooms. This could mean moving 40 lbs or more of cannabis so

that two pounds could be processed. This is an undue burden on the industry that does not increase public safety, public health, or prevention of diversion. Secondly, it is causing product to be relocated when it is not necessary, which opens more opportunity for diversion. Best business practices would involve moving as little cannabis as possible with the least frequency in order to insure better tracking, security, and sanitation. It is more difficult to catch diversion as more cannabis is moved during a day. More frequent movement also increases the chances of human error during these movements (e.g., a portion product from one harvest batch getting mixed up with another harvest batch) which could lead to misrepresentation of testing results or incorrect inventory records.

2. There is no requirement for tracking packages by room within a licensed facility

Currently, regulations do not require Metrc packages to be tracked by room within a facility. Certainly, requiring an entire harvest batch to be in the same room is an attempt to help investigators when they conduct a facility walkthrough, and expect to see a harvest batch in one location. However, harvest batches do not have weights and can be expected to be in multiple locations during the harvest/trimming/drying/curing process. Upon request, the licensee should be able to easily show an investigator the entirety of a harvest batch, even if the batch is split among multiple locations.

3. Finished product being stored in a less secure area

This operational change required to accommodate the “Change Rooms in Harvest” feature would create a liability. A harvest batch must be dried, cured and trimmed before it is ready to be packaged and tested. This results in a harvest batch that could easily be 40lbs. The wisest thing to do once the product is finished being handled is to place it in the most secure area of the building, therefore limiting access to the finished product. This new mandate requires that the harvest batch stay together. This means finished product must remain in a less secure location until the entire harvest batch is finished being processed and can be moved to a more secure location.

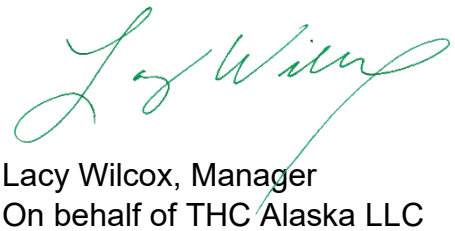
The Bottom line:

These backdoor changes to regulations via Metrc should be considered overreach as they are not following state statute. These changes should be going through the proper processes via the MCB to ensure changes are receiving public comment and MCB consideration. This process is important for allowing industry members to provide valuable feedback that can make new Metrc changes more effective in preventing diversion, while increasing public health, and safety. Good industry members are interested in preventing diversion and increasing public health and safety as much as

anyone and their perspective should be considered an invaluable tool in strengthening regulations.

Thank you for your service and consideration.

Sincerely,



Lacy Wilcox, Manager
On behalf of THC Alaska LLC

From: Marijuana Licensing (CED sponsored)
To: Marijuana, CED ABC (CED sponsored)
Subject: FW: 3 AAC 306.370(d)(1)(B)(i) - Suggestion
Date: Tuesday, September 17, 2019 3:50:09 PM
Attachments: image001.png

Forwarding.

Sincerely,

TJ Zielinski
Occupational Licensing Examiner
Alcohol & Marijuana Control Office
550 West 7th Avenue, Suite 1600
Anchorage, Alaska 99501

From: Sam Thornton PE PhD <SamThorntonPE@outlook.com>
Sent: Tuesday, September 17, 2019 12:17 PM
To: Marijuana Licensing (CED sponsored) <marijuana.licensing@alaska.gov>
Subject: Re: Smoking Room in Cannabis Corner, Ketchikan

I have a suggestion, TJ.

3 AAC 306.370 (d) (1) (B) (i) states that if consumption by inhalation is to be permitted, ventilation plans must be signed and approved by a licensed mechanical engineer.

I think that should be rewritten to state that ventilation plans must be **designed**, signed, and approved by a licensed mechanical engineer.

Here's why... and this has happened to me multiple times since I moved to Ketchikan... people think that they can have a system designed and installed by a mechanical contractor, and then all they have to do is find a mechanical engineer to stamp the drawings. They think that getting a mechanical engineer to stamp something is like getting a notary public to stamp something - a couple of bucks for the stamp, and they're good. It comes as an unwelcome surprise to find out that it's pretty expensive to have me analyze someone else's design to ensure that it is safe and meets all the code requirements, etc., before I will stamp someone else's design. (In fact, I tell them at the outset that I won't stamp anyone else's design. They hate that.) Nobody tells them to budget for mechanical design, so it comes as an unwelcome surprise, just when they think that all they are doing is checking a box on a form: get mechanical engineer to stamp drawings. Check.

So I think that it would be more fair to the applicants to let them know that one way or the other they will have to pay for ventilation design, and if the Marijuana Control Board regulations state that ventilation must be designed by a mechanical engineer, it will make things easier for everyone.

Just a thought.

Sam

From: Marijuana Licensing (CED sponsored) <marijuana.licensing@alaska.gov>
Sent: Tuesday, September 17, 2019 9:18 AM
To: Sam Thornton PE PhD <samthorntonpe@outlook.com>
Cc: Marijuana Licensing (CED sponsored) <marijuana.licensing@alaska.gov>
Subject: RE: Smoking Room in Cannabis Corner, Ketchikan

Good morning Sam,

The regulations for an onsite consumption area of a retail marijuana store can be found online at https://www.commerce.alaska.gov/web/Portals/9/pub/MCB/StatutesAndRegulations/3AAC306%208-21-19.pdf, under 3 AAC 306.370, for reference. Some pertinent sections:

(a) Unless prohibited by local or state law, a freestanding licensed retail marijuana store with an approved onsite consumption endorsement is authorized to

(1) sell marijuana and marijuana products, excluding marijuana concentrates, to patrons for consumption on the licensed premises at the time of purchase only in an area designated as the marijuana consumption area and separated from the remainder of the premises, **either by a secure door and having a separate ventilation system**, or by being outdoors in compliance with (c)(4) below;

(c) A marijuana consumption area shall have the following characteristics:

(1) the consumption area shall be isolated from the other areas of the retail marijuana store, separated by walls and a secure door, and shall have access only from the retail marijuana store;

(2) a smoke-free area for employees to monitor the marijuana consumption area;

(3) a ventilation system that directs air from the marijuana consumption area to the outside of the building through a filtration system sufficient to remove visible smoke, consistent with all applicable building codes and ordinances, and adequate to eliminate odor at the property line;

The regulations do not list more specific requirements, but I have copied AMCO Enforcement in this email in case they have any additional information. You will also want to contact the Ketchikan Gateway Borough regarding applicable building codes and ordinances. The Borough Clerk's office may be a good place to start – their contact information can be found at https://www.kgbak.us/Directory.aspx?did=7.

Sincerely,

TJ Zielinski
Occupational Licensing Examiner
Alcohol & Marijuana Control Office
550 West 7th Avenue, Suite 1600
Anchorage, Alaska 99501

From: Sam Thornton PE PhD <samthorntonpe@outlook.com>
Sent: Monday, September 16, 2019 3:29 PM
To: Marijuana Licensing (CED sponsored) <marijuana.licensing@alaska.gov>
Subject: Smoking Room in Cannabis Corner, Ketchikan

Good morning:

My name is Sam Thornton, a registered mechanical engineer living in Ketchikan. I was approached recently by the owners of a licensed cannabis operation in Ketchikan (the Cannabis Corner) about a requirement to get a mechanical engineer's stamp for approval of the HVAC system in their proposed smoking room. The owners indicated that this requirement came from the AMCO office, so I am trying to find out what it is exactly that AMCO requires in order to make their decision.

Thank you,
Sam

Samuel Thornton Mechanical Engineering
Samuel Thornton, PE PhD, Owner
PO Box 7162
Ketchikan, AK

(907) 220-7849

From: Marijuana Licensing (CED sponsored)
To: Marijuana, CED ABC (CED sponsored)
Subject: Objection to Marijuana Establishments - Wasilla and Tok
Date: Monday, October 14, 2019 12:00:35 PM
Attachments: General MJ Objection - Wasilla and Tok.pdf

An objection written on the back of a public notice for Tokin' Up, License #20844 was received in the mail by AMCO on October 11, 2019. The objection does not appear specific to this establishment, and proof that the objection was provided to the applicant (required under 3 AAC 306.065) was not included. Forwarding as a general comment.

This is probably coming to late, but I am writing any way To object to a pot store in Wasilla and especially Tok. I Live in Tok and see drunks, and people that are high walking arou Town. Pot stores will only add to The problems of drug & alcoholism, Theft, driving while impaired, Laziness, obesity, and immorality. It was a slap in the face to all hard working law abiding citizens of Alaska To legalize marijuana, The morals of our state are being cast aside by a bunch of degenerates and money hungry dope fiends

regards,

Jeff Hendricks
registered republican

From: David Shimek
To: Marijuana, CED ABC (CED sponsored)
Subject: ethnic/economic disparity in AMCO licensing
Date: Thursday, October 17, 2019 3:59:26 PM

Though I am unaware of any definitive survey, it appears to this observer that there is a large discrepancy between Alaska's ethnic makeup and the ethnic makeup of AMCO licensees.

Other marijuana-legal states have encountered similar disparities, and several have explored and even acted to ameliorate such disparities. Just this last week California adopted a law allocating $10 million to assisting "minorities and the economically disadvantaged" to participate in the industry.

As the Board is aware, license applicants in this state face a daunting challenge --- the creation of a licensed establishment requires a very substantial investment of personal savings, since bank loans are unavailable and neither Federal or state loan programs provide assistance to the industry. While this situation may change someday, it doesn't appear imminent --- and by the time it does occur the cannabis markets may be fully populated.

While the amount of personal savings needed varies by type of license, location, and size, all of them require vastly more ready cash than is held by the average American. (In 2017 the Federal Reserve Board released a report from its "Survey of Household Economics" which indicated that 47% of American households would be unable to meet a $400 "emergency" without borrowing the money!)

Given the political and economic situation of this state right now, it seems highly unlikely that a law similar to the California law mentioned above is even a remote possibility.

I would urge the Board to consider changes to the existing licensing regulations which would be feasible and would to some extent open the field to Alaskans other than those fortunate few with several hundred thousand dollars at the ready.

First, eliminate the requirement that no application will be accepted without proof that the applicant has existing legal possession of a proposed site. This requirement alone makes application prohibitive, as it essentially requires the payment of rents or purchase payments on empty premises for as long as it takes to secure all licensing and permitting by AMCO or municipal entities. No, this won't solve the problem of "wasted money" entirely -- but it may in some cases. There are no doubt landlords who will commit to the applicant's occupancy at a date certain in the future ---there are very few who will agree to provide occupancy rights ---but no rent --- until licensing has been secured.

Secondly, stop bringing licensees before the Board to "hound" them to get open. Licensees have plenty of desire to get open --- but they may very well have run short of funds. It may take a long time to save up or scrounge up the money to finish their project --- but that imposes no burden or loss on the state or AMCO (nor on other persons who wish to be in the industry, as there is no limit on licenses). Many an Alaskan has built a home or business in stages, usually because that was the only way it could be accomplished. Yes, it may take the "working man" 3 years to accomplish what the "man of wealth" can do in 6 months ---but offering up the opportunity is surely the better and fairer choice.

These changes, and others of similar intent, will not solve the problem of disproportionate licensing among ethnic or economic groups. They may help some people, though, and their consideration would indicate that the issue is one the Board is willing to think about.

Thank you,

David Shimek 360-8096

ddshimek@hotmail.cog

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Phone 630-913-1113
Main Office 907-231-3750
JDW, LLC
jana@jdwcounsel.com

October 24, 2019

MCB Board

Sent Via Electronic Mail

Re: Overlapping Premises

Dear Honorable MCB Members:

Thank you for considering my public comment for the regulation project that discusses overlapping premises for marijuana licensees. This issue keeps reappearing for licensees and is causing major injuries to the efficiency of marijuana businesses – the alleged prohibition of overlapping licensed premises. The proposed regulation should not be adopted as written. Essentially, the proposed regulation is an attempt by the Director to codify what staff has attempted to impose on licenses without written regulatory support. The draft regulation simply takes how AMCO believes the regulation should be imposed and re-writes the existing regulation to mirror the current AMCO staff belief as to how the regulations should read. It's not fixing a problem, it's further restricting the ability for these companies to act like regular businesses and more importantly, the draft regulation *undermines* public health and safety instead of promoting and protecting public health and safety.

From the beginning of licensing, the Marijuana Control Board has repeatedly approved diagrams that show co-located secured storage when there are co-located and co-owned licensed types. This has been standard industry practice and it is not prohibited in the regulations. AMCO staff recently began taking issue with this. For example, if a licensee took their original approved diagrams and made changes (not related to shared spaces) and then submitted it as an mj14 for review and approval, the staff would come back and say "you cannot have shared storage". To which, the licensee responds, "but, that was approved that way, I didn't change that part – the MCB already approved it." And staff retorts, "well it doesn't state you can do this in the regulations, so that means you cannot."

The propose regulation, instead of addressing the industry's legitimate concern that it makes sense for consumer protection and safety of their employees, to secure product in the most secure place in their facility, it just codifies the position that AMCO staff has consistently been taking. The

draft removes language from 3AAC 306.405(c)(4) – the language removed is the language that shows the original intent of the MCB to allow for some overlapping of licensed premises, furthering the codification of staff's position – and reducing the ability for overlapping of premises:

> (4) [EXCEPT AS PERMITTED UNDER A MARIJUANA PRODUCT MANUFACTURING FACILITY LICENSE,] extract, **produce, or possess** marijuana concentrate [, USING ANY PROCESS DESCRIBED IN 3 AAC 306.555,] at the licensed premises;

It's my understanding the board instructed staff to create a draft to address the concerns that the industry is not being able to utilize their facilities in the most secure manner – I do not recall the MCB requesting the staff to further the problem and further reduce the ability of licensees to utilize their facility in a manner that increases the risk to public health and safety.

Then the draft goes on to FURTHER restrict the ability for licensees to utilize their facility space:

> 3 AAC 306.710(a) is amended to read: (a) A marijuana establishment shall restrict access to any part of the licensed premises where marijuana or a marijuana product is grown, processed, tested, stored, or stocked, **or through which marijuana or a marijuana product is moved**.

Adding yet another restriction that AMCO staff has been telling licensees already existed under the regulation, and peddling that additional restriction (that was NOT included in the regulations before) to this Board despite the request to open up a project that would further the ability to have shared licenses premises space, this proposed changed undermines that ability.

Additionally, the addition of the bold and underlined language has more untended consequences – how does one move product out of the facility? Or out of a retail store? This addition of language does not make sense – it would render retail sales floors restricted access – loading docks restricted access – vehicles… the nonsensical list could go on and on..

This type of morphing what the Board requested to what the staff proposes is an alarming trend. The Board already approved and codified over-lapping premises in the regulations:

Currently, 306.405 (b) states,

> A licensed standard marijuana cultivation facility may also apply for a marijuana product manufacturing facility license and a retail marijuana store license. A standard marijuana cultivation facility that obtains a marijuana product manufacturing facility license or a retail marijuana store license shall

(1) conduct any product manufacturing or retail marijuana store operation in

a room completely separated from the marijuana cultivation facility by a secure door when co- located; and

(2) comply with each provision of this chapter that applies to any other type of marijuana establishment license that the standard marijuana cultivation facility licensee obtains.

Nothing in this regulation section prohibits the over lapping of premises or prohibits shared storage. Notably – **the staff's proposed draft that you are currently considering proposes eliminating this entire section– is this what the Board intended to do?**

The staff has previously opined that overlapping premises are not allowed in the regulations – but it's clear, the staff is incorrect and is now attempting to remove every part of the regulations that infer or provide for any form of overlapping. In addition to the regulation provisions above that staff is attempting to delete and remove, the proposed draft also proposes deleting the following provision of the current regulations:

3 AAC 306.450. Production of marijuana concentrate prohibited.
A marijuana cultivation facility may not produce or possess marijuana concentrate that was extracted using any process described in 3 AAC 306.555 **on the marijuana cultivation facility's licensed premises unless the marijuana cultivation facility also has a marijuana product manufacturing facility license.** Any extraction or production of marijuana concentrate on the premises of a licensed marijuana cultivation facility must (1) be in a separate room that (A) is physically separated by a secure door from any cultivation area; and (B) has a sign that clearly identifies the room as a marijuana concentrate production area, and warns unauthorized persons to stay out; and (2) comply with all applicable provisions of 3 AAC 306.500 - 3 AAC 306.570.

CLEARLY – the highlighted and bolded section allows for overlapping premises, and again, staff is proposing to REMOVE all of the language above. This draft regulation project is the exact opposite of what the industry needs, and it undermines protecting public (and employee) health and safety.

In the regulations as they are currently codified, there is not one mention of any prohibition of overlapping premises. The word overlap is not even mentioned. Somehow, staff *inferred* this alleged prohibition despite the repeated citations throughout the regulations that specifically provide for overlapping of premises. If staff doesn't like the regulations as written, that doesn't mean its allowed to creatively and conveniently interpret the regulations in a manipulated manner to reach a conclusion that meshes with how staff "thinks it ought to be". If staff thinks the regulations ought to be different, they should write a public comment in regard to what they believe it should be. Not cunningly draft regulation projects that simply craft their own desires and conclusions.

Under the Alaskan marijuana regulation scheme, licensees are allowed to hold all types of licenses at one time (with the exception of marijuana testing facilities). As you can imagine in any business, efficient and effective use of one's available business space is of critical importance to these business owners.

Let's take a restaurant for example – a restaurant makes the food in the back of the house and then sells it to consumers from the front of the house. Waiters go in and out of the back of the house with ease, and back to the front of the house. Supplies used by the "front of the house" staff are stored in the "back of the house" and easily accessed without barriers at all times. The cash is usually stored in a safe in the manager's office, along with the timecards, table closeouts and the calculations for how much credit card tips the server received. End of shift cash outs for servers also occurs in the back of the house for most wait staff.

Can you imagine an efficient restaurant business model where the front of the house was prohibited from storing any of the supplies it needs to service the consumers?

Can you imagine if waiters were prohibited from walking into the back of the house to grab your order and bring it to you?

Can you imagine how much business frustration would occur if the typical back/front of the house in restaurants was disrupted?

Now, let's apply the current regulation to marijuana licensees – and let's imagine a single company owns a retail and small cultivation. In the retail area (front of the house) you have budtenders, servicing the consumers and filling their orders. In the cultivation (back of the house), you have the cultivation team hard at work producing the product that fills the orders. The owner of this company looks at his/her space available, the number of employees needed to adequately staff the front and back of the house, and the safety of the company's inventory and staff.

The owner may determine that some of the front of the house staff can actually perform some work in the back of the house. The owner may determine that the secure safe product storage in the cultivation area is a much more secure location for retail inventory (and safer for employees) than out front in a glass locking cabinet. The owner may also determine that the front of the house simply doesn't have enough space to securely and properly store all the retail store's inventory. If both the retail license and cultivation license are owned by the same entity/person, all employees are employees of this single entity/person, and both licenses are housed in the same building/unit, what would be the government's rationale or prerogative to tell this business owner the following:

- You're required to store your retail inventory out front in the retail licensed space only;
- You're required to store your retail inventory in a manner that makes it more enticing to be robbed as the robber could get **all** of the retail's inventory just by breaking into the retail store; and
- You're required to use your business space in a manner that is inefficient, disrupts business flow, and doesn't make good business or security sense.

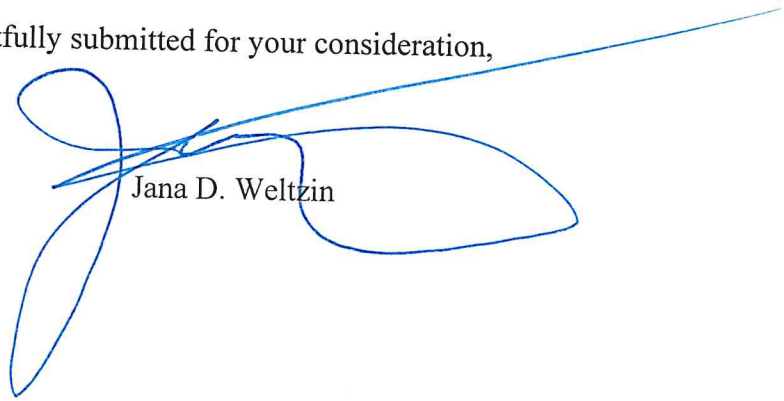
That is the effect of the proposed draft language – in the staff memo to the board regarding Alaskan Leaf denial of MJ14, dated September 11, 2019, which my office appealed to this body, the memo states that the regulations "contemplate" that marijuana/product is stored on the licensed premises. What does contemplate mean in this context? The regulations do not contemplate, they don't think or have an opinion, the regulations are words – and the WORDS of the regulations do not say you cannot have shared secured storage. Period. No contemplation or meditation needed – that is not how to interpret the law. The law is the plain meaning of the words.

A marijuana company that owns more than one license under one roof should be allowed to utilize the business space as it is secured to the highest and most efficient use possible. We should amend regulatory provisions to reduce business disruptions as opposed to continue to impose them when common sense tells us this just doesn't make any sense, and there's no real rationale basis for restricting a business use of the space that is paid for and invested in. We understand that if there are multiple licenses owned by multiple companies or persons, then there are risks that need to be addressed – but we should carve out an exception for use of space and allow for overlapping licensing use when licenses are co-owned and co-located.

Therefore, I would propose the board not adopt this regulation and either really dig into what the current regulations provide for OR create a working group with licensees to address any staff concerns and industry needs in one working body and come up with a commonsense/practical use of business space that further protection of our employees, the public, and strengthens protections for public health and safety.

We know this is a volunteer board that gives up countless hours with your family, friends and professional obligations to ensure that our industry is sustainable, and that Alaskans are protected. We very much appreciate your contributions. Thank you for your continued hard work, dedication and commitment to the success of this regulated industry.

Respectfully submitted for your consideration,



Jana D. Weltzin

From:	McConnell, Erika B (CED)
To:	Marijuana, CED ABC (CED sponsored)
Subject:	FW: AMCO November Board Meeting
Date:	Friday, October 25, 2019 2:53:56 PM
Attachments:	ATTACHMENT 1.pdf ATTACHMENT 2.pdf ATTACHMENT 3.pdf ATTACHMENT 4.pdf AMCO Letter 102519.pdf

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From: Sam Hanson [mailto:AKHansons@hotmail.com]
Sent: Friday, October 25, 2019 2:38 PM
To: McConnell, Erika B (CED) <erika.mcconnell@alaska.gov>; Marijuana Licensing (CED sponsored) <marijuana.licensing@alaska.gov>; torney.general@alaska.gov; Smoldon, Todd D (GOV) <todd.smoldon@alaska.gov>; Almeida, Jacob W (LEG) <jake.almeida@akleg.gov>; Wilson, David S (LEG) <senator.david.wilson@akleg.gov>; Jesse Sumner <jessesumnerdistrict6@gmail.com>
Subject: AMCO November Board Meeting

October 25, 2019

Erika McConnell, Director

AMCO

550 West 7th Avenue, Suite 1600

Anchorage, AK 99501

Director McConnell,

Alaska State regulations dictate that the Alaska Marijuana Control Office (AMCO) not issue a marijuana establishment license if the licensed premises will be located within 500 feet of a school ground. Regulations specify that the distance must be measured by the shortest pedestrian route from the public entrance of the marijuana establishment building to the outer boundaries of the school ground. Further, Alaska State statute clearly defines the school ground as land contained within the real property boundary line (lot line).

Alaska Statutes 2018 | Article 4. Definitions. | Sec. 11.71.900. Definitions.
AS 11.71.900 (30) ***"school grounds" means a building, structure, athletic playing***

field, playground, parking area, or land contained within the real property boundary line of a public or private preschool, elementary, or secondary school;

There is no ambiguity on these points.

The limited marijuana cultivating facility operated by Mr. Happy Farms, LLC (MHF), owned by Matthew Shelter and Thomas Dicus, is constructed on property that shares a common lot line with Shaw Elementary school. The shortest pedestrian route from the public entrance to the limited marijuana cultivating facility around the corner of the facility and to the lot line of Shaw Elementary School is estimated to be approximately 90 feet. The size of the MHF property is such that there is no physical way for the marijuana cultivating facility to be moved or re-constructed on MHF property and be 500 feet or greater distance from the school grounds and in compliance with regulations. AMCO should not allow continued operation of MHF on this property.

The purpose of this letter is to:

- Show that the owners of MHF knew the business was not in compliance with the 500-ft separation requirement, had discussed separation requirements with the Mat-Su Borough, and had been referred to AMCO for state requirements. They incorrectly certified on their application that they met the 500-ft separation requirement.
- Point out that the AMCO staff did not catch this inaccurate representation in their review of the initial application.
- Demonstrate that when this discrepancy was first brought to the attention of the AMCO Board at its July meeting questions arose on the definition of the shortest pedestrian route. The Board was to meet and establish clarity before deciding on compliance.
- Show that in the absence of clarity, at its September meeting the AMCO Board decided to allow continued operation of MHF.
- Request that AMCO find that MHF is not in compliance and revoke the license allowing continued operation of MHF at its current location, abutting the Shaw Elementary School property.

The following timeline will provide helpful context:

<u>Spring 2018</u> – In February, March, and April 2018 MHF met with Mat-Su Borough Planner, Mark Whisenhunt. They discussed the fact that the building plans showed the facility to be within close proximity of school property. Mr. Whisenhunt explained that the Borough did not have requirements for Limited Marijuana Cultivating facilities and referred MHF to the AMCO for State of Alaska requirements. MHF misrepresented this discussion to their attorney, indicating that the Borough "didn't see it as an issue due to the distance from the

actual school and the thickness of the forest", reference June 11, 2019 email from MHF attorney (Attachment 1). This is a very misleading statement and is directly countered by Mr. Whisenhunt's email (Attachment 2) in which he recalls the discussion with MHF representatives and clearly states that their office would not make opinions on State of Alaska standards and they always refer customers to AMCO.

Summer 2018– Mr. Happy Farms completed construction of the building, prior to application to AMCO. Refer to statement from Thomas Dicus (Attachment 3).

December 2018 - Matthew Shelter and Thomas Dicus certify on their application that their building is "not within 500 feet of a school ground", knowing full well that they had already constructed in close proximity to the school boundary. The drawing included as part of the application identified a 60-foot distance to the property lot line, but did not identify that property is owned by the Mat-Su Borough school district. There does not appear to be any evidence that MHF followed the recommendation of the Mat-Su Borough planner and had a discussion with AMCO staff about the proximity to school grounds. One could reasonably assume they didn't want to have this discussion because they knew the outcome would prevent their business operation. AMCO did not catch the misrepresentation during their new application review because AMCO does not apparently have a process in place to verify this requirement – unlike other qualifying statements, such as being a felon. Had AMCO staff known the business facility was in such close proximity to the school grounds, the license would surely not have been presented to the board for approval.

May 2019 - The fact that the MHF facility is in very close proximity to Shaw Elementary school grounds was brought to AMCO's attention.

July 29, 2019 – In the AMCO Board meeting, there was a discussion about the distance of the facility from school grounds. There were differing opinions offered as to how to interpret regulatory requirements, particularly as relates to the "shortest pedestrian route" between the marijuana facility and the school grounds. The Board decided to allow MHF to continue operating until the Board could meet again and gain a clearer understanding of the regulation. The July Board minutes are not yet available, however a review of the audio recording will confirm.

AMCO staff did not share in the July Meeting (not found in the July meeting audio recording) that the Board could revoke this license for misrepresentation of information as provided by Article 8. Enforcement; Civil Penalties 3 AAC 306.810. Suspension or revocation of license (1) misrepresented a material fact on an application for a marijuana establishment license, or an affidavit, report, or signed statement under AS 17.38 or this chapter.

July 30, 2019 through September 10, 2019 - AMCO staff, through their Regulations Project

Committee (headed by Loren Jones, Nick Miller, and Erika McConnell) had this time frame to complete a review and prepare for discussion with the AMCO Board. During this time, AMCO staff received several objections to this license renewal - specifically requesting they uphold the 500 foot separation requirement.

September 11, 2019 – In the AMCO Board meeting MHF was listed on agenda under License Renewal. The Board did not receive the clarity from the AMCO staff and the Regulations Project Committee because they were "still working on the project". Some Board members expressed confusion and frustration with the situation and some seemed to forget they had sought clarity before making a decision. Despite this lack of clarity, the Board approved the license renewal as being in compliance on a vote of 3 to 2. This decision was not fully informed and the Board created their own definition of regulations describing a measurement from the marijuana business to a fence on school property near the playground as an appropriate standard. This is apparent from the following excerpt from the unapproved September Board meeting minutes.

> *Motion made by Bruce Schulte to approve with delegation:*
>
> *Bruce Schulte states "that there has been lots of testimony in this matter but that he is looking at the current regulation that defines the measurement as the "shortest pedestrian route". He feels that this property meets the requirement. He addresses risk to youth and states that the playground appears to be fenced off and he believes that he does not see a rational basis for denying this renewal based on an overly restrictive interpretation of the rules.*

For full context, refer to (Attachment 4) for a copy of the unapproved September Board meeting minutes.

The AMCO staff should have recommended that the Board postpone a decision pending completion of their analysis and review by the Regulations Project Committee. The Board routinely postpones decisions and should have done so in this instance.

To further illustrate the importance of adhering to regulatory definitions, the Board appears to have not considered objections that had been submitted in writing when deciding to use the playground fence as the criteria to establish "school grounds". Information had been providing indicating that Shaw Elementary, the largest elementary school in the MSB, often sends their children into the woods on established trails (beyond the playground fence) during their daily PE classes throughout the school year. They also place Geocaches in the woods for their youth to find- provided in writing to AMCO and included in the meeting tab for September Board meeting.

On November 19th a resolution will be introduced to the Mat-Su Borough Assembly (by Assemblyman Sumner) asking AMCO to reconsider their interpretation of their regulation decision on Mr. Happy Farms and to not allow the permitting of marijuana licenses in such close proximity of schools grounds, thereby protecting Mat-Su Borough schools. The Mat-Su Borough requires 1,000 foot separation from schools for all other marijuana licenses in the Valley. They leave the enforcement of the 500 foot separation for Limited Marijuana Cultivation facilities to be upheld by the AMCO Board.

Ultimately, the AMCO Board decision on the license for Mr. Happy Farms sets precedence for future licenses and can affect other schools in Alaska.

I am requesting that this issue be placed again on the AMCO Board agenda for November with a recommendation to rescind the license for Mr. Happy Farms, LLC. I also request that AMCO consider strengthening your internal assurance process to verify future applicants are accurately representing regulatory compliance with school ground separation regulations. One way to strengthen this assurance would be to require applicants to identify adjacent property owners on their applications.

Respectfully,

Sam A. Hanson

841-6565

CC: Alaska Attorney General's Office

AMCO Licensing

Mat-Su Office of the Governor

Senator Shower

Senator Wilson

Mat-Su Borough School District

Mat-Su Borough Assembly

Attachments:

1. MHF Attorney Comments- 2019
2. MSB Planning Comments- 2019
3. Establishment of MHF Building 2018
4. 2019- September Unapproved Board Minutes

ATTACHMENT 1 | July 2019 Board Meeting | Comments

From: Jana Weltzin <jana@jdwcounsel.com>
Sent: Tuesday, June 11, 2019 4:59 PM
To: Mark Whisenhunt <Mark.Whisenhunt@matsugov.us>
Cc: Valerie Mastolier <valerie@jdwcounsel.com>

Subject: FW: 17692 Mr. Happy Farms LLC

[**EXTERNAL EMAIL** - CAUTION: Do not open unexpected attachments or links.]

HI Mark – a neighbor (sam hanson) has raised some concerns to the control board re the location of the Mr. Happy Farms limited cultivation license – ***my client Matthew informed me that you and him (or his partner) had conversations re the school but that you didn't see it as an issue due to the distance from the actual school and the thickness of the forest.*** Erika wants something in writing proving that my client consulted with the borough on this issue. Can you confirm that you did look at this particular license and the school distance and please confirm what my client told me (which is what I relayed to Director McConnell in my email below) is accurate? The school seems to be really far away so I am unsure why this is an issue this late in the game.. the license is already up and operating.. I attached an exhibit showing the school and licensed premises to jog your memory I also attached Mr. Hanson's object too so you have the whole picture and context of this issue.
Thanks Mark! Jana

From: Mark Whisenhunt <Mark.Whisenhunt@matsugov.us>
Sent: Wednesday, June 12, 2019 12:13 PM
To: Jana Weltzin <jana@jdwcounsel.com>
Cc: Valerie Mastolier <valerie@jdwcounsel.com>; erika.mcconnell@alaska.gov

Subject: RE: 17692 Mr. Happy Farms LLC

Good Morning,

I remember this location and speaking to a gentleman about it, though I do not remember his name. While I do not remember all of the specifics of our conversation, I do remember telling him this location would not be suitable for a Standard Marijuana Cultivation Facility (greater than 500sf under cultivation), because it would not meet the Borough's 1,000' setback from "School Grounds" requirement.

If I recall, it may not have met the 100' lot line setback requirement as well. However, since he was proposing one Limited Marijuana Cultivation Facility (less than 500sf under cultivation), it was exempt from the Borough permitting standards.

Here is our definition: "School grounds" means a lot or parcel with facilities primarily used for the academic education of children or young people, usually under 18 years of age. For the purpose of setback requirements under this chapter, universities, vocational trade schools, and residential structures where children receive homeschooling are not considered schools.

The Borough considers the whole parcel (in this case, about 80 acres) to be "School Grounds." We inform all of our customers that we do not know what exactly the State considers "School Grounds" (i.e. just the developed area vs. the whole parcel) or exactly how the state measures their setback requirements (i.e. pedestrian route).

Lastly, **I'd like to note that I would not have told this gentleman "I don't see an issue" with this location**. We do not make opinions on State of Alaska standards. Our office always refer customers to AMCO when there is a question regarding State standards.

While wrapping up this email, I received a call from Mr. Dicus. I informed him of this email and its contents.

Please let me know if I can be of further assistance.

Respectfully,

Mark Whisenhunt
Planning Services Manager (Acting)
Matanuska-Susitna Borough
Office: (907) 861-8527
mark.whisenhunt@matsugov.us

ATTACHMENT 2 | Meeting Dates For MHF & MSB

From: Mark Whisenhunt <Mark.Whisenhunt@matsugov.us>
Sent: Friday, August 16, 2019 1:34 PM
To: Sam Hanson <akhansons@hotmail.com>

Good Afternoon Sam,

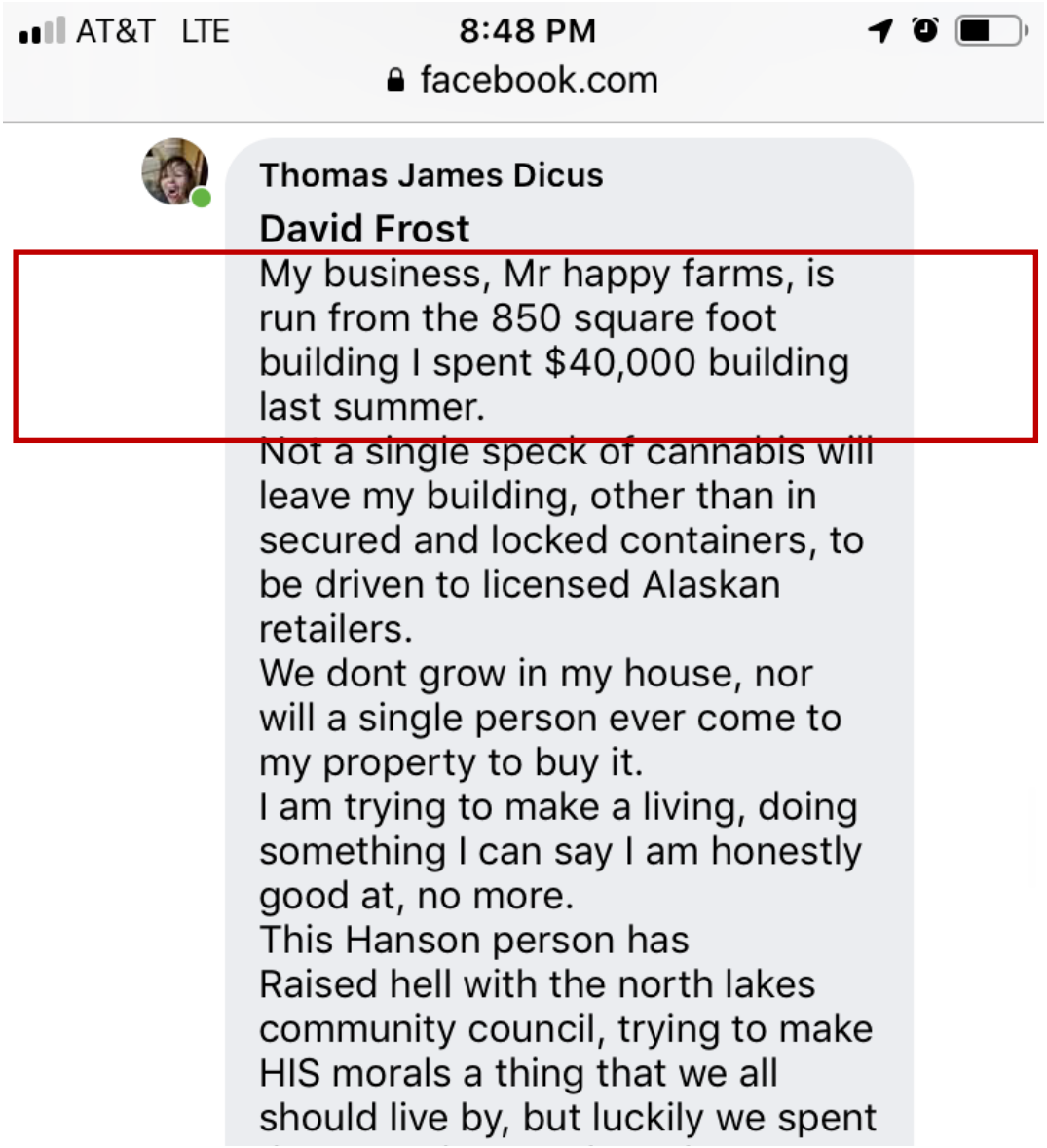
I am just getting caught up on emails after being out of the office for an extended period of time .
I apologize for the delayed response. I sent an email explaining my recollections on June 12, 2019 to Ms. Weltzin and McConnell (attached).

Looking through my phone log, it appears I spoke with Matthew Shelter in February of 2018, and Thomas Dicus in March and April of 2018.

Please let me know if you have any other questions.

Thank you.

Mark Whisenhunt
Planning Services Manager (Acting)
Matanuska-Susitna Borough
Office: (907) 861-8527
mark.whisenhunt@matsugov.us


AT&T LTE
8:48 PM
facebook.com
Thomas James Dicus
David Frost
My business, Mr happy farms, is run from the 850 square foot building I spent $40,000 building last summer.
Not a single speck of cannabis will leave my building, other than in secured and locked containers, to be driven to licensed Alaskan retailers.
We dont grow in my house, nor will a single person ever come to my property to buy it.
I am trying to make a living, doing something I can say I am honestly good at, no more.
This Hanson person has
Raised hell with the north lakes community council, trying to make HIS morals a thing that we all should live by, but luckily we spent

From: "Marijuana Licensing (CED sponsored)" <marijuana.licensing@alaska.gov>
Date: October 1, 2019 at 3:38:47 PM AKDT
To: KELLY KUZINA <kellykuzina@hotmail.com>
Cc: "Marijuana Licensing (CED sponsored)" <marijuana.licensing@alaska.gov>
Subject: RE: Mr Happy Farms Confidential Letter of Complaint

Good afternoon Kelly,

The Meeting Minutes for the September 2019 meeting have not been approved by the Board and finalized yet, which will happen at the November 2019 meeting. I do have a very rough draft of the minutes available, and can also provide audio recordings upon request. I will include the section of the minutes pertaining to this application below, but let me know if you'd like the whole draft copy. The Marijuana Control Board did move to renew this license, which passed 3-2.

1. License #17692	**Mr. Happy Farms LLC**	**TAB 1**
Licensee:	Mr. Happy Farms LLC	
License Type:	Limited Marijuana Cultivation Facility	
Premises Address:	3900 N. Sierra Street Wasilla, AK 99654	
Local Government:	Matanuska-Susitna Borough	

For Consideration: **Notice of violation regarding odor complaints – response received.**
North Lakes Community Council objects to license renewal due to the establishment's proximity to an elementary school.
Objections and comments received.

Erika McConnell states that the comments and objections are in the file.

Jana Weltzin, counsel, states that the letter of response wasn't done in time to make it to the packet but she provides copies to the board.

Mark Springer asks if this was considered recently (it was at the July meeting).

Bruce Schulte and Erika McConnell discuss the confirmation that the lots abut each other. Technically the separation is only 60 feet from the lot line. **However, it all comes down to how the shortest pedestrian route is considered. This created a regulations project headed by Loren Jones, Nick Miller and Erika McConnell, they are still working on the project.**

Jana Weltzin explains the NOV for odor.

Matthew Shelton is present via phone and answers board questions regarding when the odor complaint occurred and what he has done to resolve the NOV.

Sam Hansen board member of North Lakes Community Council is present via phone. She discusses her objections, provides information from the Borough, and references that it's the distance to the school lot line that should be considered.

Bruce Schulte asks if one or both of these properties are in the Matanuska-Susitna Borough (both) and asks about the distance between the physical structures.

Jana Weltzin summarizes the argument that the property between the two is not a practical pedestrian route due to brush and trees present.

Bruce Schulte discusses the aerial photo and the distance between the establishment and cul-de-sac.

Loren Jones discusses how the boundaries and distances are calculated. **He points out that currently it is to the boundary of the school property not the front door.**

Bruce Schulte states that the regulation states that it's the pedestrian route and the woods are not a 'pedestrian' route. **He finds the applicant not to have been dishonest in his application.**

Mark Springer discusses for the record that a couple of the objections/comments are anonymous and reads some of them.

Jana Weltzin points out that there have been no police calls regarding the matters discussed.

Matthew Shelton discusses that the stolen car was random and had just slid into the driveway. He states that it was not related to the facility.

An additional commenter states that the car was driven to the lot and then the perpetrator ran into the woods. She asserts that the theft ring is related to the area and references an aggressive Facebook page that the licensee is part of. She discusses that neighbors are afraid of this licensee.

Board and counsel discuss that the theft ring has been caught.

Christopher Jaime states that he voted no for this licensee,* the regulations speak for themselves *and it should be a no.

Jana Weltzin discusses the "pedestrian route" issue with the board.

Melody McCullah testifies via phone and states that she supports the business. The school route is only by road, and most parents drive their children because they are out of the zone. She has never experienced odor and she thinks the license should be allowed. The objectors are 'busy bodies'. ***She states that there is a big fence around the playground.***

Bruce Schulte asks about the fence and asks if it's possible to walk to the school grounds through the woods.

Melody McCullah states that it is not possible. The only entrance is from Wasilla-Fishook road.

Christopher Jaime states that fences mean nothing.

Caleb Sanders, provides comment in person. ***He states that the rules being made are "as a crow flies" and "pedestrian route". He discusses the meaning of a "pedestrian route".***

Mark Springer states* that this licensee was discussed in July *and he asks for motion.

Bruce Schulte leaves the room.

Break is called at 11:00 am.

Meeting resumes 11:10 am.

Bruce Schulte moves to approve with delegation.
Nick Miller seconds the motion.

Bruce Schulte *states that there has been lots of testimony in this matter but that* ***he is looking at the current regulation that defines the measurement as the "shortest pedestrian route". He feels that this property meets the requirement. He addresses risk to youth and states that the playground appears to be fenced off and he believes that he does not see a rational basis for denying this*** **renewal based on an overly restrictive interpretation of the rules.**

Mark Springer states that when the license was first approved in December 2018 the license passed unanimously.

Erika McConnell clarifies that no one was aware of the location situation in December.

Mark Springer states that "School Ground" and Pedestrian Route matters are under discussion. He finds breaking a trail impedes this access being a pedestrian route. *He gives very little weight to anonymous comments.*

Erika McConnell clarifies that the anonymous letters are considered "comments" not official objections.

Nick Miller states that **lots was done in July** ***and the fact that the past measurements having been done show the distance is over 500 feet and he will support renewal***

Nick Miller, Bruce Schulte, and Mark Springer vote yes, Loren Jones and Christopher Jaime vote no.

Motion carries 3-2.

Sincerely,

TJ Zielinski
Occupational Licensing Examiner
Alcohol & Marijuana Control Office
550 West 7th Avenue, Suite 1600
Anchorage, Alaska 99501

October 25, 2019

Ericka McConnell, Director
AMCO
550 West 7th Avenue, Suite 1600
Anchorage, AK 99501

Director McConnell,

Alaska State regulations dictate that the Alaska Marijuana Control Office (AMCO) not issue a marijuana establishment license if the licensed premises will be located within 500 feet of a school ground. Regulations specify that the distance must be measured by the shortest pedestrian route from the public entrance of the marijuana establishment building to the outer boundaries of the school ground. Further, Alaska State statute clearly defines the school ground as land contained within the real property boundary line (lot line).

> Alaska Statutes 2018 | Article 4. Definitions. | Sec. 11.71.900. Definitions.
> AS 11.71.900 (30) *"**school grounds" means a building, structure, athletic playing field, playground, parking area, or land contained within the real property boundary line** of a public or private preschool, elementary, or secondary school;*

There is no ambiguity on these points.

The limited marijuana cultivating facility operated by Mr. Happy Farms, LLC (MHF), owned by Matthew Shelter and Thomas Dicus, is constructed on property that shares a common lot line with Shaw Elementary school. The shortest pedestrian route from the public entrance to the limited marijuana cultivating facility around the corner of the facility and to the lot line of Shaw Elementary School is estimated to be approximately 90 feet. The size of the MHF property is such that there is no physical way for the marijuana cultivating facility to be moved or re-constructed on MHF property and be 500 feet or greater distance from the school grounds and in compliance with regulations. AMCO should not allow continued operation of MHF on this property.

The purpose of this letter is to:

- Show that the owners of MHF knew the business was not in compliance with the 500-ft separation requirement, had discussed separation requirements with the Mat-Su Borough, and had been referred to AMCO for state requirements. They incorrectly certified on their application that they met the 500-ft separation requirement.

- Point out that the AMCO staff did not catch this inaccurate representation in their review of the initial application.
- Demonstrate that when this discrepancy was first brought to the attention of the AMCO Board at its July meeting questions arose on the definition of the shortest pedestrian route. The Board was to meet and establish clarity before deciding on compliance.
- Show that in the absence of clarity, at its September meeting the AMCO Board decided to allow continued operation of MHF.
- Request that AMCO find that MHF is not in compliance and revoke the license allowing continued operation of MHF at its current location, abutting the Shaw Elementary School property.

The following timeline will provide helpful context:

Spring 2018 – In February, March, and April 2018 MHF met with Mat-Su Borough Planner, Mark Whisenhunt. They discussed the fact that the building plans showed the facility to be within close proximity of school property. Mr. Whisenhunt explained that the Borough did not have requirements for Limited Marijuana Cultivating facilities and referred MHF to the AMCO for State of Alaska requirements. MHF misrepresented this discussion to their attorney, indicating that the Borough "didn't see it as an issue due to the distance from the actual school and the thickness of the forest", reference June 11, 2019 email from MHF attorney (Attachment 1). This is a very misleading statement and is directly countered by Mr. Whisenhunt's email (Attachment 2) in which he recalls the discussion with MHF representatives and clearly states that their office would not make opinions on State of Alaska standards and they always refer customers to AMCO.

Summer 2018– Mr. Happy Farms completed construction of the building, prior to application to AMCO. Refer to statement from Thomas Dicus (Attachment 3).

December 2018 - Matthew Shelter and Thomas Dicus certify on their application that their building is "not within 500 feet of a school ground", knowing full well that they had already constructed in close proximity to the school boundary. The drawing included as part of the application identified a 60-foot distance to the property lot line, but did not identify that property is owned by the Mat-Su Borough school district. There does not appear to be any evidence that MHF followed the recommendation of the Mat-Su Borough planner and had a discussion with AMCO staff about the proximity to school grounds. One could reasonably assume they didn't want to have this discussion because they knew the outcome would prevent their business operation. AMCO did not catch the misrepresentation during their new application review because AMCO does not apparently have a process in place to verify this requirement – unlike other qualifying statements, such as being a felon. Had AMCO staff known the business facility was in such close proximity to the school grounds, the license would surely not have been presented to the board for approval.

May 2019 - The fact that the MHF facility is in very close proximity to Shaw Elementary school grounds was brought to AMCO's attention.

July 29, 2019 – In the AMCO Board meeting, there was a discussion about the distance of the facility from school grounds. There were differing opinions offered as to how to interpret regulatory requirements, particularly as relates to the "shortest pedestrian route" between the marijuana facility and the school grounds. The Board decided to allow MHF to continue operating until the Board could meet again and gain a clearer understanding of the regulation. The July Board minutes are not yet available, however a review of the audio recording will confirm.

AMCO staff did not share in the July Meeting (not found in the July meeting audio recording) that the Board could revoke this license for misrepresentation of information as provided by Article 8. Enforcement; Civil Penalties 3 AAC 306.810. Suspension or revocation of license (1) misrepresented a material fact on an application for a marijuana establishment license, or an affidavit, report, or signed statement under AS 17.38 or this chapter.

July 30, 2019 through September 10, 2019 - AMCO staff, through their Regulations Project Committee (headed by Loren Jones, Nick Miller, and Erika McConnell) had this time frame to complete a review and prepare for discussion with the AMCO Board. During this time, AMCO staff received several objections to this license renewal - specifically requesting they uphold the 500 foot separation requirement.

September 11, 2019 – In the AMCO Board meeting MHF was listed on agenda under License Renewal. The Board did not receive the clarity from the AMCO staff and the Regulations Project Committee because they were "still working on the project". Some Board members expressed confusion and frustration with the situation and some seemed to forget they had sought clarity before making a decision. Despite this lack of clarity, the Board approved the license renewal as being in compliance on a vote of 3 to 2. This decision was not fully informed and the Board created their own definition of regulations describing a measurement from the marijuana business to a fence on school property near the playground as an appropriate standard. This is apparent from the following excerpt from the unapproved September Board meeting minutes.

> *Motion made by Bruce Schulte to approve with delegation:*
> *Bruce Schulte states "that there has been lots of testimony in this matter but that he is looking at the current regulation that defines the measurement as the "shortest pedestrian route". He feels that this property meets the requirement. He addresses risk to youth and states that the playground appears to be fenced off and he believes that he does not see a rational basis for denying this renewal based on an overly restrictive interpretation of the rules.*

For full context, refer to (Attachment 4) for a copy of the unapproved September Board meeting minutes.

The AMCO staff should have recommended that the Board postpone a decision pending completion of their analysis and review by the Regulations Project Committee. The Board routinely postpones decisions and should have done so in this instance.

To further illustrate the importance of adhering to regulatory definitions, the Board appears to have not considered objections that had been submitted in writing when deciding to use the playground fence as the criteria to establish "school grounds". Information had been providing indicating that Shaw Elementary, the largest elementary school in the MSB, often sends their children into the woods on established trails (beyond the playground fence) during their daily PE classes throughout the school year. They also place Geocaches in the woods for their youth to find- provided in writing to AMCO and included in the meeting tab for September Board meeting.

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Ultimately, the AMCO Board decision on the license for Mr. Happy Farms sets precedence for future licenses and can affect other schools in Alaska.

I am requesting that this issue be placed again on the AMCO Board agenda for November with a recommendation to rescind the license for Mr. Happy Farms, LLC. I also request that AMCO consider strengthening your internal assurance process to verify future applicants are accurately representing regulatory compliance with school ground separation regulations. One way to strengthen this assurance would be to require applicants to identify adjacent property owners on their applications.

Respectfully,

Sam A. Hanson

CC: Alaska Attorney General's Office
AMCO Licensing

Mat-Su Office of the Governor
Senator Shower
Senator Wilson
Mat-Su Borough School District
Mat-Su Borough Assembly

Attachments:

1. MHF Attorney Comments- 2019
2. MSB Planning Comments- 2019
3. Establishment of MHF Building 2018
4. 2019- September Unapproved Board Minutes

From:	Lacy Wilcox
To:	McConnell, Erika B (CED); Hoelscher, James C (CED)
Cc:	Marijuana, CED ABC (CED sponsored)
Subject:	Letter from AMIA to AMCO and MCB
Date:	Friday, October 25, 2019 4:26:57 PM
Attachments:	Letter to AMCO 10_25_19.pdf

Dear Director McConnell and Investigator Hoelscher,

Please see the attached letter from the Alaska Marijuana Industry Association (AMIA). Please feel free to contact me at this email address with any questions or concerns.

Thank you most kindly,

Lacy Wilcox, President
Alaska Marijuana Industry Association

October 25, 2019
Via email

Erika McConnell, Director
Alcohol and Marijuana Control Office

Dear AMCO Director and Staff:

Alaska cannabis business owners are deeply invested in their operations and hoping for the best as product prices and enforcement of the unregulated market continue to decline.

We feel time is of the essence and that many of the issues listed in this letter require a response or remediation by the Alcohol and Marijuana Control Office or the Marijuana Control Board.

When representatives of the Alaska Marijuana Industry Association met with you on October 10, we were asked to bring our concerns directly to your office first before making public statements. We would agree to do so in the future, but it has taken the association time to compile feedback from industry members. Therefore, the MCB is copied herein.

Below is an extensive — but by no means complete — account of concerns from our membership and others in the industry. Responses to these items will be shared with our membership.

Please keep in mind that we aim to present a broad perspective on these issues. We've not suggested specific policy or regulatory solutions, as we feel many issues can be resolved through collaboration with licensees, consistent staff interpretations, or changes to agency priorities and operations.

Lack of communication

AMCO's most common form of communication with licensees is through Notice of Violations (NOV), which the agency now seeks to monetize with an egregious fine schedule. Licensees are not being adequately informed of changes to regulations or new interpretations of existing regulations. Business owners have been told by the agency that it is solely their responsibility to be up-to-date on regulations and agency expectations, however AMCO is not forthcoming with this information.

Audio of MCB meetings has been requested several times by our members but they've been told the audio isn't available. We found out at the October 3 Alcohol Beverage Control Board meeting that those recordings actually are available. So why is this audio not being posted to the website, with the meeting documents, so the public can access it?

As we've all learned, it's not enough to know the regulations; licensees must also understand how those regulations will be interpreted and the intent behind them. That's impossible without timely access to all relevant documents and meeting recordings. This issue is further complicated when interpretations aren't consistent.

To illustrate our point, below is a list of the subject lines of all emails we believe were sent to all licensees so far in 2019:

- Marijuana Waste Advisory and new waste disposal notice form (1/10/19)
- Temporary ID's (1/14/19)
- Advisory - Manifest and Virtual Transfers (1/24/19)
- Information regarding handler permit status (4/4/19)
- Onsite Consumption Endorsement (4/11/19)
- Adding an onsite consumption endorsement to an existing license (4/16/19)
- 2019/2020 Marijuana Establishment License Renewal Application Notice (5/1/19)
- Advisory-Warnings/License Number & Inspection and Investigation (5/8/19)
- Handler Card Updates (5/31/19)
- Advisory for Retail regarding clones and Transport advisory (6/12/19)
- In-state Metrc Training in October (9/2/19)
- Hashade Batch 8/12/19 (9/30/19)

None of these emails are intended to communicate changes made to regulations at scheduled MCB meetings; some only clarify interpretation of existing regulations. The advisory notices (which are hidden in the meeting documents section on the AMCO

website, and not easily accessible in a central location) communicated only the following:

- Licensees can be issued a violation for mistakes such as:
    - Reporting the incorrect day and time on a manifest, even though METRC will allow a manifest to be created with an arrival date/time that is earlier than the departure date/time.
    - Reporting weights in ounces instead of grams, even though METRC allows this and the requirement isn't explicit in the regulations.
    - Accepting moldy or seeded marijuana, even though no business owner would knowingly accept such a product only to report it to AMCO later. Often such problems only become apparent as the flower is being handled for packaging or processing. AMCO should work with licensees on the matter of defective cannabis products to ensure safety and quality, while limiting unsellable inventory held onsite and preventing diversion.
- Employees must admit entry to an AMCO investigator when presented with state-issued credentials and badges. Examples of valid credentials not provided with the advisory notice.
- Retailers may only water clones and must destroy them once they reach 8". Further maintenance of the plants is considered a violation as it constitutes "cultivation."
- The TSA requests marijuana transporters arrive at the airport 2.5 hours ahead of scheduled departure; marijuana may not be transported as checked baggage.
- Licensees must comply with advertising regulations.

If AMCO's short list of communication with licensees is an indication of anything, it's that the agency has no apparent priorities or guiding vision of how to regulate cannabis so that consumers are safe and licensees are compliant with regulations and competitive against the unregulated market. It also shows that AMCO enforcement and its director expects licensees to act perfectly at all times, despite ample opportunity for simple and often harmless mistakes to be made.

Heavy-handed or non-responsive enforcement

Many licensees have told the AMIA that they are afraid of self-reporting mistakes since doing so will almost certainly result in a violation. Similarly, licensees are often hesitant to ask questions or seek clarification from the agency for fear it might result in an unexpected violation or questioning by enforcement.

Those who decide to inquire further about a particular issue often wait days or weeks for a response; some report receiving incomplete responses or no response at all. We've heard reports of licensees receiving a phone call from AMCO staff with a response to an inquiry but then refusing to formalize that response by communicating it via email.

Some degree of leniency for a licensee that self-reports a low-level violation should be standard practice; perhaps a documented warning would suffice in many cases. AMCO should review the most common and least harmful types of violations and find ways to ensure future compliance through education. A violation is a severe way to deal with most first-time compliance issues.

We've also heard from licensees that feel a few AMCO employees treat cannabis businesses as inherently criminal in nature. If licensees are going to be treated like criminals and be subject to interrogation, then they should also be read their rights and allowed counsel.

All of these issues create a dynamic that is counterproductive to the goal of a transparent and regulated cannabis industry.

Regulatory inconsistency

Interpretation of regulation is a critical issue for the AMIA. There have been numerous cases of questionable interpretations of regulations by the director and enforcement that do not allow for public comment or the board vetting process.

If something is not specifically allowed in the regulations, some AMCO employees believe that means it's prohibited. We disagree with such interpretations as they only serve to enhance the unregulated market.

AMCO has requested adjustments to METRC which the industry believes amounts to de facto regulation changes. We understand the AMCO director believes differently.

The state's tracking system for cannabis may be administered by a private entity, but that entity is under contract with the state of Alaska. AMCO should be actively managing the outcomes of that contract, to include efforts to change or adapt the system to meet state regulations.

In the future we expect METRC trainings be informed by Alaska regulations, statutes, and common sense. There was a tremendous amount of concern after recent training events in which attendees felt they'd wasted their time and were disrespected.

Many mid-sized and larger cannabis businesses have to employ someone full-time just to deal with METRC. Does AMCO have any one employee dedicated to ensuring Alaska's version of METRC is effective and accurately reflects regulatory requirements?

Licensees should be able to expect that the fields of entry METRC requires are based on approved Alaska regulations. Anything less increases the chance of a preventable violation; anything more amounts to unvetted regulation.

Inefficient, bureaucratic system

AMCO staff have told licensees that the wait for review on change forms is 2-3 weeks when the agency is fully staffed; approval can take longer. These forms are required for a business to change its name, floor plan or operating plan, and to introduce new manufactured products or change ownership. All of these forms are reviewed and approved in the order in which they are received.

Not all of these changes require the same level of review. An application to make complex changes to operating or floor plans could be forwarded to the licensee's primary investigator; applications for simpler changes could be detected shortly after submission and approved by staff. These changes often are needed to improve business operations and their quick approval is a key part of increasing trust, efficiency, and compliance in the cannabis industry.

The AMIA urges AMCO to create and maintain a comprehensive public database of all approved and unapproved manufactured products. Listings should include details from the original product application, amendments suggested by staff or requested by the MCB, and a final status of the product.

Such a database would be extremely helpful for licensees; some are concerned about consistency in approvals of similarly manufactured products. A database would also enhance consumer trust and help inform public health and medical professionals about legal cannabis products.

Future progress

We would like AMCO to utilize the wealth of knowledge available to them through collaborative relationships with licensees. Going forward, all regulations projects should develop with an eye toward core issues of public health and safety and business efficiency.

We would prefer to bring you these concerns with more time to work on them, and could do so if workgroups were organized and maintained. Regulations and NOVs are not the most effective tools when it comes to ensuring Alaskans have access to high-quality cannabis products.

Respectfully,

Lacy Wilcox, President
Trevor Haynes, Vice President
Kim Kole, Secretary
Ryan Tunseth, Treasurer
Carroll Carrigan, Executive Director

CC James Hoelscher, Enforcement Supervisor
Mark Springer, MCB Chair
Christopher Jaime, MCB Member
Loren Jones, MCB Member
Nick Miller, MCB Member
Bruce Schulte, MCB Member