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JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Hepatitis C Virus Infection in Adolescents and Adults
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Roger Chou, MD; Tracy Dana, MLS; Rongwei Fu, PhD; Bernadette Zakher, MBBS, MPH; Jesse Wagner, MA; Shaun Ramirez, MPH; Sara Grusing, BA; Janice H. Jou, MD, MHS

IMPORTANCE A 2013 review for the US Preventive Services Task Force (USPSTF) of hepatitis C virus (HCV) screening found interferon-based antiviral therapy associated with increased likelihood of sustained virologic response (SVR) and an association between achieving an SVR and improved clinical outcomes. New direct-acting antiviral (DAA) regimens are available.

OBJECTIVE To update the 2013 review on HCV screening to inform the USPSTF.

DATA SOURCES Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews through February 2019, with surveillance through September 2019.

STUDY SELECTION Randomized clinical trials (RCTs) and nonrandomized treatment studies of HCV screening and DAA therapy; cohort studies on screening, antiviral therapy, and the association between an SVR after antiviral therapy and clinical outcomes.

DATA EXTRACTION AND SYNTHESIS One investigator abstracted data; a second checked accuracy. Two investigators independently rated study quality.

MAIN OUTCOMES AND MEASURES Mortality, morbidity, quality of life, screening and treatment harms, and screening diagnostic yield.

RESULTS Eight RCTs of DAA therapy vs placebo or an outdated antiviral regimen, 48 other treatment studies, and 33 cohort studies, with a total of 179 230 participants, were included. No study evaluated effects of HCV screening vs no screening. One new study since the 2013 review (n = 5917) found similar diagnostic yield of risk-based screening (sensitivity, 82%; number needed to screen to identify 1 HCV case, 15) and birth cohort screening (sensitivity, 76%; number needed to screen, 29), assuming perfect implementation. Ten open-label studies (n = 3292) reported small improvements in some quality-of-life and functional outcomes (eg, less than 3 points on the 0 to 100 36-Item Short Form Health Survey physical and mental component summary scales) after DAA treatment compared with before treatment. Two cohort studies (n = 24 686) found inconsistent associations of antiviral therapy vs no therapy with risk of hepatocellular carcinoma. Forty-nine treatment studies (n = 10 181) found DAA regimens associated with pooled SVR rates greater than 95% across genotypes, and low short-term rates of serious adverse events (1.9%) and withdrawal due to adverse events (0.4%). An SVR after antiviral therapy was associated with decreased adjusted risk of all-cause mortality (13 studies, n = 36 986; pooled hazard ratio [HR], 0.40 [95% CI, 0.28-0.56) and hepatocellular carcinoma (20 studies, n = 84 491; pooled HR, 0.29 [95% CI, 0.23 to 0.38]) vs no SVR.

CONCLUSIONS AND RELEVANCE Direct evidence on the effects of HCV screening on clinical outcomes remains unavailable, but DAA regimens were associated with SVR rates greater than 95% and few short-term harms relative to older antiviral therapies. An SVR after antiviral therapy was associated with improved clinical outcomes compared with no SVR.

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It has been estimated that from 2013 to 2016 approximately 4.1 million people in the US were hepatitis C virus (HCV) antibody–positive, indicating past exposure, and that of these, approximately 2.4 million had active infection.[1] Persons born between 1945 and 1965 were estimated to account for approximately three-fourths of HCV infections. However, recent increases in acute HCV incidence have mostly affected young persons who inject drugs.[2,3]

In 2013, the US Preventive Services Task Force (USPSTF) recommended HCV screening for adults born between 1945 and 1965 ("birth cohort" screening) and those at high risk of infection (B recommendation).[4] The recommendation was based on the effectiveness of then-current antiviral therapies with interferon. HCV treatment has subsequently evolved to direct-acting antiviral (DAA) regimens without interferon.

This evidence report was conducted to update the 2013 USPSTF review on HCV screening in adults[5,6] and a comparative effectiveness review on antiviral treatments,[7,8] to inform the USPSTF for an updated recommendation statement. This report focused on currently recommended DAA regimens and was expanded to include adolescents.

Methods

Scope of the Review

Detailed methods and evidence tables with additional study details are available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/hepatitis-c-screening1. **Figure 1** shows the analytic framework and key questions (KQs) that guided the review. KQs on prenatal HCV screening (KQ 1b) and interventions to prevent vertical HCV transmission during labor and delivery (KQ5) are addressed in the full report.

Data Sources and Searches

Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were searched from 2013 through February 2019 (eMethods 1 in the Supplement). Searches were supplemented by reference list review of relevant systematic reviews; studies from the prior USPSTF review[6,9] meeting inclusion criteria were carried forward. Ongoing surveillance was conducted to identify major studies published since February 2019 that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on September 20, 2019, and identified no studies affecting review conclusions.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using predefined eligibility criteria. The population for screening was asymptomatic adults and adolescents without prior HCV infection. For treatment, to evaluate patients more likely to be asymptomatic and identified by screening, inclusion was restricted to studies in which 20% or less of patients had cirrhosis at baseline (≤30% for cohort studies that controlled for fibrosis stage). Randomized clinical trials (RCTs) of screening and currently recommended DAA regimens vs placebo or an outdated antiviral regimen[10] were included. Because of few randomized trials of DAA therapy vs placebo or an outdated antiviral regimen, nonrandomized clinical research treatment studies of DAA therapy (including those with a single group) and randomized trials that compared different DAA regimens were also included. The latter were classified as nonrandomized treatment studies rather than randomized trials in this review because data from relevant DAA regimens were analyzed separately (ie, the randomized comparison was not used). Cohort studies that controlled for potential confounders were included for screening; for associations of antiviral therapy (including older regimens) with mortality, hepatocellular carcinoma, and cirrhosis; and for the association between SVR after antiviral therapy and clinical outcomes. Outcomes were mortality, morbidity (eg, cirrhosis, hepatic decompensation, liver transplant, extrahepatic manifestations of HCV infection), quality of life, HCV transmission, sustained virologic response (SVR), harms, and screening yield (sensitivity and number of new diagnoses per test performed). Studies that focused on persons co-infected with HIV or hepatitis B virus, patients receiving transplants, and persons with advanced kidney disease were excluded.

Data Abstraction and Quality Rating

One investigator abstracted details about the study design, patient population, setting, interventions, analysis, follow-up, and results from each study. A second investigator reviewed abstracted data for accuracy. Two independent investigators assessed the quality of each study as good, fair, or poor using predefined criteria developed by the USPSTF (eMethods 2 in the Supplement).[7] Discrepancies were resolved through a consensus process. In accordance with the USPSTF Procedure Manual,[7] studies rated poor quality because of critical methodological limitations were excluded.

Data Synthesis

Random effects meta-analysis was performed to summarize the proportion of patients experiencing SVR and adverse events using a generalized linear mixed-effects model with a logit link. Analyses were stratified according to DAA regimen. For SVR, separate analyses were performed for each HCV genotype. A random-effects (linear mixed-effects) meta-analysis was also performed on adjusted hazard ratios (HRs) for SVR after antiviral therapy vs no SVR and for clinical outcomes (mortality, liver-related mortality, cirrhosis, and hepatocellular carcinoma). If necessary, the adjusted HR for SVR vs no SVR was calculated from the adjusted HRs for SVR and no SVR vs no treatment. Statistical heterogeneity was assessed using the I^2 statistic.[11]

Subgroup analyses were conducted on geographic setting (US or Europe; multinational; other), fibrosis stage (cirrhosis excluded or some patients [up to 20%] with cirrhosis), prior treatment status (naive or experienced to interferon-based therapies, boceprevir, or telaprevir), quality, and for cohort studies, full adjustment for key confounding variables (age, sex, fibrosis stage, and genotype). Stratified analyses were assessed for interactions using a test for heterogeneity across subgroups. For the association between DAA therapy and SVR rates, sensitivity analysis was performed by excluding studies in which ribavirin or dasabuvir

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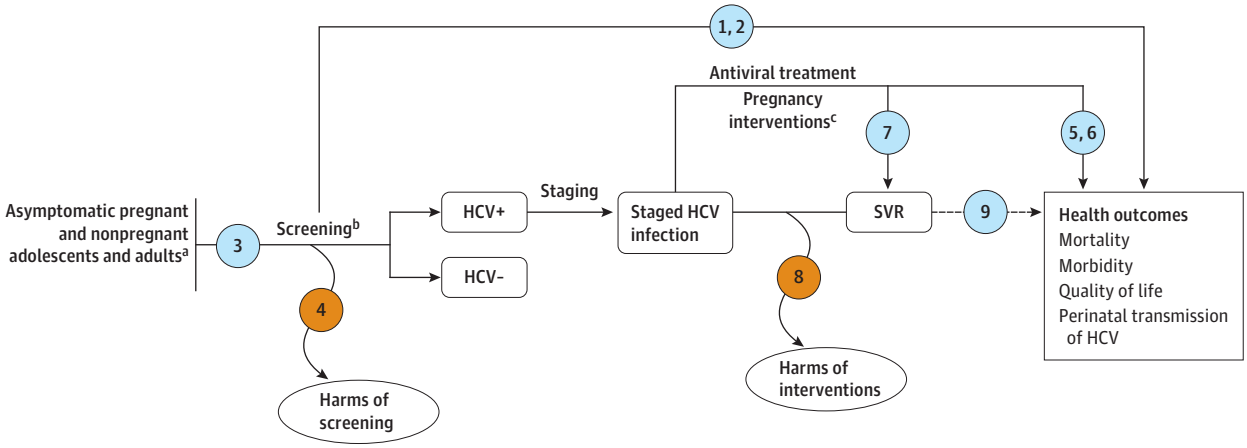
Figure 1. Analytic Framework: Screening for Hepatitis C Virus Infection in Adolescents and Adults



Key questions

1 a. 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?

b. Does prenatal screening for HCV infection reduce risk of vertical transmission of HCV infection?[d]

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 1-time vs 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 (eg, 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?[d]

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?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. A dashed line indicates a health outcome that immediately follows an intermediate outcome. See USPSTF Procedure Manual.[7] HCV indicates hepatitis C virus; SVR, sustained virologic response.

[a] Includes persons without abnormal laboratory values. Adolescents are defined as those aged 12 to 17 years. Excludes persons living with HIV, transplant recipients, and patients with renal failure.

[b] Defined as HCV antibody testing with confirmatory HCV RNA testing as indicated.

[c] Includes interventions that may affect vertical transmission of HCV, such as cesarean delivery, amniocentesis, fetal monitoring, management of ruptured membranes, breastfeeding, and antiviral treatment.

[d] Addressed in the full evidence report.

was not used as recommended. For the association between SVR vs no SVR after antiviral therapy and clinical outcomes, sensitivity analysis was performed by excluding cohort studies with potentially overlapping populations to ensure that results were not sensitive to double counting of patients. For analyses of harms, trials of ribavirin-containing regimens were excluded except for ombitasvir/paritaprevir/ritonavir/dasabuvir, which is recommended for genotype 1b infection.

Meta-analyses were conducted using SAS version 9.4 (SAS Institute Inc) and RevMan version 5.3.5 (Nordic Cochrane Centre), and

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forest plots were created using Stata/SE version 14.0 (StataCorp). All significance testing was 2-tailed; $P < .05$ was considered statistically significant.

Results

Across all KQs addressed in this article, 8 (n = 3397) RCTs (in 6 publications),[12-17] 48 (n = 7132) nonrandomized treatment studies (in 45 publications),[18-62] 33 (n = 168 701) cohort studies,[63-95] 2 additional pooled analyses,[96,97] and 1 retrospective study (n = 5917)[98] on the yield of alternative screening strategies in a cohort of patients in a national survey were included (**Figure 2**). Eighty-three studies[12-62,64,66-74,77,79,81-83,85-92,95-98] were new for this update, and 9[63,65,75,76,78,80,84,93,94] were carried forward from the previous USPSTF review.

Benefits of Screening

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?

No study met inclusion criteria for this KQ.

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

No study met inclusion criteria for this KQ.

Key Question 3. What is the yield (number of new diagnoses per tests performed) of 1-time vs repeat screening or alternative screening strategies for HCV infection, and how does the screening yield vary in different risk groups?

A retrospective study (n = 5917) compared the yield of risk-based HCV screening vs birth cohort screening in a cohort of patients sampled from the National Health and Nutrition Examination Survey.[98] It found that applying risk-based guidelines perfectly would screen 24.7% of the US general population and identify 82% of HCV cases, with a number needed to screen to identify 1 HCV case of 14.6. Applying the birth cohort strategy would screen 45% of the general population and identify 76% of cases, with a number needed to screen of 28.7. No study evaluated the yield of 1-time vs repeat screening, the yield of alternative screening strategies in different risk groups, or the yield of currently recommended screening vs expanded screening strategies.

Harms of Screening

Key Question 4. What are the harms of screening for HCV infection (eg, anxiety and labeling)?

No study compared harms of HCV screening vs no screening. Poor-quality evidence from the prior USPSTF review suggested potential negative psychological and social effects of screening but was uncontrolled and did not meet inclusion criteria for this update.

Benefits of Treatment

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

Adults

Quality of Life/Function | Ten open-label treatment studies (n = 2404) reported quality-of-life and functional outcomes before and after receipt of current DAA regimens (eTable 1 in the Supplement). Seven studies were included in 2 pooled analyses,[95,96] and there were 3 additional studies (reported in 2 publications).[12,99]

At 12 weeks after treatment, 2 pooled analyses found sofosbuvir/velpatasvir (4 trials) or sofosbuvir/ledispavir (3 trials) associated with improvements in some measures of quality of life or function compared with before treatment, though differences were small (eg, less than 3 points on the 36-Item Short Form Health Survey physical and mental component summary scales [range, 0-100 points] or 0.04 to 0.05 points on the 6-Dimensional Health State Form health utility scale), and not all differences were statistically significant.[95,96] Results were similar in 2 studies of ombitasvir/paritaprevir/ritonavir/dasabuvir[12] or elbasvir/grazoprevir.[99]

Mortality | Thirty-one treatment studies (in 28 publications; n = 3848) reported mortality at 12 to 36 weeks after completion of DAA therapy but were not designed to assess this outcome.[14-19,24,25,27,28,30-32,36,37,39,41-44,46,48,49,51-55] Twenty-one studies reported no deaths, and the remaining 10 studies reported 17 deaths (0.4% overall. Ten deaths occurred in 3 studies of persons reporting recent injection drug use or use of opioid substitution therapy.[31,32,55]

Other Clinical Outcomes | Three cohort studies (n = 58 892) evaluated other clinical outcomes (eTable 2 in the Supplement).[67,68,83] Follow-up ranged from 1.1 to 7.4 years. One study found DAA therapy, vs interferon-based therapy or antiviral therapy, was associated with decreased risk of cardiovascular events, including acute myocardial infarction, congestive heart failure, and stroke (incidence rate per 1000 person-years of follow-up, 16.3 [95% CI, 14.7 to 18.0] for DAA therapy; 23.5 [95% CI, 21.8 to 25.3] for interferon-based therapy; and 30.4 [95% CI, 29.2 to 31.7] for no therapy; $P < .001$ for antiviral therapy vs no therapy).[67] One study found DAA and interferon-based therapy associated with similar incidence of hepatocellular carcinoma that was lower than with no antiviral therapy (incidence rate per 1000 person-years, 7.5 [95% CI, 6.5 to 8.6] and 7.9 [95% CI, 6.0 to 10.4] for antiviral therapy and 10.9 [95% CI, 9.92 to 11.97] for no therapy; P value not reported).[83] The third study found no difference between DAA therapy vs no antiviral therapy in risk of hepatocellular carcinoma (adjusted HR, 1.02 [95% CI, 0.40 to 2.61]); point estimates for associations with all-cause mortality favored DAA therapy, but the difference was not statistically significant (adjusted HR, 0.74 [95% CI, 0.43 to 1.28]).[68]

Adolescents

Three treatment studies of adolescents (n = 200) reported changes of 2 to 13 points on Pediatric Quality of Life Inventory (scale, 0-100) scores after treatment with DAA therapy compared with baseline; effects were not always statistically significant (eTable 3 in the Supplement).[59,61,100] Treatment studies of DAA therapy in adolescents were not designed to evaluate mortality (no deaths in 3 studies)[57,61,62] or long-term clinical outcomes.

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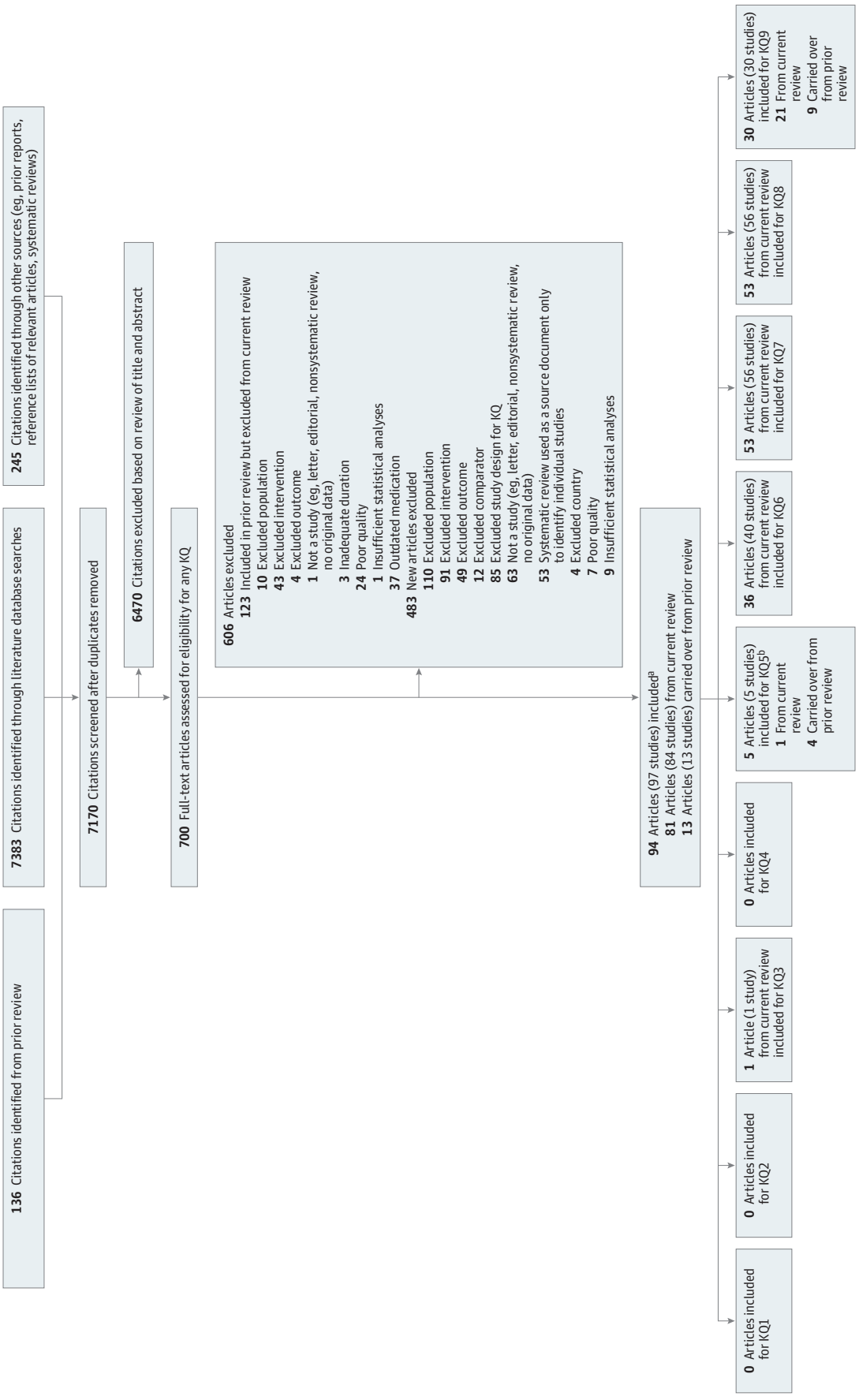
Figure 2. Literature Search Flow Diagram: Screening for Hepatitis C Virus Infection in Adolescents and Adults



[a] Some studies were included for multiple key questions (KQs).

[b] Addressed in the full evidence report.

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Key Question 7. What is the effectiveness of currently recommended antiviral treatments in achieving an SVR in patients with HCV infection?

Adults

Forty-nine studies (in 44 publications; n = 10 181) reported effects of current DAA treatment regimens on SVR in patients with HCV infection.[12-55] SVR was measured 12 weeks after the completion of therapy in all studies except for 1, which measured SVR at 14 weeks. Sample sizes ranged from 20 to 706, mean age ranged from 45 to 68 years, and the proportion of women ranged from 18% to 64%; the studies evaluated 7 different antiviral regimens (eTable 4 in the Supplement). One study was a randomized trial that compared a current DAA regimen vs placebo,[14] 2 randomized trials (reported in 1 publication) compared a current DAA regimen vs a regimen with telaprevir,[12] and 2 randomized trials (reported in 1 publication) compared a current vs older DAA regimen.[15] The other treatment studies did not compare a current DAA regimen vs placebo or an older regimen.

Thirteen studies were rated as good quality[12-14,17,19,28,29,33,35,36,46,51,54] and the remainder as fair quality (eTable 5 in the Supplement). Methodological limitations included unclear randomization or enrollment methods. Loss to follow-up was low (range, 0%-3%). All of the trials were industry-funded.

SVR Rates in Comparative Trials | Few studies compared DAA interventions with placebo or older interventions (eTable 5 in the Supplement). One randomized trial found sofosbuvir/velpatasvir associated with very high likelihood of SVR vs placebo in persons with mixed-genotype (1, 2, 4, 5, or 6) infection (99% vs 0%; relative risk [RR], 231.6 [95% CI, 14.6 to 3680]).[14] Two randomized trials found ombitasvir/paritaprevir/ritonavir/dasabuvir (with or without ribavirin) associated with increased likelihood of SVR vs telaprevir/pegylated interferon/ribavirin in treatment-naive persons with genotype 1 infection (98% vs 80%; RR, 1.22 [95% CI, 1.08 to 1.37]) or persons previously treated with interferon therapy (99% vs 66%; RR, 1.50 [95% CI, 1.22 to 1.85]).[12] Two randomized trials found sofosbuvir/velpatasvir for 12 weeks associated with increased likelihood of SVR vs sofosbuvir/ribavirin for 24 weeks for genotype 2 (99% vs 94%; RR, 1.06 [95% CI, 1.01 to 1.11]) and for genotype 3 infection (noncirrhosis subgroup, 97% vs 87%; RR, 1.11 [95% CI, 1.05 to 1.18]).[15]

Pooled SVR Rates | For genotype 1 HCV infection, the most common genotype in the US, DAA therapy was associated with a pooled SVR rate of 97.7% (95% CI, 96.6% to 98.4%; I^2 = 82%) based on 32 studies (n = 6055) (**Figure 3**). Evidence for genotypes 2 through 6 was more limited, ranging from 75 to 742 participants per genotype (eTable 7 in the Supplement). The pooled SVR rates ranged from 95.5% to 98.9%; for other common US genotypes, the pooled SVR was 98.9% (95% CI, 97.5% to 99.5%; I^2 = 4%) for genotype 2 (5 studies, n = 526) (eFigure 1 in the Supplement), 95.5% (95% CI, 91.6% to 97.7%; I^2 = 66%) for genotype 3 (6 studies, n = 742) (eFigure 2 in the Supplement), and 98.2% (95% CI, 94.7% to 99.4%; I^2 = 50%) for genotype 4 (10 studies, n = 485) (eFigure 3 in the Supplement). Across genotypes, SVR estimates were consistent when studies were stratified according to study quality, geographic setting, prior HCV treatment, inclusion of some patients with cirrhosis at baseline, and use of ribavirin as recommended (eTable 7 in the Supplement).

Adolescents

Seven studies (n = 348) evaluated the effects of DAA regimens on SVR in adolescents (eTable 8 in the Supplement).[56-62] Mean age ranged from 12 to 15 years, and the proportion of female participants ranged from 35% to 66%. Three of the 7 studies were conducted in Egypt and focused on genotype 4 infection, 1 study enrolled patients with genotype 1, and 3 studies enrolled mixed genotypes. Four studies evaluated DAA regimens approved by the US Food and Drug Administration (FDA) for use in adolescents,[57-59,61] and the others evaluated DAA regimens recommended for adults but not FDA-approved for adolescents.[56,60,62] Across all intervention studies of DAA in adolescents, the SVR rate ranged from 97% to 100%.

Harms of Treatment

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

Adults

Forty-nine treatment studies (in 44 publications; n = 10 181) of DAA regimens without interferon reported the proportion of patients who experienced adverse events at short-term follow-up (ie, while taking antiviral therapy through up to 12 weeks after completion of therapy).[12-55]

Adverse Events in Comparative Trials | Four randomized trials (total n = 2113) reported adverse events associated with current DAA regimens vs placebo (eTable 9 in the Supplement).[13,14,16,17] DAA regimens were associated with slightly increased risk of any adverse event (4 trials; RR, 1.12 [95% CI, 1.02 to 1.24]; I^2 = 46%; absolute risk difference [ARD], 8% [95% CI, 8% to 15%]) (eTable 9 in the Supplement). DAA therapy was also associated with increased risk of nausea (3 trials; RR, 1.42 [95% CI, 1.00 to 2.03]; I^2 = 10%; ARD, 4% [95% CI, −3% to 10%]); the association with increased risk of diarrhea was not statistically significant (2 trials; RR, 1.53 [95% CI, 0.88 to 2.68]; I^2 = 29%). There were no differences between DAA regimens vs placebo in risk of serious adverse events, withdrawal due to adverse events, headache, or fatigue.

Two randomized trials (reported in 1 publication; n = 457) compared a DAA regimen (ombitasvir/paritaprevir/ritonavir/dasabuvir with or without ribavirin) vs telaprevir/pegylated interferon/ribavirin for genotype 1 infection (eTable 10 in the Supplement).[12] DAA therapy was associated with decreased risk of serious adverse events (RR, 0.08 [95% CI, 0.02 to 0.34]; I^2 = 0%; ARD, −8% [95% CI, −15% to −1%]) and 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%]) vs the telaprevir regimen. DAA therapy was also associated with decreased risk of fatigue, headache, nausea, anemia, and rash (eTable 10 in the Supplement).

Pooled Adverse Event Rates for DAA Regimens | DAA therapy was frequently associated with experiencing any adverse event (44 trials, n = 8045; 73.3% [95% CI, 68.0% to 78.1%]; I^2 = 95%) (eFigure 4 in the Supplement), though serious adverse events (44 studies, n = 8070; 1.9% [95% CI, 1.5% to 2.4%]; I^2 = 33%) (eFigure 5 in the Supplement) and withdrawal due to adverse events (44 studies, n = 8060; 0.4% [95% CI, 0.3% to 0.6%]; I^2 = 0%) (eFigure 6 in the Supplement) were infrequent (eTable 11 in the Supplement). Pooled

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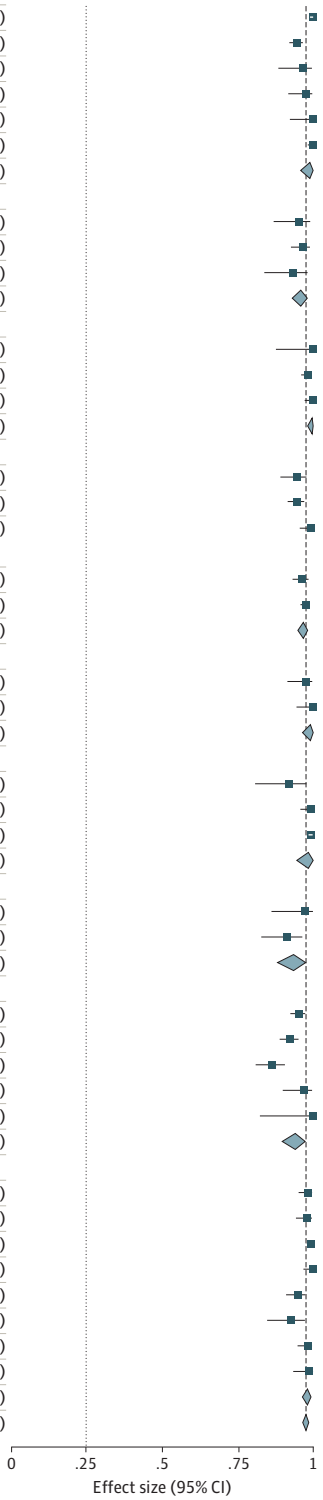
Figure 3. Direct-Acting Antiviral Regimens and Pooled Sustained Virologic Response Rates in People With Genotype 1 Hepatitis C Virus Infection

Source	Country	Age, y	Women, %	Fibrosis stage (% cirrhosis)	Treatment naive	Events/ total	Effect size (95% CI)
Ledipasvir/sofosbuvir							
Afdhal et al,[35] 2014	Multinational	52	41	0	Yes	357/357	1.000 (0.990-1.000)
Kowdley et al,[35] 2014	US	53	40	0	Yes	408/431	0.947 (0.921-0.966)
Lawitz et al,[40] 2014	US	48	38	0	Yes	58/60	0.967 (0.885-0.996)
Chuang et al,[27] 2016	Taiwan	55	58	≤20	Mixed	83/85	0.976 (0.918-0.997)
Lim et al,[42] 2016	Korea	54	61	≤20	Yes	46/46	1.000 (0.923-1.000)
Wei et al,[53] 2018	China	47	50	≤20	No	206/206	1.000 (0.982-1.000)
Subtotal: I^2 = 88.7%, P <.001							0.994 (0.952-0.999)
Simeprevir/sofosbuvir							
Lawitz et al,[39] 2014	US	56	29	0	Mixed	61/64	0.953 (0.869-0.990)
Kwo et al,[37] 2016	Canada and US	56	47	0	Mixed	150/155	0.968 (0.926-0.989)
Pott-Junior et al,[46] 2019	Brazil	53	48	0	Mixed	56/60	0.933 (0.838-0.982)
Subtotal: I^2 = 0.0%, P = .50							0.957 (0.926-0.975)
Sofosbuvir/velpatasvir							
Everson et al,[28] 2015	US	49	39	0	Yes	28/28	1.000 (0.877-1.000)
Feld et al,[14] 2015	Multinational	54	40	0	Mixed	251/255	0.984 (0.960-0.996)
Wei et al,[17] 2019	Multinational	45	47	≤20	No	129/129	1.000 (0.972-1.000)
Subtotal: I^2 = 26.6%, P = .26							0.990 (0.954-0.998)
Elbasvir/grazoprevir							
Sulkowski et al,[49] 2015	Multinational	51	51	0	Yes	122/129	0.946 (0.891-0.978)
Zeuzem et al,[54] 2015	Multinational	52	46	≤20	Yes	273/288	0.948 (0.916-0.971)
Sperl et al,[47] 2016	Multinational	48	57	≤20	Mixed	122/123	0.992 (0.956-1.000)
Ng et al,[99] 2018							
Kumada et al,[36] 2017	Japan	61	62	0	Mixed	219/227	0.965 (0.932-0.985)
Wei et al,[53] 2019	Multinational	48	56	≤20	Yes	422/432	0.977 (0.958-0.989)
Subtotal: I^2 = 54.6%, P = .07							0.967 (0.950-0.978)
Sofosbuvir/daclatasvir							
Sulkowski et al,[48] 2014	US	55	50	≤20	Yes	80/82	0.976 (0.915-0.997)
Pott-Junior et al,[46] 2019	Brazil	56	52	00	Mixed	65/65	1.000 (0.945-1.000)
Subtotal: I^2 = 45.3%, P = .18							0.986 (0.947-0.997)
Glecaprevir/pibrentasvir							
Poordad et al,[45] 2017	US	58	18	00	No	46/50	0.920 (0.808-0.978)
Chayama et al,[26] 2018	Japan	64	64	Unclear/NR	Mixed	128/129	0.992 (0.958-1.000)
Zeuzem et al,[55] 2018	Multinational	53	51	00	No	663/667	0.994 (0.985-0.998)
Subtotal: I^2 = 77.9%, P = .01							0.986 (0.941-0.997)
Ombitasvir/paritaprevir/ritonavir/dasabuvir							
Lalezari et al,[38] 2015	US	48	34	0	Mixed	37/38	0.974 (0.862-0.999)
Grebely et al,[32] 2018	Multinational	48	23	0	Yes	73/80	0.913 (0.828-0.964)
Subtotal: I^2 = 26.7%, P = .24							0.932 (0.870-0.966)
Ombitasvir/paritaprevir/ritonavir/dasabuvir (genotype 1a)							
Feld et al,[13] 2014	Multinational	49	43	Unclear/NR	Yes	307/322	0.953 (0.924-0.974)
Ferenci et al,[29] 2014	Multinational	51	35	0	Yes	282/305	0.925 (0.889-0.952)
Kowdley et al,[34] 2014	Multinational	50	42	0	Mixed	183/212	0.863 (0.809-0.906)
Dore et al,[12] 2016[a]	Multinational	46	39	0	Mixed	67/69	0.971 (0.899-0.996)
Dore et al,[12] 2016[b]	Multinational	47	46	0	Mixed	19/19	1.000 (0.824-1.000)
Subtotal: I^2 = 77.2%, P = .002							0.937 (0.890-0.965)
Ombitasvir/paritaprevir/ritonavir/dasabuvir (genotype 1b)							
Andreone et al,[22] 2014	Multinational	54	46	0	No	176/179	0.983 (0.952-0.997)
Feld et al,[13] 2014	Multinational	49	43	Unclear/NR	Yes	148/151	0.980 (0.943-0.996)
Ferenci et al,[29] 2014	Multinational	48	54	0	Yes	416/419	0.993 (0.979-0.999)
Kowdley et al,[34] 2014	Multinational	50	47	0	Mixed	113/113	1.000 (0.968-1.000)
Kumada et al,[16] 2015	Japan	61	63	0	Mixed	204/215	0.949 (0.910-0.974)
Lawitz et al,[41] 2015	Multinational	55	51	0	Mixed	76/82	0.927 (0.848-0.973)
Dore et al,[12] 2016[a]	Multinational	46	54	0	Mixed	164/167	0.982 (0.948-0.996)
Dore et al,[12] 2016[b]	Multinational	47	46	0	Mixed	81/82	0.988 (0.934-1.000)
Subtotal: I^2 = 68.5%, P = .002							0.982 (0.964-0.991)
Heterogeneity between groups: P = .005							0.977 (0.966-0.984)
Overall: I^2 = 81.6%, P <.001							



The area of each square represents each pooled estimate (subgroup or overall analysis), and the width of each diamond represents the confidence interval for the pooled estimate. The dashed line indicates the overall measure of effect. SVR indicates sustained virologic response.

[a] Treatment-naive.

[b] Treatment-experienced.

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rates for specific adverse events ranged from 2.4% (anemia) to 18.7% (headache) (eTables 12 and 13 in the Supplement). There was some variability by DAA regimen in estimates of adverse events; estimates were generally higher for ombitasvir/paritaprevir/ritonavir/dasabuvir with ribavirin than without ribavirin (eTables 11-13 in the Supplement). Adverse event estimates were generally similar when studies were stratified according to baseline cirrhosis status and prior antiviral therapy experience.

Adolescents

Seven treatment studies (n = 348) of DAA regimens in adolescents reported harms, but methods for reporting and assessing harms were generally not well described (eTable 14 in the Supplement).[56-62] Rates of any adverse event were 27% in 1 study[62] and ranged from 71% to 87% in 4 studies.[57,59-61] There were no withdrawals due to adverse events reported in 5 studies,[57,59-62] and 1 study[61] reported 1 serious adverse event (a grade 3 joint injury). Rates of other adverse events were highly variable. For example, 3% to 48% of study participants reported headache. Stratification according to DAA regimen did not explain the observed variability.

SVR and Health Outcomes

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

Thirty cohort studies reported associations between achieving SVR after antiviral treatment vs no SVR and clinical outcomes (eTable 15 in the Supplement).[63-66,68-82,84-94] Sample sizes ranged from 131 to 50 886 (total n = 116 659), mean age ranged from 42 to 69 years, and the proportion of women ranged from 1% to 56%. Seventeen studies were conducted in Japan (including some with overlapping populations),[63,64,71,73-75,78-81,84-86,89,90,92,93] 4 in other Asian countries,[82,88,91,94] 7 in the US (all except for 1[87] conducted in Veterans Affairs populations),[65,66,69,70,72,77,87] and 2 in Europe.[68,76] When genotype was reported, genotype 1 was generally the most common (36%-89%) and genotype 2 the second most common (6%-52%). Mean follow-up ranged from 1.5 to 10 years in all studies except for 1 study that described follow-up of at least 1 year.[88] Twenty-six studies evaluated interferon-based therapies. Three studies focused on DAAs,[66,68,77] 1 study evaluated interferon-based treatments and DAAs,[77] and 1 study did not report what type of treatment was administered (likely primarily interferon-based therapies).[72] All studies were rated fair quality (eTable 16 in the Supplement).

SVR was associated with significantly decreased risk of all-cause mortality (13 studies, n = 36 986; HR, 0.40 [95% CI, 0.28 to 0.56]; I^2 = 52%) (**Figure 4**).[63,65,66,68-70,75,76,80,84,87,93,94] Studies with longer duration of follow-up (>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 follow-up (pooled HR, 0.64 [95% CI, 0.56 to 0.74]) (P = .003 for interaction). SVR was also associated with decreased risk of hepatocellular carcinoma (20 studies, n = 84 491; pooled HR, 0.29 [95% CI, 0.23 to 0.38]; I^2 = 19%) (Figure 4),[63,64,68,70-74,77-79,81,82,84-86,89,90,92,94] liver-related mortality (4 studies, n = 5953; pooled HR, 0.11 [95% CI, 0.04 to 0.27]; I^2 = 0%) (eFigure 7 in the Supplement),[63,75,80,93] and cirrhosis (4 cohorts reported in 3 studies, n = 16 735; pooled HR, 0.36 [95% CI, 0.33 to 0.40]; I^2 = 0%) (eFigure 8 in the Supplement).[69,72,91] There were no statistically significant interactions when studies were stratified according to how well they adjusted for key confounders, duration of follow-up, country/setting, or the proportion of participants with cirrhosis at baseline (eTable 15 in the Supplement). Results were also similar when studies with potentially overlapping populations were excluded.

Discussion

The findings in this evidence report are summarized in the **Table**. Since the prior USPSTF recommendation, there has been a major shift in antiviral therapy to all-oral DAA regimens without interferon. New pooled evidence indicates that SVR rates with currently recommended all-oral DAA regimens are substantially higher (>95%) than with interferon-based therapies evaluated in the prior review (68%-78%).[9] Although statistical heterogeneity was present in pooled estimates of SVR rates, findings were robust when studies were stratified according to the DAA regimen evaluated, study quality, prior treatment status, and cirrhosis status. Few randomized trials directly compared a current DAA regimen vs placebo or an older antiviral regimen, but those available also found DAA therapy associated with greater effectiveness. DAA regimens were associated with fewer harms than older interferon-containing therapies. Evidence on DAA therapies in adolescents was limited, but consistently reported high (97%-100%) SVR rates.

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 hepatocellular carcinoma 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 nonstandard regimen.[101-108] Studies of DAA therapies were not designed to assess effects on mortality or other long-term clinical outcomes. There were few cohort studies of antiviral therapy vs no therapy, results were somewhat inconsistent, and findings were susceptible to residual confounding. Given the limited direct evidence on the effects of antiviral therapy on clinical outcomes, cohort studies of the association between SVR after antiviral therapy vs no SVR and clinical outcomes may help to understand potential clinical effects of DAA therapy. As in the prior USPSTF review, there was a consistent association between SVR after antiviral therapy and improved clinical outcomes, including mortality and hepatocellular carcinoma.[9]

The findings in this evidence report regarding the benefits and harms of current DAA regimens were consistent with a recent systematic review that also reported high (>95%) SVR rates in genotype 1 infection without cirrhosis, high SVR rates but more limited evidence for other HCV genotypes, low rates of serious adverse events and treatment discontinuation, and higher adverse event rates with ribavirin.[109] The 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[110]; unlike that review, this one also evaluated the indirect chain of evidence linking DAA therapy with SVR, and SVR with clinical outcomes. This review is consistent with prior reviews that found a consistent association between an SVR after antiviral therapy and reduced risk of mortality and hepatocellular carcinoma.[111-113]

Research is needed to better understand the association between use of current DAA therapy and clinical outcomes. Long-term

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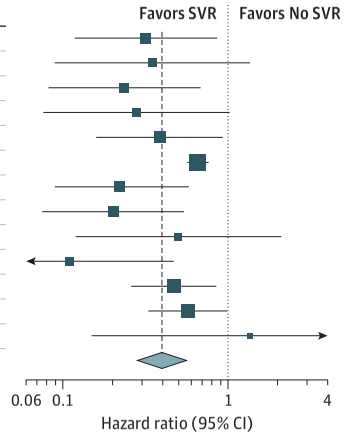
Figure 4. Association of Sustained Virologic Response With Clinical Outcomes

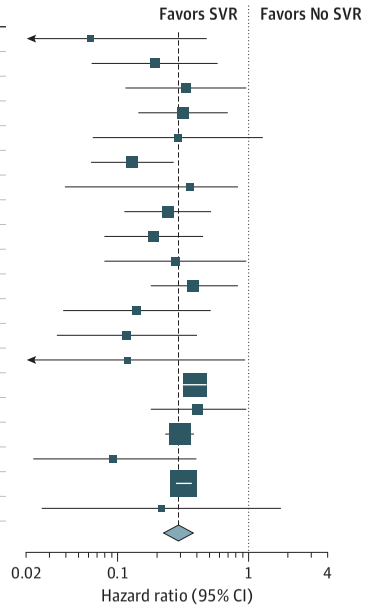
A SVR vs no SVR: all-cause mortality

Source	Duration, y	Country	Restricted to F0-F1	Cirrhosis, %	Treatment	Adjustment	% Genotype 1	SVR/no SVR	Hazard ratio (95% CI)
Yoshida et al,[93] 2002	5.4	Asia	No	0-10	Interferon	Partial	NR	817/1613	0.32 (0.12-0.86)
Imazeki et al,[75] 2003	8.2	Asia	No	>10	Interferon	Partial	74	116/239	0.35 (0.09-1.36)
Kasahara et al,[80] 2004	5.7	Asia	No	>10	Interferon	Partial	NR	738/1930	0.24 (0.08-0.68)
Yu et al,[94] 2006	5.2	Asia	No	>10	Interferon	Full	46	715/342	0.28 (0.08-1.02)
Arase et al,[63] 2007	7.4	Asia	No	>10	Interferon	Full	60	140/360	0.39 (0.16-0.93)
Backus et al,[65] 2011	3.8	US	No	>10	Interferon	Full	72	7434/9430	0.66 (0.57-0.76)
Innes et al,[76] 2011	5.3	Europe	No	>10	Interferon	Full	36	560/655	0.22 (0.09-0.58)
Maruoka et al,[84] 2012	9.9	Asia	No	0-10	Interferon	Full	73	221/356	0.20 (0.08-0.54)
Cozen et al,[69] 2013	10.0	US	No	0-10	Interferon	Full	61	69/71	0.50 (0.12-2.10)
Singal et al,[87] 2013	5.0	US	No	>10	Interferon	Full	68	83/159	0.11 (0.03-0.47)
Dieperink et al,[70] 2014	7.5	US	No	>10	Interferon	Full	70	222/314	0.47 (0.26-0.85)
Butt et al,[66] 2017	1.5	US	Yes	>10	DAA	Full	85	6371/599	0.57 (0.33-0.99)
Carrat et al,[68] 2019	2.8	Europe	No	0-10	DAA	Full	67	3286/146	1.36 (0.15-12.35)
Overall: I^2 = 52.1%, P = .02									0.40 (0.28-0.56)



B SVR vs no SVR: hepatocellular carcinoma

Source	Duration, y	Country	Restricted to F0-F1	Cirrhosis, %	Treatment	Adjustment	% Genotype 1	SVR/no SVR	Hazard ratio (95% CI)
Imai et al,[74] 1999	4.0	Asia	No	0-10	Interferon	Partial	NR	151/268	0.06 (0.01-0.48)
Kasahara et al,[79] 1998	3.1	Asia	No	0-10	Interferon	Full	58	313/405	0.19 (0.06-0.58)
Ikeda et al,[73] 1999	5.4	Asia	No	>10	Interferon	Full	67	606/585	0.33 (0.12-0.96)
Yoshida et al,[92] 1999	4.3	Asia	No	0-10	Interferon	Partial	70	789/1568	0.32 (0.14-0.70)
Tanaka et al,[89] 2000	4.8	Asia	No	0-10	Interferon	Full	75	175/419	0.29 (0.07-1.28)
Okanoue et al,[85] 2002	5.6	Asia	No	0-10	Interferon	Partial	NR	426/358	0.13 (0.06-0.27)
Izumi et al,[78] 2005		Asia	No	0-10	Interferon	Unclear	50	155/340	0.36 (0.04-0.83)
Yu et al,[94] 2006	5.2	Asia	No	>10	Interferon	Full	46	715/342	0.24 (0.11-0.52)
Arase et al,[63] 2007	7.4	Asia	No	>10	Interferon	Full	60	140/360	0.19 (0.08-0.45)
Kurokawa et al,[81] 2009	3.0	Asia	No	0-10	Interferon	Partial	73	139/264	0.28 (0.08-0.96)
Asahina et al,[64] 2010	7.5	Asia	No	0-10	Interferon	Full	70	686/1356	0.38 (0.18-0.83)
Tateyama et al,[90] 2011	8.2	Asia	No	>10	Interferon	Full	72	139/234	0.14 (0.04-0.52)
Maruoka et al,[84] 2012	9.9	Asia	No	0-10	Interferon	Full	73	221/356	0.12 (0.03-0.41)
Osaki et al,[86] 2012	4.1	Asia	No	0-10	Interferon	Partial	60	185/197	0.12 (0.01-0.94)
Dohmen et al,[71] 2013	4.8	Asia	No	NR/unclear	Interferon	Partial	67	285/189	0.39 (0.32-0.48)
Dieperink et al,[70] 2014	7.5	US	No	>10	Interferon	Full	70	222/314	0.41 (0.18-0.96)
El-Serag et al,[72] 2014	5.2	US	NR/unclear	NR/unclear	NR	Full	55	7577/8767	0.30 (0.23-0.38)
Lee et al,[82] 2017	2.6	Asia	No	>10	Interferon	Full	51	306/183	0.09 (0.02-0.40)
Ioannou et al,[77] 2018	6.1	US	No	>10	Mixed	Full	77	28655/23231	0.32 (0.28-0.37)
Carrat et al,[68] 2019	2.8	Europe	No	0-10	DAA	Full	67	3286/146	0.22 (0.03-1.76)
Overall: I^2 = 18.7%, P = .22									0.29 (0.23-0.38)



The area of each square represents each pooled estimate (subgroup or overall analysis), and the width of each diamond represents the confidence interval for the pooled estimate. Dashed lines indicate the overall measures of effect; overall estimates were from mixed-effects models. DAA indicates direct-acting antiviral; IFN, interferon; NR, not reported; SVR, sustained virologic response.

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Table. Summary of Evidence

Study design	Summary of findings	Consistency and precision	Overall quality	Body of evidence limitations	EPC assessment of strength of evidence for KQ	Applicability
KQ1: Benefits of screening						
No studies	NA	NA	NA	NA	NA	NA
KQ2: Screening strategies						
No studies	NA	NA	NA	NA	NA	NA
KQ3: Screening strategies and yield						
Prior review: 5 studies (4 cross-sectional studies [n = 7615] and 1 case-control study [n = 429]) New evidence: 1 retrospective study evaluating screening yield (n = 5917)	The prior review included 5 studies that found risk-based screening associated with sensitivities of >90% and NNSs <20 to identify 1 case of HCV infection One new study found that perfect application of risk-based guidelines would identify 82% of HCV cases with an NNS of 14.6 to identify 1 case of HCV infection, while applying a birth cohort strategy would result in 76% of cases identified with an NNS of 28.7	Reasonably consistent and precise	Fair	Studies were retrospective, and in some studies significant proportions of patients were not tested No studies of the yield of 1-time vs repeat screening, alternative screening strategies in different risk groups, or the yield of currently recommended screening vs 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
KQ4: Harms of screening						
Prior review: 5 studies (1 cross-sectional study [n = 34], 3 intervention series studies [n = 220], 1 controlled trial [n = 34]) New evidence: no new studies	Poor-quality evidence from the prior review suggested potential negative psychological and social effects of screening; these studies did not meet inclusion criteria for this update No new studies on harms of screening meeting inclusion criteria 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
KQ6: Effect of treatment on health outcomes—adults						
Prior review: NA (outdated regimens) New evidence: 37 studies (34 treatment studies [n = 4434], 2 pooled analyses [n = 2706], 3 observational studies [n = 58 892])	Two pooled analyses of 3 and 4 studies each and data from 3 other studies not included in pooled analyses found small, short-term improvements in quality of life scale scores after DAA therapy compared with before In 31 DAA therapy studies reporting short-term (<1 y) mortality, there were no deaths in 21 studies; mortality was low in the remaining 10 studies (0.4% [17/3848] overall) Two large observational studies found use of both DAA regimens 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 follow-up	Consistent; imprecise	Fair	Studies reporting quality of life and function were not randomized, used an open-label design, and did not have a non-DAA comparison group Studies provided short-term follow-up 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	Studies 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 individuals (3%-4%)
KQ6: Effect of treatment on health outcomes—adolescents						
3 Treatment studies in 5 publications (n = 230)	There were no deaths in 3 studies 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 with baseline	Could not be determined (for quality of life); imprecise	Fair	Studies 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 study data	Low	One study evaluated a DAA regimen not FDA-approved for use in adolescents

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Table. Summary of Evidence (continued)

Study design	Summary of findings	Consistency and precision	Overall quality	Body of evidence limitations	EPC assessment of strength of evidence for KQ	Applicability
KQ7: Effect of treatment on SVR—adults						
Prior review: NA (outdated regimens) New evidence: 49 studies (8 RCTs and 41 nonrandomized treatment studies; n = 10 181)	DAA vs placebo (1 RCT): SVR, 99% vs 0%; RR, 231.6 (95% CI, 14.6-3680) DAA vs telaprevir (2 RCTs): SVR, 98% vs 80%; RR, 1.22 (95% CI, 1.09-1.37) and 99% vs 66%; RR, 1.50 (95% CI, 1.22-1.85) In 49 treatment studies, 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 studies 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 studies enrolled predominantly white participants Persons with current or recent drug use excluded from most trials Most trials were conducted in the US or Europe or were multinational
KQ7: Effect of treatment on SVR—adolescents						
Prior review: NA New evidence: 7 nonrandomized treatment studies (n = 348)	In 7 treatment studies, 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 studies were industry-funded	Fair	Three studies evaluated DAA regimens not FDA-approved for use in adolescents Four studies were multinational (primarily US and Europe) and 3 were conducted in Egypt
KQ8: Harms of treatment—adults: DAA vs placebo						
4 Randomized trials (n = 2113)	Pooled adverse event rates, DAA vs placebo: Any adverse event (4 trials): RR, 1.12 (95% CI, 1.02-1.24); I^2 = 46% Serious adverse events (4 trials): RR, 1.90 (95% CI, 0.73-4.95), I^2 = 0% Withdrawal due to adverse events (4 trials): RR, 0.47 (95% CI, 0.14-1.58); I^2 = 14% Headache (4 trials): RR, 1.12 (95% CI, 0.91-1.37); I^2 = 0% Nausea (3 trials): RR, 1.42 (95% CI, 1.00-2.03); I^2 = 10% Diarrhea (2 trials): RR, 1.53 (95% CI, 0.88-2.68); I^2 = 29% Fatigue (3 trials): RR, 1.05 (95% CI, 0.78-1.40); I^2 = 32% Anemia (1 trial): RR, 2.21 (95% CI, 0.11-46)	Consistent; precise	Fair	Few trials compared a DAA regimen with placebo Reporting of methods used to assess and define was suboptimal Trials did not report long-term follow-up	Moderate	See KQ7
KQ8: Harms of treatment—adults: DAA vs other antiviral treatment						
2 RCTs (n = 459)	Pooled adverse event rates, DAA vs other antiviral treatment: Any adverse event (2 trials): RR, 0.65 (95% CI, 0.50-0.84); I^2 = 87% Serious adverse events (2 trials): RR, 0.08 (95% CI, 0.02-0.34); I^2 = 0% Headache (2 trials): RR, 0.78 (95% CI, 0.58-1.04); I^2 = 0% Withdrawal due to adverse events (2 trials): RR, 0.06 (95% CI, 0.01-0.29); I^2 = 0% Fatigue (2 trials): RR, 0.37 (95% CI, 0.21-0.63); I^2 = 32% Headache (2 trials): RR, 0.70 (95% CI, 0.52-0.95); I^2 = 0% Nausea (2 trials): RR, 0.31 (95% CI, 0.16-0.59); I^2 = 65% Anemia (2 trials): RR, 0.09 (95% CI, 0.04-0.23); I^2 = 41% Rash (2 trials): RR, 0.19 (95% CI, 0.06-0.58); I^2 = 48%	Consistent; precise	Fair	Few trials compared a DAA regimen with an older antiviral regimen Reporting of methods used to assess and define was suboptimal Trials did not report long-term follow-up	Moderate	See KQ7

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Table. Summary of Evidence (continued)

Study design	Summary of findings	Consistency and precision	Overall quality	Body of evidence limitations	EPC assessment of strength of evidence for KQ	Applicability
KQ8: Harms of treatment—adults: overall						
Prior review: NA (outdated regimens) New evidence: 49 treatment studies (n = 10 181)	Pooled adverse events rates for currently recommended DAA regimens: Any adverse event (44 studies): 73.3% (95% CI, 68.0%-78.1%); I^2 = 95% Serious adverse events (44 studies): 1.9% (95% CI, 1.5%-2.4%); I^2 = 33% Withdrawal due to adverse events (44 studies): 0.4% (95% CI, 0.3%-0.6%); I^2 = 0% Anemia (13 studies): 2.4% (95% CI, 0.9%-6.3%); I^2 = 85% Fatigue (37 studies): 18.4% (95% CI, 15.6%-21.7%); I^2 = 90% Headache (42 studies): 18.7% (95% CI, 15.6%-22.2%); I^2 = 90% Insomnia (18 studies): 8.1% (95% CI, 6.7%-9.9%); I^2 = 58% Nausea (36 studies): 11.1% (95% CI, 9.1%-13.5%); I^2 = 82% Diarrhea (19 studies): 8.7% (95% CI, 7.0%-10.8%); I^2 = 69% Vomiting (6 studies): 5.8% (95% CI, 3.4%-9.7%); I^2 = 43% Rash (17 studies): 5.4% (95% CI, 4.1% to 7.1%); I^2 = 70%	Consistent; precise	Fair	Estimates were without a non-DAA comparison group Reporting of methods used to assess and define was suboptimal Studies did not report long-term follow-up	Moderate	See KQ7
KQ8: Harms of treatment—adolescents						
Prior review: NA New evidence: 7 treatment studies (n = 348)	Five studies reported no withdrawals due to adverse events There was 1 serious adverse event (grade 3 joint injury) in 1 study The rate of any adverse event was 27% in 1 study and 71%-87% in 4 studies Specific adverse event rates: Headache (7 studies): 3%-48% Fatigue (7 studies): 5%-53% Gastrointestinal adverse events (5 studies): 3%-28% Insomnia (1 study): 23%	Inconsistent; imprecise	Fair	Studies 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 follow-up (>48 wk) was not reported	Fair	See KQ6—adolescents
KQ9: Association between SVR and health outcomes						
Prior review: 19 cohort studies (n = 30 692) New evidence: 30 studies (n = 116 659 [n = 26 191 from cohort studies included in the prior report + n = 90 468 from new studies])	Pooled estimates for health outcomes for SVR vs 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, 0.28-0.56); I^2 = 52% Liver mortality (4 studies, 0 new): HR, 0.11 (95% CI, 0.04-0.27); I^2 = 0% Cirrhosis (4 cohorts reported in 3 studies, all new): HR, 0.36 (95% CI, 0.33-0.40); I^2 = 0% Hepatocellular carcinoma (20 studies, 16 new): HR, 0.29 (95% CI, 0.23-0.38); 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 (13) of the studies did not address 4 prespecified 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 2 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 7 US studies conducted in VA populations More than one-half of studies conducted in Asia, but results similar in US/Europe studies

Abbreviations: 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; NNS, number needed to screen; RCT, randomized clinical trial; RR, relative risk; SVR, sustained virologic response; VA, Veterans Affairs.

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randomized trials of treatment vs no treatment would be ethically challenging and difficult to carry out. Alternatively, large cohort studies that measure important confounders could be highly informative. Trials and cohort studies that measure effects on quality of life, function, and extrahepatic effects of HCV infection would also be helpful for understanding effects of DAA regimens on these 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 DAA therapies. Additional studies would be helpful for confirming the effectiveness of DAA regimens in adolescents, including long-term outcomes.[114] Well-designed prospective studies are needed to understand the effects of different HCV screening strategies, including repeat screening, on diagnostic yield.

Limitations

This review has several limitations. First, because there were few randomized trials of current DAA regimens, nonrandomized treatment studies were included, among which were studies without a non-DAA therapy comparison group. Causality cannot be concluded from such studies. Nonetheless, such studies were considered highly informative for SVR, an objective measure with rates without treatment 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. Second, no study of DAA therapy was conducted in screen-detected patients, and few studies reported presence or severity of baseline symptoms. Therefore, to evaluate effectiveness of DAA therapies in populations likely to be identified by screening, this report selected studies based on proxy factors, specifically a low prevalence of cirrhosis and prior DAA experience. Research studies of DAA therapy could overestimate SVR rates compared with typical clinical practice. However, observational studies reported SVR rates of 90%, only modestly lower than observed in the trials.[115,116]

Third, some studies of DAA therapy in adolescents evaluated regimens approved for adults but not children. Fourth, evidence on potential long-term harms of DAA therapy exposure was limited. However, limited evidence indicates no increased risk of hepatocellular carcinoma with DAA therapy compared with interferon-based therapy through around 3 years of follow-up.[68]

Fifth, non–English-language articles were excluded. Sixth, formal assessment for small sample effects (a potential marker of publication bias) using graphical or statistical methods was not performed because of the small number of randomized trials.

Conclusions

Direct evidence on the effects of HCV screening on clinical outcomes remains unavailable, but all-oral DAA regimens were associated with SVR rates greater than 95% and few short-term harms relative to older antiviral therapies. An SVR after antiviral therapy was associated with improved clinical outcomes compared with no SVR.

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Concept and design: Chou, Wagner, Jou.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Chou, Dana, Fu, Wagner, Ramirez, Grusing.
Critical revision of the manuscript for important intellectual content: Chou, Zakher, Jou.
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