

The Changing Burden of Hepatitis C Virus Infection in the United States: Model-Based Predictions

Mina Kabiri, MS; Alison B. Jazwinski, MD; Mark S. Roberts, MD; Andrew J. Schaefer, PhD; and Jagpreet Chhatwal, PhD

Background: Chronic hepatitis C virus (HCV) infection causes a substantial health and economic burden in the United States. With the availability of direct-acting antiviral agents, recently approved therapies and those under development, and 1-time birth-cohort screening, the burden of this disease is expected to decrease.

Objective: To predict the effect of new therapies and screening on chronic HCV infection and associated disease outcomes.

Design: Individual-level state-transition model.

Setting: Existing and anticipated therapies and screening for HCV infection in the United States.

Patients: Total HCV-infected population in the United States.

Measurements: The number of cases of chronic HCV infection and outcomes of advanced-stage HCV infection.

Results: The number of cases of chronic HCV infection decreased from 3.2 million in 2001 to 2.3 million in 2013. One-time birth-cohort screening beginning in 2013 is expected to identify 487 000 cases of HCV infection in the next 10 years. In contrast, 1-time universal screening could identify 933 700 cases. With the availabil-

ity of highly effective therapies, HCV infection could become a rare disease in the next 22 years. Recently approved therapies for HCV infection and 1-time birth-cohort screening could prevent approximately 124 200 cases of decompensated cirrhosis, 78 800 cases of hepatocellular carcinoma, 126 500 liver-related deaths, and 9900 liver transplantations by 2050. Increasing the treatment capacity would further reduce the burden of HCV disease.

Limitation: Institutionalized patients with HCV infection were excluded, and empirical data on the effectiveness of future therapies and on the future annual incidence and treatment capacity of HCV infection are lacking.

Conclusion: New therapies for HCV infection and widespread implementation of screening and treatment will play an important role in reducing the burden of HCV disease. More aggressive screening recommendations are needed to identify a large pool of infected patients.

Primary Funding Source: National Institutes of Health.

Ann Intern Med. 2014;161:170-180. doi:10.7326/M14-0095
For author affiliations, see end of text.

www.annals.org

Chronic hepatitis C virus (HCV) infection is a major health problem in the United States, affecting 3.2 million persons (1). This condition is the leading cause of chronic liver disease and hepatocellular carcinoma (HCC) and the leading indication for liver transplantation in the United States (2). The number of deaths from HCV infection in the United States surpassed that from HIV infection in 2007 (3). In 2011, the estimated economic burden associated with chronic HCV infection in the United States was \$6.5 billion (4).

Treatment of HCV infection has rapidly evolved over the past 2 decades. The launch of direct-acting antivirals (DAAs) in 2011 and recent availability of the first all-oral regimens for HCV infection represent an important shift in the treatment paradigm for this condition (5). The sustained virologic response (SVR) rates for certain patients increased to 97% (6). New treatments under investigation have shown potential to further increase response rates, decrease treatment duration, and improve adverse effect profiles. These therapies are being studied as combinations of DAAs, with and without ribavirin and interferon (7, 8).

In addition to advances in treatment, key changes in screening recommendations for HCV infection have taken place. The Centers for Disease Control and Prevention and the U.S. Preventive Services Task Force expanded their screening recommendations for HCV infection to include 1-time screening for anyone born between 1945 and 1965 (9, 10). Modeling studies have shown that this strategy can be cost-effective and can reduce the burden of HCV disease (11–13). Finally, the Patient Protection and Affordable Care Act might facilitate the implementation of recommended screening strategies for HCV infection and linkage to care and treatment (14).

The launch of DAA therapies and the new screening recommendations are collectively expected to substantially reduce the burden of HCV infection in the United States; however, the effect of these changes has not yet been quantified. Previous studies did not project the burden of infection under these changing dynamics but instead limited the analyses to the old standard of care—peginterferon and ribavirin (PEG-RBV) without screening for HCV infection (4, 15)—or evaluated only the cost-effectiveness of screening without projecting the changing burden of infection (11, 16, 17). The effect of limited treatment capacity on the burden of infection also has not been studied. Our objective was to project the burden of HCV disease in the United States by considering recent therapeutic advances, treatment capacity, and the implementation of 1-time birth-cohort or universal screening.

See also:

**Web-Only
Supplement**

METHODS

Characterization of the HCV-Infected Population

We developed an individual-level state-transition model (18) that simulated the HCV-infected population of the United States from 2001 to 2050. We used a nationally representative distribution of patient age, sex, awareness of HCV infection status, HCV genotype, disease stage, and treatment history using data from NHANES (National Health and Nutrition Examination Survey) 1999–2002 and published clinical studies (Table 1 of the Supplement, available at www.annals.org) (11, 15, 19–22). We added new HCV infections to the model on the basis of the annual number of new HCV infections reported by the Centers for Disease Control and Prevention (Table 2 of the Supplement) (23). Each newly infected patient was added as an acute case that could progress to the chronic phase (19).

Patients could become aware of their HCV infection status in the course of disease progression (Table 3 of the Supplement). At any given time, patients occupied one of the health states (Figure 1) and could transition to another state with a predefined probability depending on their current state (Table 4 of the Supplement).

Natural History of HCV Infection

The chronic phase of the infection was defined using the Meta-analysis of Histologic Data in Viral Hepatitis (METAVIR) scoring system: F0 indicates no fibrosis of the liver, F1 indicates portal fibrosis without septa, F2 indicates portal fibrosis with few septa, F3 indicates many septa without cirrhosis, and F4 indicates cirrhosis. Patients could progress to decompensated cirrhosis (DC) or HCC, receive a liver transplant, or die of liver-related complications (Figure 1). The model assumed an age limit on liver transplantation of 75 years (24). Table 1 of the Supplement shows all probabilities of disease progression. Patients who achieved SVR in F0 to F3 states were assumed to be cured of HCV infection; however, those who achieved SVR in an F4 state could progress to DC, HCC, or both but at a slower rate than HCV-infected patients.

Simulation Scenario: Current Clinical Practice

We simulated the current clinical practice as our base case, that is, 1-time birth-cohort screening for HCV infection starting in 2013 and treatment with PEG-RBV or protease inhibitor (PI)-based triple therapy before 2014, sofosbuvir- and simeprevir-based therapies starting in 2014, and future drugs as they become available. We implemented 1-time birth-cohort screening for HCV infection in persons born between 1945 and 1965 that detected prevalent cases unaware of their infection status. We also included risk-based screening in this scenario.

We assumed that 91% of these patients would accept screening and 90% of those who tested positive would receive their results (11). We assigned the uptake of screening such that most of these patients would gradually receive screening during 5 years beginning in 2013. We es-

Context

Strategies for screening and treating hepatitis C virus (HCV) infection are rapidly evolving.

Contribution

A model was developed that shows dramatic declines in the prevalence of HCV infection and the incidence of advanced-stage outcomes, such as cirrhosis, hepatocellular carcinoma, liver transplantations, and liver-related deaths, with the implementation of current screening policies and use of newly developed antiviral therapies. Adoption of 1-time universal screening and improved treatment capacity would add to declines in these outcomes.

Caution

Estimates about the long-term efficacy and toxicity of recently identified antiviral drugs for HCV infection used in the model are uncertain.

Implication

Hepatitis C virus infection could become a rare disease in the United States by 2036.

—The Editors

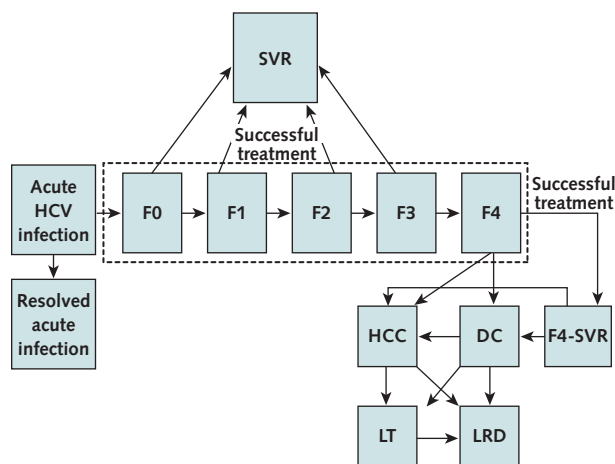
timated that 80% of the patients aware of their HCV infection status would initiate treatment (11, 25, 26). We assigned treatment regimens on the basis of patients' treatment history, HCV genotype, and contraindication to interferon and the standard of care at the time of treatment.

For patients with genotype 1 HCV, we assigned PEG-RBV during 2001 to 2011, followed by a combination of a first-generation PI (boceprevir or telaprevir) and PEG-RBV in 2012 to 2013. For patients with non-genotype 1 HCV, we assigned PEG-RBV during the entire period of 2001 to 2013. We assumed that patients in whom PEG-RBV treatment failed could be re-treated once more at the most with PEG-RBV or PI-based therapy. We also assumed that patients in whom PI-based therapy failed were not eligible for re-treatment with a drug from the same class.

Based on recently published evidence, higher treatment response rates would be expected in all patients after 2013 because of the availability of new therapies, albeit at different intervals (27–40). Therefore, we assumed that these therapies could be divided into 2 major waves on the basis of therapy availability, cure rates, and target populations (Table 1). We also assumed that during 2012 to 2013, 75% of the eligible patients with mild fibrosis (F0 to F2) and 25% of the eligible patients with bridging fibrosis (F3) waited for newer therapies (41).

We assumed that wave 1 of new treatments would start in 2014 and that, with wave 1, the SVR rates would increase to 90% in the groups of patients with genotypes 1 to 6 HCV without cirrhosis (Table 1). Although the reported SVR rates were as high as 97% in some patients, we

Figure 1. State-transition diagram showing the states of the simulation model.



At any given time, a patient is represented by one of the health states, which are shown by squares. Arrows between states represent possible transitions based on annual probabilities (Table 1 of the **Supplement**, available at www.annals.org). Patients whose disease is successfully treated transition to the SVR state. Patients who achieve SVR from F0 to F3 states are assumed to be cured; however, patients in an F4 state who are successfully treated transition to an F4-SVR state and may develop further complications. Patients in HCC, DC, and LT states have a higher mortality rate than the general population and therefore may transition to an LRD state. All other patients have the same risk for death as the general population. The probability of death from other causes exists in every state, but deaths from other causes are not shown. According to the Meta-analysis of Histologic Data in Viral Hepatitis (METAVIR) scoring system, F0 indicates no fibrosis of the liver, F1 indicates portal fibrosis without septa, F2 indicates portal fibrosis with few septa, F3 indicates many septa without cirrhosis, and F4 indicates cirrhosis. DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; LRD = liver-related death; LT = liver transplantation; SVR = sustained virologic response.

used a conservative estimate of 90% in certain patients to account for lower SVR rates in real life (42). The first wave also included therapies for patients with genotypes 1 to 6 HCV who had cirrhosis, but we assumed that the response rates among these patients would remain suboptimal (Figure 1 of the **Supplement**) (43).

We assumed that the second wave of treatment would begin in 2017 and increase the response rates to 90% in all patients. We included re-treatment with wave 1 or 2 therapies of patients in whom PEG-RBV or PI-based therapy failed before 2014. Table 1 and the **Supplement** show the SVR rates by treatment history, genotype, fibrosis stage, and interferon contraindication. Figure 1 of the **Supplement** shows the treatment used for each category of patients at different intervals.

Because treating all HCV-infected patients within a year is impracticable, we introduced an annual constraint on the number of persons who could access treatment. Our rationale was to model the effect of limited treatment uptake and limited resources (for example, budget and number of physicians) available to treat all eligible patients. For

our base case, we used historical data to determine the national treatment uptake (44) and did sensitivity analyses.

Simulation Scenario: Ideal Case

We simulated the effect of a hypothetically ideal scenario that represented an upper limit of the benefits that ongoing advancements in therapies and policy-level changes could achieve. We simulated the best possible combination of 1-time universal screening in all adults, adoption of new drugs as they become available, and unlimited treatment capacity. We distributed the uptake of screening proportionally over a 5-year period beginning in 2013.

Simulation Scenario: Pre-DAAs and Natural History

For the purpose of estimating the incremental benefits of therapeutic advancements and policy-level changes, we simulated 2 comparator scenarios: a pre-DAA scenario and a natural-history scenario. The pre-DAA scenario represented screening and treatment practice until the launch of DAAs. It simulated treatment of HCV infection with PEG-RBV only, from 2001 onward, solely with risk-based screening. The natural-history scenario simulated the burden of HCV infection with no screening and no treatment. Table 2 summarizes the 4 clinical scenarios that were simulated.

Data Synthesis and Analysis

Model Outcomes

We projected the prevalence of HCV infection from 2001 to 2050. We also projected the prevalence and incidence of early stages of HCV infection (fibrosis states F0 to F4), advanced stages of disease, DC and HCC, and the number of liver transplantations and liver-related deaths.

Model Validation

Using the model outcomes from 2001 to 2013, we validated our model with several published studies. First, we compared the predicted prevalence of HCV infection with that from a recently published NHANES 2003–2010 (45). Second, we compared the predicted incidence and prevalence by stages of HCV disease with those from published studies and reports from the Centers for Disease Control and Prevention (15, 22, 46–48). Third, we compared the natural history of HCV infection according to our model with that from a multicenter follow-up study of patients with advanced fibrosis (49). Finally, we cross-validated our model with earlier modeling studies (4, 15) by comparing the results of the natural-history and pre-DAA scenarios.

Sensitivity Analyses

We tested the effect of the SVR rates, the timing of the availability of future therapies, treatment capacity, patients' decision to wait for new drugs, and changing annual incidence of HCV infection on the burden of HCV disease. We did deterministic sensitivity analyses on the natural-

Table 1. Estimated Effectiveness of Treatment for HCV Infection in the United States From 2001 to 2050*

Treatment History and Genotype	HCV State	PEG-RBV	BOC/TEL Plus PEG-RBV	Wave 1† (2014)	Wave 2‡ (2017)	Reference
Naive						
Genotype 1	F0–F2	0.54	0.75	0.90	–	28, 33, 35, 36, 40, 57–64
	F3	0.54	0.62	0.90	–	
	F4	0.36	0.62	0.80	0.90	
Genotype 2	F0–F3	0.82	–	0.90	–	58, 65–68
	F4	0.64	–	0.80	0.90	
Genotype 3	F0–F3	0.70	–	0.90	–	58, 65, 66, 68, 69
	F4	0.49	–	0.80	0.90	
Genotypes 4–6	F0–F3	0.58	–	0.90	–	58, 62, 70
	F4	0.32	–	0.80	0.90	
Relapse§						
Genotype 1	F0–F2	0.27	0.87	0.90	–	20, 27, 30, 34, 35, 61, 64, 67, 71, 72
	F3	0.27	0.85	0.90	–	
	F4	0.13	0.84	0.80	0.90	
Genotype 2	F0–F3	0.71	–	0.90	–	21, 43, 67, 73
	F4	0.56	–	0.70	0.90	
Genotype 3	F0–F3	0.66	–	0.85	–	21, 43, 69, 73
	F4	0.52	–	0.60	0.90	
Genotypes 4–6	F0–F3	0.31	–	0.90	–	21, 58, 62, 70
	F4	0.24	–	0.75	0.90	
Partial response						
Genotype 1	F0–F2	0.18	0.72	0.90	–	20, 27, 30, 34, 35, 61, 64, 67, 71, 72
	F3	0.18	0.56	0.90	–	
	F4	0.10	0.34	0.75	0.90	
Genotype 2	F0–F3	0.69	–	0.90	–	21, 43, 67, 73
	F4	0.55	–	0.70	0.90	
Genotype 3	F0–F3	0.64	–	0.85	–	21, 43, 69, 73
	F4	0.51	–	0.60	0.90	
Genotypes 4–6	F0–F3	0.31	–	0.90	–	21, 58, 62, 70
	F4	0.24	–	0.75	0.90	
Null response¶						
Genotype 1	F0–F2	0.10	0.41	0.90	–	20, 27, 30, 34, 35, 61, 64, 67, 71, 72
	F3	0.10	0.39	0.90	–	
	F4	0.05	0.14	0.75	0.90	
Genotype 2	F0–F3	0.54	–	0.90	–	21, 43, 67, 73
	F4	0.42	–	0.70	0.90	
Genotype 3	F0–F3	0.50	–	0.85	–	21, 43, 69, 73
	F4	0.39	–	0.60	0.90	
Genotypes 4–6	F0–F3	0.31	–	0.90	–	21, 58, 62, 70
	F4	0.24	–	0.75	0.90	
Contraindicated with modifiable reasons**						
Genotype 1	F0–F2	–	–	0.90	–	20, 28, 36, 61, 67, expert opinion
	F3	0.43	0.50	0.90	–	
	F4	0.28	0.36	0.70	0.90	

Continued on following page

Table 1—Continued

Treatment History and Genotype	HCV State	PEG-RBV	BOC/TEL Plus PEG-RBV	Wave 1† (2014)	Wave 2‡ (2017)	Reference
Genotype 2	F0–F3	0.66	–	0.90	–	43, 67, expert opinion
	F4	0.51	–	0.70	0.90	
Genotype 3	F0–F3	0.56	–	0.90	–	43, 69, 73, expert opinion
	F4	0.40	–	0.60	0.90	
Genotypes 4–6	F0–F3	0.46	–	0.90	–	70, expert opinion
	F4	0.26	–	0.70	0.90	
Contraindicated with nonmodifiable reasons††						
Genotypes 1, 2, and 4–6	F0–F3	–	–	0.90	–	28, 36, 43, 67, expert opinion
	F4	–	–	0.70	0.90	
Genotype 3	F0–F3	–	–	0.90	–	43, 69, 73, expert opinion
	F4	–	–	0.60	0.90	
Failed triple therapy‡‡						
Genotype 1	F0–F3	–	–	0.95	–	61, expert opinion
	F4	–	–	0.75	0.90	

BOC/TEL = boceprevir or telaprevir; HCV = hepatitis C virus; PEG-RBV = peginterferon and ribavirin.

* The sustained virologic response rates were derived directly from the references or indirectly inferred on the basis of the references. According to the Meta-analysis of Histologic Data in Viral Hepatitis (METAVIR) scoring system, F0 indicates no fibrosis of the liver, F1 indicates portal fibrosis without septa, F2 indicates portal fibrosis with few septa, F3 indicates many septa without cirrhosis, and F4 indicates cirrhosis.

† New therapies launched in 2014 that increased treatment response rates to 90% in patients without cirrhosis and 60% to 80% in patients with cirrhosis.

‡ Future therapies that we assumed would be launched in 2017 and would increase treatment response rates to 90% in patients with cirrhosis.

§ A patient whose HCV RNA level became undetectable during treatment with PEG-RBV but reappeared after the end of treatment.

|| A patient whose HCV RNA level decreased by $\geq 2 \log_{10}$ IU/mL at 12 wk of treatment with PEG-RBV but was detectable at 24 wk.

¶ A patient whose HCV RNA level decreased $< 2 \log_{10}$ IU/mL at 12 wk of treatment with PEG-RBV.

** A patient who had contraindications to regimens that included PEG-RBV, such as anemia, depression, and substance abuse, that were modifiable by medical or psychiatric interventions.

†† A patient who had contraindications to regimens that included PEG-RBV, such as autoimmune disease, coronary artery disease, and retinopathy, that were not modifiable by medical or psychiatric interventions.

‡‡ A patient whose HCV RNA level became detectable after treatment with PEG-RBV combined with a first-generation protease inhibitor.

history parameters of HCV infection and patient characteristics (Table 4 and Table 5 of the Supplement). We also evaluated the effect of treatment capacity on the burden of HCV infection (Table 6 of the Supplement).

Role of the Funding Source

The study was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health. The funding source played no role in study design, conduct, or analysis or the decision to submit the manuscript for publication.

RESULTS

Validation

Our model projected that the average number of cases of chronic HCV infection in 2003 to 2010 was 2.7 million, which is equal to the reported values in NHANES 2003–2010 (45) (Table 7 of the Supplement). The projected average prevalence of HCC in 2001 to 2004 was within 3% of the reported values (46). The incidence of HCC and liver-related deaths in 2005 was within 1% to 15% of the reported values (22). The projected distribution of different stages of chronic HCV infection closely

matched that of another modeling study (15). Finally, our model's 10-year cumulative incidence rates of DC, HCC, and combined liver-related deaths and liver transplantations closely matched those of a recently published multicenter follow-up study (Table 8 of the Supplement) (49).

Burden of HCV Infection

Our model projected that the cases of chronic HCV infection in the United States decreased from 3.2 million in 2001 to 2.3 million in 2013 (Figure 2). From 2001 to 2013, a total of 157 300 HCV-infected persons died of liver-related complications, 415 000 died of other causes, and 589 100 achieved SVR. During the same period, 251 000 new persons became chronically infected with HCV. Considering the population growth in the United States (50), we projected that HCV infection would become a rare disease by 2036 (that is, it would affect approximately 1 in 1500 persons, or less.) (51).

In 2001, a total of 682 400 persons born between 1945 and 1965 were chronically infected with HCV and were unaware of their disease. However, by 2013, only 531 200 HCV-infected patients (24% of the total HCV-infected population in the United States) were eligible for

Table 2. Default Characteristics of the Scenarios in Our Model of the Burden of HCV Infection in the United States From 2001 to 2050

Scenario	HCV Treatment (Period)*	Screening	Treatment Capacity
Natural history†	No treatment	No screening	NA
Pre-DAA‡	PEG-RBV (2001–2050)	Risk-based screening	Variant based on historical data (2001–2007) Constant at 83 270 (2008–2050)
Base case§	PEG-RBV (2001–2011) BOC/TEL plus PEG-RBV (2012–2013) Wave 1 (2014–2016) Wave 2 (2017–2050)	Risk-based and birth-cohort screening	Variant based on historical data (2001–2007) Constant at 83 270 (2008–2050)
Ideal	PEG-RBV (2001–2011) BOC/TEL plus PEG-RBV (2012–2013) Wave 1 (2014–2016) Wave 2 (2017–2050)	Universal screening	Unlimited

BOC/TEL = boceprevir or telaprevir; DAA = direct-acting antiviral; HCV = hepatitis C virus; NA = not applicable; PEG-RBV = peginterferon and ribavirin.

* Wave 1 indicates new therapies launched in 2014 for all patients that increased treatment response rates to 90% in patients without cirrhosis and 60% to 80% in patients with cirrhosis. Wave 2 indicates future therapies that we assumed would be launched in 2017 and would increase treatment response rates to 90% in patients with cirrhosis.

† A simulation scenario with no screening and no treatment.

‡ A simulation scenario with risk-based screening and PEG-RBV treatment.

§ A simulation scenario with risk-based and birth-cohort screening, treatment with PEG-RBV and/or DAAs before 2014 and newly approved and future therapies starting in 2014, and limited treatment capacity.

|| A simulation scenario with universal screening, treatment with PEG-RBV and/or DAAs before 2014 and newly approved and future therapies starting in 2014, and unlimited treatment capacity.

birth-cohort screening (that is, unaware of their disease status and still between fibrosis states F0 and F4). The implementation of 1-time birth-cohort screening beginning in 2013 is expected to identify 487 000 cases of HCV infection in this cohort in the next 10 years. In the base-case scenario, our model projected that the prevalence of DC, HCC, and liver-related deaths will peak during 2019 to 2020 and start declining afterward (Figure 3).

Ideal Scenario

In the ideal scenario, HCV infection could become a rare disease by 2026 (that is, 10 years earlier than in the base-case scenario) (Figure 2). The implementation of 1-time universal screening could identify 933 700 cases of HCV infection in the next 10 years. Compared with the base-case scenario (current clinical practice), the ideal scenario could reduce the total number of cases of DC by 135 800 (46%), cases of HCC by 96 300 (40%), liver-related deaths by 161 500 (37%), and liver transplantations by 13 900 (37%) during 2014 to 2050 (Table 3).

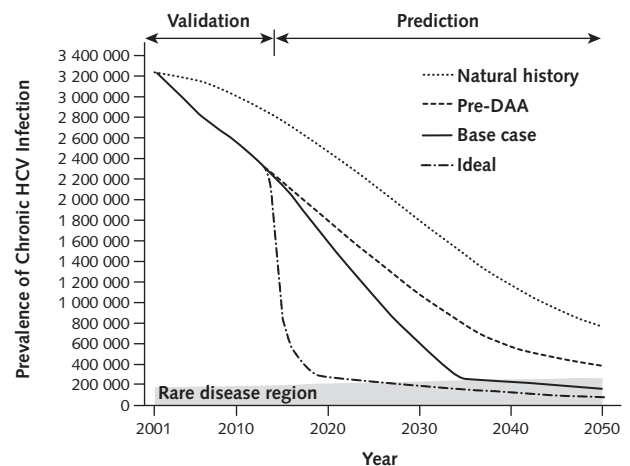
Pre-DAA Scenario

In the pre-DAA scenario, HCV infection did not become a rare disease. Compared with the base-case scenario, the pre-DAA scenario would have increased the number of cases of DC by 124 200 (30%), cases of HCC by 78 700 (25%), liver-related deaths by 126 500 (23%), and liver transplantations by 9900 (21%) during 2014 to 2050 (Table 3).

Sensitivity Analyses

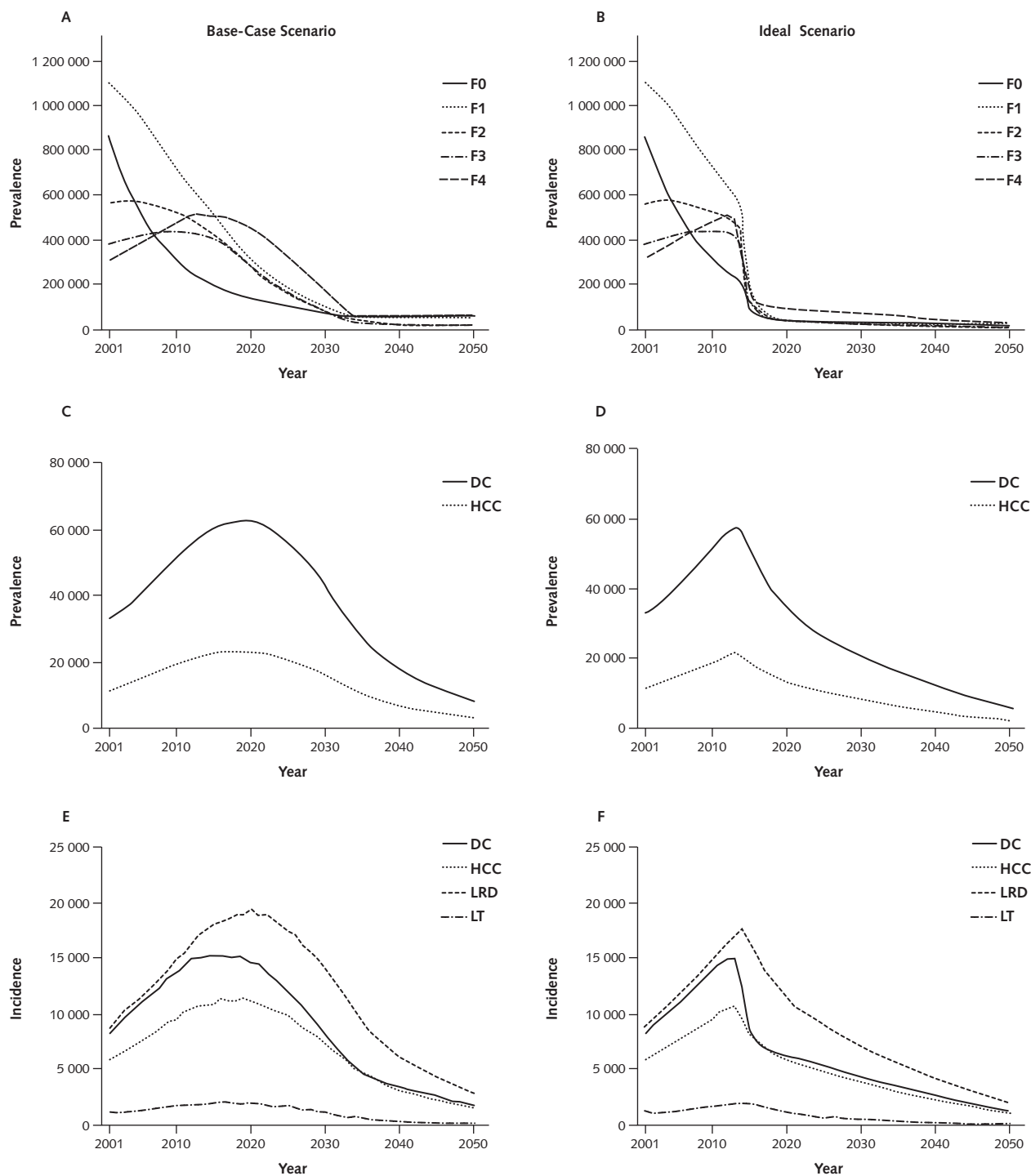
We evaluated the effect of increased treatment capacity on disease burden (Table 6 of the Supplement). Compared with the base-case scenario, a 10% increase in treatment capacity in 2012 and a 50% increase beyond 2014 (scenario 1) would reduce the number of cases of DC and HCC, liver-related deaths, and liver transplantations by 9% to 14%; a 20% decrease in treatment capacity beyond

2014 (scenario 2) would increase the corresponding adverse outcomes by 16% to 22%. Compared with the base-case scenario, unlimited treatment capacity from 2014 on-

Figure 2. Estimated prevalence of cases of chronic HCV infection in the United States from 2001 to 2050 under different simulation scenarios.

The rare disease region is calculated on the basis of the definition of a rare disease and adjusted to the U.S. population. On the basis of the Rare Diseases Act of 2002 (51), a rare disease affects approximately 1 in 1500 persons. The rare disease region is increasing with time because of population growth. Natural history indicates a simulation scenario with no screening and no treatment. Pre-DAA indicates a simulation scenario with risk-based screening and PEG-RBV treatment. Base case indicates a simulation scenario with risk-based and birth-cohort screening, treatment with PEG-RBV and/or DAAs before 2014 and newly approved and future therapies starting in 2014, and limited treatment capacity. Ideal indicates a simulation scenario with 1-time universal screening, treatment with PEG-RBV and/or DAAs before 2014 and newly approved and future therapies starting in 2014, and unlimited treatment capacity. DAA = direct-acting antiviral; HCV = hepatitis C virus; PEG-RBV = peginterferon and ribavirin.

Figure 3. Model results according to the base-case and ideal scenarios of the burden of HCV infection in the United States from 2001 to 2050.



Base case indicates a simulation scenario with risk-based and birth-cohort screening, treatment with PEG-RBV and/or DAAs before 2014 and newly approved and future therapies starting in 2014, and limited treatment capacity. Ideal indicates a simulation scenario with universal screening, treatment with PEG-RBV and/or DAAs before 2014 and newly approved and future therapies starting in 2014, and unlimited treatment capacity. **Figure 2** of the **Supplement** (available at www.annals.org) shows the results of the natural-history and pre-DAA scenarios. DAA = direct-acting antiviral; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; LRD = liver-related death; LT = liver transplantation; PEG-RBV = peginterferon and ribavirin. A and B. Prevalence of fibrosis stages. C and D. Prevalence of DC and HCC. E and F. Incidence of DC, HCC, LRD, and LT.

ward (scenario 3) would prevent 128 800 cases of DC, 91 000 cases of HCC, 153 200 liver-related deaths, and 13 400 liver transplantations.

When we reduced the SVR rates of available and future drugs by 10%, the cumulative incidence of DC and HCC and the number of liver-related deaths and liver transplantations increased by 4% to 23%, depending on the simulation scenario (Table 9 of the Supplement). Delayed or early launch of the second wave of therapies for HCV infection did not substantially change the disease burden (Table 10 of the Supplement). In addition, we found that the results were not sensitive to the percentage of patients in states F0 to F3 who might choose to wait for future therapies instead of initiating treatment with PI-based therapies (Table 11 of the Supplement). Among the natural-history parameters, the probability of developing DC and HCC in patients with cirrhosis had the greatest effect on the disease burden.

We also did a sensitivity analysis on the prevalence of HCV infection. Assuming that 4.9 million persons were infected with HCV in 2001, which was the upper limit of the 95% CI of the NHANES 1999–2002 estimate (19), we determined that the cumulative incidence of DC, HCC, and liver-related deaths increased by 23% to 25% compared with that of the base-case scenario (Table 12 and Table 13 of the Supplement). Finally, we evaluated the impact of decreasing and increasing annual incidence of HCV infection and found no substantial effect on the outcomes (Table 14 of the Supplement).

DISCUSSION

Our model estimated that 2.3 million persons were chronically infected with HCV in the beginning of 2013 compared with 3.2 million persons in 2001. With the implementation of birth-cohort screening and the availability of highly effective new therapies, HCV infection could become a rare disease by 2036. In addition, these changes could substantially decrease the overall clinical burden associated with HCV infection in the United States.

Our study also identified trends in HCV disease burden that have not been previously reported. We estimated that the current number of chronic cases in the United States is actually lower than the commonly reported estimate of 3.2 million, as corroborated by recently published data from NHANES 2003–2010. Prevalence decreased mainly because of deaths and successful treatments in this cohort. Also, our model projected that fewer patients are eligible for birth-cohort screening than estimated in a previously published study (11). Our results differed because we accounted for the possibility that patients in the birth cohort progressed beyond cirrhosis or became aware of their disease before the implementation of screening in 2013.

Our study underscores the need for more aggressive screening strategies and higher treatment capacity to further reduce the burden of HCV infection. Birth-cohort

Table 3. Estimated Effect of Each Scenario on the Outcomes of Advanced-Stage HCV Infection According to Our Model of the Burden of HCV Infection in the United States From 2014 to 2050

Outcome of Advanced-Stage Disease	Scenario			
	Natural* History	Pre-DAA†	Base Case‡	Ideal§
Decompensated cirrhosis				
Cumulative incidence (2014–2050)	647 000	418 100	293 900	158 100
Peak annual prevalence	90 700	68 000	62 700	56 000
Year of peak annual prevalence	2025	2022	2019	2014
Peak annual incidence	22 800	16 800	15 300	12 000
Year of peak annual incidence	2023	2020	2014	2014
Hepatocellular carcinoma				
Cumulative incidence (2014–2050)	473 000	318 900	240 200	143 900
Peak annual prevalence	33 200	25 000	23 200	20 800
Year of peak annual prevalence	2025	2021	2019	2014
Peak annual incidence	16 300	12 200	11 400	9 500
Year of peak annual incidence	2025	2021	2019	2014
Liver-related death				
Total deaths (2014–2050)	811 600	560 100	433 600	272 100
Peak annual deaths	27 500	20 600	19 300	17 500
Year of peak annual deaths	2025	2023	2020	2014
Liver transplantation				
Total transplantations (2014–2050)	67 100	47 800	37 900	24 000
Peak annual liver transplantations	2700	2100	2100	2000
Year of peak annual liver transplantations	2024	2021	2016	2014

DAA = direct-acting antiviral; HCV = hepatitis C virus; PEG-RBV = peginterferon and ribavirin.

* A simulation scenario with no screening and no treatment.

† A simulation scenario with risk-based screening and PEG-RBV treatment.

‡ A simulation scenario with risk-based and birth-cohort screening, treatment with PEG-RBV and/or DAAs before 2014 and newly approved and future therapies starting in 2014, and limited treatment capacity.

§ A simulation scenario with universal screening, treatment with PEG-RBV and/or DAAs before 2014 and newly approved and future therapies starting in 2014, and unlimited treatment capacity.

screening would decrease this burden but would fail to identify a large pool of existing patients with HCV infection who could advance to severe disease stages without treatment. In addition, the number of patients who are able to receive treatment greatly affects the potential disease burden. This number depends on treatment capacity, availability of new drugs, treatment cost, and insurance coverage.

With the launch of all-oral drugs that can simplify treatment, primary care physicians or infectious disease specialists also may take on the role of treating patients with HCV infection, thus alleviating the burden on hepatologists (52). Furthermore, such programs as the Exten-

sion for Community Healthcare Outcomes can help to increase the treatment capacity by improving access to care for underserved populations (53). However, the high price of new therapies could become a barrier to the timely treatment of HCV infection and inhibit the full potential of therapeutic advances and screening recommendations (54).

Our study has limitations. First, the historical number of cases of HCV infection in the model was based on data from NHANES 1999–2002, which underestimate the prevalence of HCV infection in the United States by excluding the institutionalized population. However, we tested the effect of higher prevalence of HCV infection on the future burden of this disease in a sensitivity analysis. Second, we estimated the total number of patients who received treatment from data on drug prescriptions reported by insurance companies (44), which may underestimate the number of patients who received treatment. Third, our model did not account for co-infections and other risk factors, such as alcohol consumption, that affect disease progression (55, 56). These limitations may have resulted in an underestimation of the projected burden of HCV infection. Fourth, we do not consider the potential effect of treatment on disease transmission. Although improved treatment would be expected to decrease transmission of HCV infection, new cases of this disease are a small proportion of the number of existing cases.

Information about SVR rates and the launch time of new therapies is limited. We based our SVR rates on results from several phase 2 and 3 clinical studies, but real rates may differ. We also based our assumptions about the launch time of new therapies on the end dates of clinical trials. Finally, due to the lack of information on re-treatment of patients in whom recently approved and future therapies will fail, the analysis of the re-treatment of these patients is beyond the scope of our analysis.

In conclusion, we evaluated the effect of the availability of DAAs, recently approved and potential future therapies, and changes in screening recommendations for HCV infection on the future burden of HCV disease in the United States. We found that, with ongoing therapeutic advancements and screening policy changes, HCV infection could become a rare disease within the next 22 years. We also found that the current screening recommendations are helpful in decreasing the future burden, but more aggressive recommendations should be proposed in conjunction with an increase in the treatment capacity for this condition.

From the University of Pittsburgh and University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, and The University of Texas MD Anderson Cancer Center, Houston, Texas.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the views of the National Institutes of Health.

Acknowledgment: The authors thank Elamin Elbasha, PhD, and Katherine Bornschlegel, MPH, for their constructive comments that im-

proved the quality of the manuscript; John Grefenstette, PhD, for technical support on simulation runs; and Jill Delsigne, PhD, and Diane Hackett for editing the manuscript.

Financial Support: By the National Center for Advancing Translational Sciences, National Institutes of Health (award KL2TR000146). Ms. Kabiri is supported by the Department of Health Policy and Management, University of Pittsburgh Graduate School of Public Health.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-0095.

Reproducible Research Statement: *Study protocol:* Not applicable. *Statistical code and data set:* Available from Dr. Chhatwal (e-mail, jchhatwal@mdanderson.org).

Requests for Single Reprints: Jagpreet Chhatwal, PhD, Department of Health Services Research, Unit 1444, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030; e-mail, JChhatwal@mdanderson.org.

Current author addresses and author contributions are available at www.annals.org.

References

1. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009;49:1335-74. [PMID: 19330875]
2. Rosen HR. Clinical practice. Chronic hepatitis C infection. *N Engl J Med*. 2011;364:2429-38. [PMID: 21696309]
3. Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med*. 2012;156:271-8. [PMID: 22351712]
4. Razavi H, Elkhoury AC, Elbasha E, Estes C, Pasini K, Poynard T, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology*. 2013;57:2164-70. [PMID: 23280550]
5. Drenth JP. HCV treatment—no more room for interferonologists? [Editorial]. *N Engl J Med*. 2013;368:1931-2. [PMID: 23607592]
6. American Association for the Study of Liver Diseases; Infectious Diseases Society of America. Recommendations for testing, managing, and treating hepatitis C. 2014. Accessed at www.hcvguidelines.org/full-report-view on 27 February 2014.
7. Dieterich D. The end of the beginning for hepatitis C treatment [Editorial]. *Hepatology*. 2012;55:664-5. [PMID: 22174100]
8. Liang TJ, Ghany MG. Current and future therapies for hepatitis C virus infection. *N Engl J Med*. 2013;368:1907-17. [PMID: 23675659]
9. Moyer VA; U.S. Preventive Services Task Force. Screening for hepatitis C virus infection in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2013;159:349-57. [PMID: 23798026]
10. Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Teo CG, et al; Centers for Disease Control and Prevention. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep*. 2012;61(RR-4):1-32. [PMID: 22895429]
11. Rein DB, Smith BD, Wittenborn JS, Lesesne SB, Wagner LD, Roblin DW, et al. The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. *Ann Intern Med*. 2012;156:263-70. [PMID: 22056542]
12. Hagan LM, Schinazi RF. Best strategies for global HCV eradication. *Liver Int*. 2013;33 Suppl 1:68-79. [PMID: 23286849]
13. Gonzalez SA, Davis GL. Demographics of hepatitis C virus today. *Clinical Liver Disease*. 2012;1:2-5.
14. Ngo-Metzger Q, Ward JW, Valdiserri RO. Expanded hepatitis C virus screening recommendations promote opportunities for care and cure [Editorial]. *Ann Intern Med*. 2013;159:364-5. [PMID: 23797155]
15. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort

model of HCV prevalence and disease progression. *Gastroenterology*. 2010;138:513-21. [PMID: 19861128]

16. Coffin PO, Scott JD, Golden MR, Sullivan SD. Cost-effectiveness and population outcomes of general population screening for hepatitis C. *Clin Infect Dis*. 2012;54:1259-71. [PMID: 22412061]

17. McGarry LJ, Pawar VS, Panchmatia HR, Rubin JL, Davis GL, Younossi ZM, et al. Economic model of a birth cohort screening program for hepatitis C virus. *Hepatology*. 2012;55:1344-55. [PMID: 22135116]

18. Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, et al; ISPOR-SMDM Modeling Good Research Practices Task Force. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force—3. *Value Health*. 2012;15:812-20. [PMID: 22999130]

19. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med*. 2006;144:705-14. [PMID: 16702586]

20. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al; REALIZE Study Team. Telaprevir for retreatment of HCV infection. *N Engl J Med*. 2011;364:2417-28. [PMID: 21696308]

21. Poynard T, Colombo M, Bruix J, Schiff E, Terg R, Flamm S, et al; Epic Study Group. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. *Gastroenterology*. 2009;136:1618-28. [PMID: 19208349]

22. Centers for Disease Control and Prevention. Surveillance for viral hepatitis—United States, 2011. 2013. Accessed at www.cdc.gov/hepatitis/Statistics/2011Surveillance/index.htm on 20 November 2013.

23. Blatt LM, Mutchnick MG, Tong MJ, Klion FM, Lebovics E, Freilich B, et al. Assessment of hepatitis C virus RNA and genotype from 6807 patients with chronic hepatitis C in the United States. *J Viral Hepat*. 2000;7:196-202. [PMID: 10849261]

24. Kim WR, Stock PG, Smith JM, Heimbach JK, Skeans MA, Edwards EB, et al. OPTN/SRTR 2011 Annual Data Report: liver. *Am J Transplant*. 2013;13 Suppl 1:73-102. [PMID: 23237697]

25. Falck-Ytter Y, Kale H, Mullen KD, Sarbah SA, Sorescu L, McCullough AJ. Surprisingly small effect of antiviral treatment in patients with hepatitis C. *Ann Intern Med*. 2002;136:288-92. [PMID: 11848726]

26. Honeycutt AA, Harris JL, Khavjou O, Buffington J, Jones TS, Rein DB. The costs and impacts of testing for hepatitis C virus antibody in public STD clinics. *Public Health Rep*. 2007;122 Suppl 2:55-62. [PMID: 17542455]

27. Feld J, Jacobson I, Jensen D, Foster GR, Pol S, Tam E, et al. Up to 100% SVR4 rates with ritonavir-boosted danoprevir (DNVr), mericitabine (MCB), and ribavirin (R) ± peginterferon alfa-2a (40KD) (P) in HCV genotype 1-infected partial and null responders: results from the MATTERHORN study [Abstract]. *Hepatology*. 2012;56(Suppl 1):231-2A.

28. Gane EJ, Pockros P, Zeuzem S, Marcellin P, Shikhan A, Bernaards C, et al. Interferon-free treatment with a combination of mericitabine and danoprevir/R with or without ribavirin in treatment-naïve HCV genotype 1-infected patients [Abstract]. *J Hepatol*. 2012;56(Suppl 2):S55-6.

29. Lok AS, Gardiner DF, Lawitz E, Martorell C, Everson GT, Ghalib R, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. *N Engl J Med*. 2012;366:216-24. [PMID: 22256805]

30. Kowdley K, Lawitz E, Poordad F. A 12-week interferon-free treatment regimen with ABT-450/r, ABT-267, ABT-333 and ribavirin achieves SVR12 rates (observed data) of 99% in treatment-naïve patients and 93% in prior null responders with HCV genotype 1 infection [Abstract]. *Hepatology*. 2012;56(Suppl 1):1515A.

31. Gane EJ, Stedman CA, Hyland RH, Sorensen RD, Symonds WT, Hinds R, et al. Once daily sofosbuvir (GS-7977) plus ribavirin in patients with HCV genotypes 1, 2, and 3: the ELECTRON trial [Abstract]. *Hepatology*. 2012;56(Suppl 1):306-7A.

32. Zeuzem S, Soriano V, Asselah T, Bronowicki JP, Lohse AW, Mullhaupt B, et al. Interferon (IFN)-free combination treatment with the HCV NS3/4A protease inhibitor BI 201335 and the nonnucleoside NS5B inhibitor BI 207127 ± ribavirin (R): final results of SOUND-C2 and predictors of response [Abstract]. *Hepatology*. 2012;56(Suppl 1):308-9A.

33. Soriano V, Gane E, Angus P, Stickel F, Bronowicki JP, Roberts SK, et al. Efficacy and safety of the interferon (IFN)-free combination of BI 201335 + BI 207127 ± ibavirin (RBV) in treatment-naïve patients with HCV genotype (GT) 1 infection and compensated liver cirrhosis: results from the SOUND-C2 study [Abstract]. *Hepatology*. 2012;56(Suppl 1):234A.

34. Jacobson IM, Jensen DM, Pol S, Foster GR, Feld JJ, Yoshida EM, et al. Safety and efficacy of ritonavir-boosted danoprevir (DNVr), peginterferon alpha-2a (40KD) (P), and ribavirin (R) with or without mericitabine in HCV genotype (G) 1-infected treatment-experienced patients with advanced hepatic fibrosis [Abstract]. *Hepatology*. 2012;56 (Suppl 1):232-3A.

35. Poordad F, Fried M, Zeuzem S, Ferenci P, Lenz O, Sinha R, et al. Efficacy and tolerability of TMC435 150 mg once daily with peginterferon α-2a and ribavirin for treatment of HCV genotype 1 infection in patients with Metavir score F3 and F4 (PILLAR and ASPIRE trials) [Abstract]. *Hepatology*. 2012;56(Suppl 1):233A.

36. Jacobson IM, Sulkowski MS, Gane EJ, Koziel MJ, De Souza C, Kieffer TL, et al. VX-222, telaprevir, and ribavirin in treatment-naïve patients with genotype 1 chronic hepatitis C: results of the ZENITH study interferon-free regimen [Abstract]. *Hepatology*. 2012;56 (Suppl 1):308A.

37. Pawlotsky JM, Sarin SK, Foster GR, Peng CY, Rasenack J, Flisiak R, et al. Alisporivir plus ribavirin achieves high rates of sustained HCV clearance (SVR24) as interferon (IFN)-free or IFN-add-on regimen in treatment-naïve patients with HCV GT2 or GT3: final results from VITAL-1 study [Abstract]. *Hepatology*. 2012;56 (Suppl 1):309-10A.

38. Osinusi A, Heytens L, Lee YJ, Bon D, Shivakumar B, Nelson A, et al. High efficacy of GS-7977 in combination with low or full dose ribavirin for 24 weeks in difficult to treat HCV infected genotype 1 patients: interim analysis from the SPARE trial [Abstract]. *Hepatology*. 2012;56 (Suppl 1):1518A.

39. Everson G, Sims K, Rodriguez-Torres M. An interferon-free, ribavirin-free 12-week regimen of daclatasvir (DCV), asunaprevir (ASV), and BMS-791325 yielded SVR4 of 94% in treatment-naïve patients with genotype (GT) 1 chronic hepatitis C virus (HCV) infection [Abstract]. *Hepatology*. 2012;56 (Suppl 1):LB3.

40. Doyle JS, Aspinall E, Liew D, Thompson AJ, Hellard ME. Current and emerging antiviral treatments for hepatitis C infection. *Br J Clin Pharmacol*. 2013;75:931-43. [PMID: 22882367]

41. Aronsohn A, Jensen D. Informed deferral: a moral requirement for entry into the hepatitis C virus treatment warehouse [Editorial]. *Hepatology*. 2012;56:1591-2. [PMID: 22807004]

42. Kanwal F, El-Serag HB. Hepatitis C virus treatment: the unyielding chasm between efficacy and effectiveness [Editorial]. *Clin Gastroenterol Hepatol*. 2014. [PMID: 24607698]

43. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al; POSITRON Study. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013;368:1867-77. [PMID: 23607593]

44. Volk ML, Tocco R, Saini S, Lok AS. Public health impact of antiviral therapy for hepatitis C in the United States. *Hepatology*. 2009;50:1750-5. [PMID: 19824079]

45. Denniston MM, Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med*. 2014;160:293-300. [PMID: 24737271]

46. Rein DB, Wittenborn JS, Weinbaum CM, Sabin M, Smith BD, Lesesne SB. Forecasting the morbidity and mortality associated with prevalent cases of pre-cirrhotic chronic hepatitis C in the United States. *Dig Liver Dis*. 2011;43:66-72. [PMID: 20739252]

47. El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology*. 2004;127:S27-34. [PMID: 15508094]

48. Lang K, Danchenko N, Gondek K, Shah S, Thompson D. The burden of illness associated with hepatocellular carcinoma in the United States. *J Hepatol*. 2009;50:89-99. [PMID: 18977551]

49. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA*. 2012;308:2584-93. [PMID: 23268517]

50. United States Census Bureau. 2012 national population projections. 2012. Accessed at www.census.gov/population/projections/data/national/2012.html on 30 November 2013.

51. Rare Diseases Act of 2002, Pub. L. No. 107-280 (2002). Accessed at www.gpo.gov/fdsys/pkg/PLAW-107publ280/content-detail.html on 30 November 2013.

52. McGovern BH. Editorial commentary: Hepatitis C virus and the infectious disease physician: a perfect match [Editorial]. *Clin Infect Dis*. 2012;55:414-7. [PMID: 22491341]

53. Arora S, Thornton K, Murata G, Deming P, Kalishman S, Dion D, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. *N Engl J Med*. 2011;364:2199-207. [PMID: 21631316]
54. Hoofnagle JH, Sherker AH. Therapy for hepatitis C—the costs of success [Editorial]. *N Engl J Med*. 2014;370:1552-3. [PMID: 24725236]
55. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. *J Hepatol*. 2001;34:730-9. [PMID: 11434620]
56. Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfecting patients. The Multivirc Group. *Hepatology*. 1999;30:1054-8. [PMID: 10498659]
57. Bourlière M, Khaloun A, Wartelle-Bladou C, Oules V, Portal I, Benali S, et al. Future treatment of patients with HCV cirrhosis. *Liver Int*. 2012;32 Suppl 1:113-9. [PMID: 22212581]
58. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013;368:1878-87. [PMID: 23607594]
59. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al; ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med*. 2011;364:2405-16. [PMID: 21696307]
60. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al; SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364:1195-206. [PMID: 21449783]
61. Jacobson IM, Ghalib R, Rodriguez-Torres M. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: the COSMOS study [Abstract]. Presented at the 64th Annual Meeting of the American Association for the Study of Liver Diseases, Washington, DC, 1–5 November 2013. Abstract no. LB-3.
62. Nguyen MH, Keeffe EB. Prevalence and treatment of hepatitis C virus genotypes 4, 5, and 6. *Clin Gastroenterol Hepatol*. 2005;3:S97-101. [PMID: 16234071]
63. Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naïve and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. *Lancet*. 2014;383:515-23. [PMID: 24209977]
64. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med*. 2014;370:1973-82. [PMID: 24725237]
65. Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Solá R, et al; ACCELERATE Investigators. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med*. 2007;357:124-34. [PMID: 17625124]
66. Dore G, Lawitz E, Hezode C, Shafraan S, Ramji A, Tatum H, et al. Daclatasvir combined with peginterferon alfa-2A and ribavirin for 12 or 16 weeks in patients with HCV genotype 2 or 3 infection: COMMAND GT2/3 study [Abstract]. *J Hepatol*. 2013;58 (Suppl 1):S570-1.
67. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med*. 2013;368:34-44. [PMID: 23281974]
68. Lawitz E, Lalezari JP, Hassanein T, Kowdley KV, Poordad FF, Sheikh AM, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naïve patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infect Dis*. 2013;13:401-8. [PMID: 23499158]
69. Zeuzem S, Dusheiko G, Salupere R, Mangia A, Flisiak R, Hyland R. Sofosbuvir + ribavirin for 12 or 24 weeks for patients with HCV genotype 2 or 3: the VALENCE trial [Abstract]. *Hepatology*. 2013;58 (Suppl 1):733A.
70. Ruane P, Ain D, Raid J, Meshrekey R, Stryker R, Wolfe P. Sofosbuvir plus ribavirin in the treatment of chronic HCV genotype 4 infection in patients of Egyptian ancestry [Abstract]. *Hepatology*. 2013;58 (Suppl 1):736A.
71. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al; HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364:1207-17. [PMID: 21449784]
72. Bronowicki J, Davis M, Flamm S, Gordon S, Lawitz E, Yoshida E, et al. Sustained virologic response (SVR) in prior peginterferon/ribavirin (PR) treatment failures after retreatment with boceprevir (BOC) + PR: PROVIDE study interim results [Abstract]. *J Hepatol*. 2012;56 (Suppl 2):S6.
73. Lawitz E, Poordad F, Brainard D. Sofosbuvir in combination with pegIFN and ribavirin for 12 weeks provides high SVR rates in HCV-infected genotype 2 or 3 treatment experienced patients with and without compensated cirrhosis: results from the LONESTAR-2 study [Abstract]. Presented at the 64th Annual Meeting of the American Association for the Study of Liver Diseases, Washington, DC, 1–5 November 2013. Abstract no. LB4.

Current Author Addresses: Ms. Kabiri and Dr. Roberts: Department of Health Policy and Management, 130 De Soto Street, Pittsburgh, PA 15261.

Dr. Jazwinski: Division of Gastroenterology, Hepatology and Nutrition, Center for Liver Diseases, 3471 Fifth Avenue, 900 Kaufmann Building, Pittsburgh, PA 15213.

Dr. Schaefer: Department of Industrial Engineering, 1048 Benedum Hall, University of Pittsburgh, Pittsburgh, PA 15261.

Dr. Chhatwal: Department of Health Services Research, Unit 1444, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030.

Author Contributions: Conception and design: M. Kabiri, A.B. Jazwinski, M.S. Roberts, J. Chhatwal.

Analysis and interpretation of the data: M. Kabiri, M.S. Roberts, A.J. Schaefer, J. Chhatwal.

Drafting of the article: M. Kabiri, A.B. Jazwinski, J. Chhatwal.

Critical revision of the article for important intellectual content: M. Kabiri, A.B. Jazwinski, M.S. Roberts, A.J. Schaefer, J. Chhatwal.

Final approval of the article: M. Kabiri, A.B. Jazwinski, M.S. Roberts, A.J. Schaefer, J. Chhatwal.

Statistical expertise: M. Kabiri, J. Chhatwal.

Obtaining of funding: A.J. Schaefer, J. Chhatwal.

Administrative, technical, or logistic support: M. Kabiri.

Collection and assembly of data: M. Kabiri.