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# Hepatitis C Retreatment in the Era of Direct-Acting Antivirals: Projections in the United States

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## Abstract

**Background—**The introduction of oral direct-acting antivirals (DAAs) has dramatically changed the landscape of HCV treatment. However, a small percentage of patients fail to achieve sustained virologic response (SVR). Understanding the number of people who fail on DAAs and require re-treatment is important for budget impact and disease burden projections.

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**AUTHORSHIP STATEMENT**

Dr. Chhatwal is acting as the submission's guarantor and is responsible for this work.
All authors have approved the final version of the manuscript.

Authors contributions:
Study concept and design: Chhatwal, Chen, Ayer, Bethea, Kanwal, Kowdley, Wang, Roberts, Gordon; experiments and procedures: Chhatwal, Chen; writing of article: Chhatwal, Chen, Ayer, Bethea, Kanwal, Kowdley, Wang, Roberts, Gordon.

**STATEMENT OF INTEREST**

Authors' declaration of personal interests: Other authors have nothing to declare.

**Aim—**To quantify the number of HCV patients who fail to achieve SVR on oral DAAs (NS5A vs. non-NS5A) and require re-treatment.

**Methods—**We used a mathematical model to simulate clinical management of HCV in the United States, which included the implementation of HCV screening, treatment, and disease progression. We simulated different waves of DAA treatment and used real-world data to extract SVR rates and market shares of available therapies.

**Results—**Our model projected that the number of people living without viremia (i.e., cured) would increase from 0.70 million in 2014 to 1.78 million by 2020. Between 2014 and 2020, 1.50 million people would receive treatment with DAAs, of whom 124,000 (8.3%) are projected to fail to achieve SVR. Among those treatment failures, 66,600 (53.7%) patients would fail treatment with NS5A inhibitors and 69,600 (56.1%) would have cirrhosis. During the same period 34,200 people would progress to decompensated cirrhosis and 27,300 would develop hepatocellular carcinoma after failing to achieve SVR.

**Conclusions—**Even in the era of highly-effective DAAs, a significant number of patients will fail to achieve SVR and will require re-treatment options. Timely and effective re-treatment is essential to prevent the long-term sequelae of HCV.

### Keywords

Outcomes research; Viral hepatitis; Health Economics; Epidemiology

## INTRODUCTION

Chronic hepatitis C is the leading cause of cirrhosis, hepatocellular carcinoma, and death from liver diseases; it is also one of the leading indication for liver transplantation in the United States (1). The availability of all-oral direct-acting antivirals (DAAs) has dramatically changed the hepatitis C virus (HCV) treatment landscape. These therapies are highly effective—results from clinical trials as well as those from real-world studies have shown sustained virologic response (SVR) rates of 90–100% with the new DAAs (2). In addition, an increasing number of patients are eligible for therapy due to the absence of interferon and ribavirin in these new therapy regimens.

Oral DAAs offer an opportunity to eliminate HCV infection as a public health problem. The United States' National Academies of Science, Engineering, and Medicine recently set targets for HCV elimination, which includes treating 80% of all eligible persons with chronic HCV by 2030. Despite the high SVR rates achievable with oral DAA regimens, a small percentage of patients fail to achieve SVR due to virological failure. Timely treatment of this population is required to prevent long-term sequelae of HCV in these patients and to aid in reaching the elimination targets.

Currently recommended first-line antiviral therapies in the United States include all-oral DAA regimens containing a nonstructural protein 5A (NS5A) inhibitor or non-NS5A inhibitor (3). Among patients who have failed NS5A inhibitors, previous retreatment options were limited and emerging resistance was an important consideration for retreatment selection. The AASLD-IDSA guidance recently revised their recommendation for re-

treatment of patients with recently available DAAs in whom previous treatment with any HCV NS5A or non-NS5A inhibitors had failed (3). Because the costs of new DAAs are different from available DAAs, understanding the number of people who require re-treatment or will fail to achieve SVR even after multiple treatments is important for budget impact and disease burden projections, especially for payers.

The total number of treatment failures at the population level depends on several factors such as the number of patients newly diagnosed with HCV, current treatment penetration rates, treatment access restrictions by fibrosis stage or other factors (4), and market share of NS5A versus non-NS5A inhibitors. Our objective was to project the number of patients infected with HCV who will fail currently approved oral DAA therapies (including NS5A vs. non-NS5A inhibitor-containing regimens) and will require re-treatment.

## METHODS

### Model Overview

We used a previously developed mathematical disease model, *Hepatitis C Disease Burden Simulation model* (*HEP-SIM*), to simulate the changing HCV environment and predict number of HCV patients needing re-treatment (5, 6). The HEP-SIM model simulates the current clinical management of HCV including the implementation of birth-cohort and risk-based screening, approval of multiple DAAs, treatment access, HCV awareness status, and the changing prevalence of HCV in the United States from 2001 onwards. The model has been validated with the results of the National Health and Nutrition Examination Survey (NHANES) 1999–2002 and 2003–2009 studies (7, 8), reports from the Centers for Disease Control and Prevention (CDC) (9), and a large multicenter follow-up study of patients with advanced fibrosis (10). We projected the number of patients undergoing treatment between 2014 and 2020; and the number of patients who failed DAAs including both NS5A and non-NS5A inhibitors. Below we describe the key components of *HEP-SIM*; further details can be found elsewhere (5, 6).

### Patient Demographics

The base-case population in *HEP-SIM* represented HCV-infected patients in the United States. We defined the age distributions and sex based on the NHANES data, and defined HCV genotype, stage of liver disease, and prior HCV treatment history based on published studies (Supplementary Table S1). An updated HCV incidence was defined based on the recently reported data by the CDC (Supplementary Table S2).

### Natural History of HCV

The natural history of HCV was defined using METAVIR fibrosis scores (no fibrosis [F0], portal fibrosis without septa [F1], portal fibrosis with few septa [F2], numerous septa without fibrosis [F3], or cirrhosis [F4]), decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, and liver-related death. We used a published meta-analysis to estimate fibrosis progression from F0 to F4 (Supplementary Table S3) (11). We estimated disease progression in cirrhosis and decompensated cirrhosis from published observational studies

(12, 13). Patients who developed decompensated cirrhosis or hepatocellular carcinoma were eligible to receive a liver transplant (14–16) and had higher mortality rates (17).

### HCV Awareness and Screening

HEP-SIM simulated the actual clinical practice of HCV management from 2001 onwards. We implemented risk-based screening until 2013 and added one-time birth-cohort screening for people born between 1945 and 1965 starting in 2013, reflecting recent changes in CDC guidelines on HCV screening (18). We assumed that 90% of the patients covered by healthcare insurance and 10% of those who were uninsured were offered HCV testing (19). Similar to the assumptions made by the CDC's study to evaluate birth-cohort HCV screening, we assumed that among those who were offered testing, 91% would accept it, and 90% of those who tested positive would receive those results (19). We assigned the uptake of screening such that the majority of these patients would receive screening gradually over 7 years beginning in 2013. In addition to birth-cohort screening, we implemented HCV diagnosis through usual care, which also included risk-based screening (Supplementary Tables S4–6).

### HCV Treatment Waves

We modeled HCV treatment in different waves reflecting clinical practice starting with peginterferon+ribavirin until 2011, followed by the launch of first-generation protease inhibitors, boceprevir and telaprevir, in May 2011 (Figure 1). We started with older therapies to keep track of prior treatment history. These patients were eligible for re-treatment with new antivirals (NS5A as well as non-NS5A inhibitors). From 2014, we simulated the availability of non-NS5A inhibitors sofosbuvir and simeprevir (denoted as DAA1 non-NS5A wave). From 2015, we simulated all-oral DAA combinations including both non-NS5A and NS5A inhibitors (denoted by DAA1 non-NS5A and DAA1 NS5A), followed by the availability of next wave of NS5A inhibitors (denoted by DAA2 NS5A) from 2018 onwards. The type of regimen patients received was determined by their treatment history (naïve or prior drug type experience) and the year treatment was offered. Therefore, we differentiated treatment regimens by HCV genotype, presence of cirrhosis and prior treatment failure (NS5A or non-NS5A inhibitor). SVR rates were obtained from multiple clinical trials as well as real-world data from the TRIO and TARGET studies (Supplementary Table S7).

### HCV Treatment uptake and Prioritization

We used published studies and drug sales as a surrogate to estimate the number of patients receiving treatment in a given year (Supplementary Table S8). In 2014, approximately 150,000 patients initiated DAA treatment (20). In 2015 and 2016, 280,000 initiated treatment based on reported drug sales (21). From 2017 onwards, we assumed that the maximum annual treatment capacity would not exceed 280,000 and the actual number of patients receiving treatment was dependent on patients' awareness status, prior treatment history, and insurance status. We used commercial claims data from QuintilesIMS and IPSOS to estimate the market share of NS5A versus non-NS5A inhibitor-containing regimens by HCV genotype (Supplementary Table S9).

Consistent with clinical practice, we assigned priority to F3 and F4 patients for HCV treatment as observed in 2014. However, we assumed that F0–F2 patients would get treatment if the total number of candidates needing treatment decreased below the annual treatment capacity. Prior to 2018, among patients who failed treatment with an NS5A inhibitor, only cirrhotic patients are eligible for re-treatment with non-NS5A inhibitors, including simprevir+sofosbuvir, ledipasvir/sofosbuvir+ribavirin, sofosbuvir/velpatasvir +ribavirin, sofosbuvir+zepatier+ribavirin, sofosbuvir+Viekira Pak+ribavirin (3). F0–F3 patients who failed treatment with an NS5A inhibitor would wait for retreatment until the next wave of DAA therapies (DAA2 NS5A wave). From 2018 onwards, all patients who failed on previous DAAs, irrespective of their fibrosis level or prior DAA regimen, would be eligible for retreatment with DAA2 NS5A inhibitors, which includes the next wave of drug combinations such as glecaprevir/pibrentasvir, in selected subgroups, or sofosbuvir/ velpatasvir/voxilaprevir (22–24). Though these dru`gs became available in mid 2017, the SVR status of patients receiving them would become available from 2018 onwards; therefore, we noted 2018 as the year for this wave of DAAs.

### Model Outcomes

We projected the number of patients who failed to achieve SVR in the era of DAAs from 2014 to 2020. We presented these outcomes by drug regimen (NS5A vs non-NS5A failure), presence or absence of cirrhosis, and HCV genotype. To account for uncertainty in model inputs we conducted probabilistic sensitivity analysis and presented 95% uncertainty intervals for the model outcomes. In addition, to further assess the robustness of model results, we ran five scenarios (see Appendix: Scenario Analysis) that accounted for (1) increasing trend in HCV incidence rate from 2016 onwards (Supplementary Table S10), (2) higher treatment uptake rate of 500,000 patients per year from 2018 onwards, (3) changes in the market share of NS5A vs non-NS5A inhibitors from 2017 onwards, (4) scaling-up birth-cohort screening by 25% (relative to the base case), and (5) scaling-down birth-cohort screening by 25% (relative to the base case).

## RESULTS

Figure 2A shows the number of patients alive who either are viremic or achieved SVR over time. In 2014, the estimated number of patients with SVR was 705,000, increasing to 1.40 million by 2017, and further projected to increase to 1.78 million by 2020. In contrast, the number of viremic patients is expected to decrease from 2.1 million in 2014 to 844,000 in 2020. Figure 2A also shows the 95% uncertainty intervals generated by probabilistic sensitivity analysis, which accounted for uncertainty in all model inputs simultaneously. In 2014, 1 million patients (48% of all viremic patients in 2014) were unaware of their infection, and by 2020, 673,000 patients (80% of all viremic patients in 2020) would still remain unaware of their infection (Figure 2B).

Figures 3A–C present the number of patients who would receive treatment from 2014 to 2020 with NS5A inhibitor-containing regimens versus non-NS5A inhibitor-containing regimens, HCV genotype, and presence or absence of cirrhosis. Our model projected that between 2014 and 2020, around 1.50 million people would receive treatment with DAAs, of

whom 1.19 million (79.5%) would receive treatment with NS5A inhibitors. The characteristics of patients receiving treatment would be: 31.8% with cirrhosis, 75.8% infected with GT1, 12.0% infected with GT2, 7.8% infected with GT3, and 4.9% infected with GT4–6. Under the current screening and treatment practice, the number of patients receiving treatment in 2020 would drop to 61,000 in spite of the fact that around 844,000 patients would still be viremic in that year.

Next, we projected the number of patients who would fail to achieve SVR in the era of DAAs. Figure 4A shows the number of patients living with HCV after failing to achieve SVR after treatment with at least one HCV regimen (including non-DAAs). The number of such treatment-experienced patients dropped from 278,000 in 2014 to 92,000 in 2017 and was further projected to drop to 14,000 by 2020. The decline in treatment-experienced patients is primarily due to the availability and use of highly-effective oral DAAs. In addition, between 2014 and 2020, 34,200 people who failed to achieve SVR with at least one prior treatment attempt (with pre-DAA or DAA) would develop decompensated cirrhosis and among those 3,300 failed on at least one DAA. During the same time period, 27,300 people would develop hepatocellular carcinoma who failed to achieve SVR with at least one prior treatment attempt (with pre-DAA or DAA) and among those 1,800 failed on at least one DAA. Among patients who failed prior treatment, the proportion of those who developed advanced sequelae increased from 5% in 2014 to 42% 2020. Figure 4B shows the 95% uncertainty intervals for the number of people alive who failed to achieve SVR with at least one treatment attempt. The estimated number of patients who never failed on NS5A inhibitors had a wide uncertainty interval.

Of the 1.50 million patients receiving treatment with DAAs between 2014 and 2020, 123,800 (8.3%) are projected to fail to achieve SVR, of whom 66,500 (53.7%) would fail treatment with NS5A inhibitors. The characteristics of the 123,800 patients who would fail on DAAs would be: 56.1% with cirrhosis, 72.7% infected with GT1, 11.2% infected with GT2, 13.1% infected with GT3, and 3.0% infected with GT4–6. Figures 5A–C show the number of patients who would fail DAAs each year by NS5A inhibitor-containing versus non-NS5A inhibitor-containing regimens, HCV genotype, and cirrhosis status. Because the number of patients who would receive treatment is expected to decrease over time, we observed a drop in the number of those who fail treatment from 2014 to 2020. The number of patients who fail treatment in 2015 was marginally higher than that in 2014 because the number of patients receiving treatment in 2015 increased substantially—from 150,000 to 280,000. We observed that, from 2015 onwards, the majority of those who failed treatment would have been treated by NS5A inhibitors, because the majority of patients overall would be receiving treatment with these agents.

Outcomes of the scenario analyses showed that results were not sensitive to the rising HCV incidence trends or change in the uptake of HCV screening. However, compared with the base case, the number of people who failed to achieve SVR (NS5A or non-NS5A inhibitors) changed by more than 10% when the treatment capacity was increased to 500,000/year or when the market share of NS5A inhibitors was changed to 90% (Supplementary Table S11). In addition, the number of alive patients in a given year who failed at least one treatment were also sensitive to the treatment capacity (Supplementary Table S12), and the number of

people aware of their HCV infection (in year 2018) were sensitive to the treatment capacity (Supplementary Table S13).

## DISCUSSION

The availability of well-tolerated and highly effective DAAs offers a new hope to eliminate HCV as a public health threat. However, even with the newer generations of DAAs, a small proportion of patients will fail to achieve SVR and could develop advanced sequelae such as decompensated cirrhosis and HCC. In this study, we simulated the current clinical landscape of HCV treatment and projected the number of patients in the United States who would receive treatment, achieve SVR, or require re-treatment. We found that in the era of DAAs, a total of 1.50 million people would receive treatment between 2014 and 2020 and around 124,000 (8.3%) would fail to achieve SVR; the majority of those who fail treatment would have been exposed to NS5A inhibitors. Timely and effective retreatment of these patients could prevent the long-term sequelae of HCV.

Earlier studies have estimated the number of patients who would remain viremic in the era of DAAs (6), and projected disease burden under different screening and treatment scenarios (5, 6, 25, 26). This study adds new information by estimating the number of patients who would fail to achieve SVR, especially with NS5A inhibitors, and require retreatment in the era of DAAs. Providing this data allows payers to assess the budget impact of HCV treatment and disease burden projections. Even though the DAAs have been shown to be cost-effective/saving (27, 28), budget needed to treat all HCV patients remains challenging in some settings (29).

We observed that under current clinical practice, the number of patients receiving treatment would drop to 61,000 by 2020 in spite of the fact that around 844,000 patients would still be viremic in that year. This is because the majority of viremic patients aware of their status would have received treatment by this time, whereas, those unaware of their HCV status would not be able to avail the benefits of DAA therapy. This finding emphasizes the need to update the current screening policies to diagnose patients who otherwise would remain unaware and untreated. In addition, there is a need to remove treatment barriers for patients who are already aware of their HCV status but not yet linked to care, such as many injection drug users and people in prisons.

National and global health policy initiatives have stressed the desirability of eliminating HCV as a public health threat by 2030. In order to achieve this goal, a comprehensive strategy of patient identification, linkage to care and treatment access is required (30). Additionally, the availability of effective treatment options for patients who fail to achieve SVR after initial therapy is necessary. Even though the number of such patients is relatively small compared with the current burden of HCV, these patients could become a non-significant portion of the viremic population in the future. Successful retreatment of these patients, who are already linked to care, could reduce the risk of long-term clinical sequelae. While viral clearance would prevent development of advanced sequelae from chronic HCV, other external factors such as abuse of alcohol or drugs would also need to be addressed via appropriate interventions to achieve the full benefits of viral clearance with DAA therapy.

Our study also shows a growing population of patients alive following HCV cure. As this patient population increases, disease management efforts focused on regular surveillance of persons with pre-treatment advanced fibrosis or cirrhosis is important, as they remain at risk of developing hepatocellular carcinoma (31). In addition, the burden of management for these patients may also shift from specialists to general practitioners. If this transition does take place, future efforts should also focus on increasing the awareness among general practitioners and internists regarding appropriate medical care for patients cured of HCV.

This modeling-based study has some limitations. First, the analysis only included non-institutionalized HCV-infected persons as estimated by the NHANES studies. Therefore, our results likely underestimated the number of viremic patients. Secondly, recent data suggests that the uptake of birth-cohort screening in practice remains low, therefore, our model may have over-estimated the number of patients who would become aware of their HCV status. Thirdly, we did not include in the model HIV-HCV co-infection, which is beyond the scope of the current work. Fourth, we did not consider the possibility of regression of fibrosis after SVR, which is unlikely to effect the results presented in this study. Finally, we made assumptions about future treatment capacity, which could vary over time.

In conclusion, we found that even in the era of highly effective DAAs, there are still going to be challenges. In order to achieve HCV elimination a national strategy will need to support the development of systems aimed at increasing the diagnosis of HCV and plans outlining the effective and timely retreatment of patients who have failed on DAAs.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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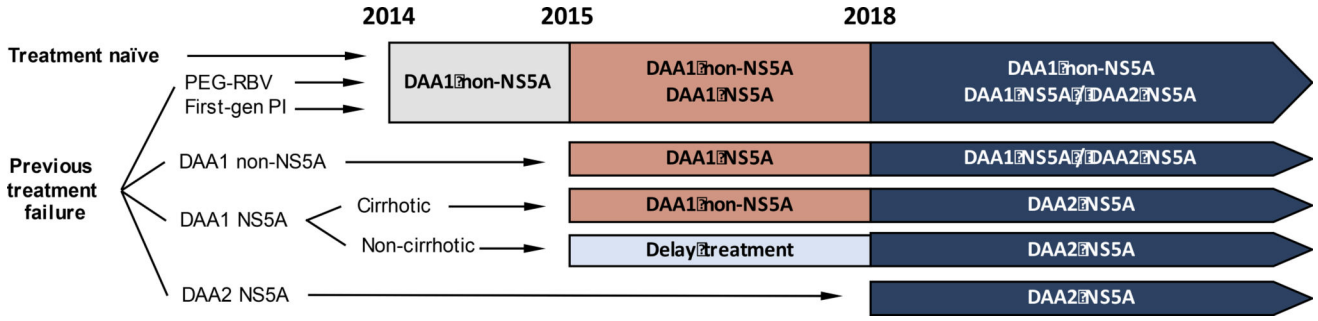



**Figure 1.**

Direct-acting antiviral treatment landscape from 2014 onwards by HCV genotypes 1, 2, 3 and 4–6. Figure shows the drug regimen type for a patient by treatment history (naïve or type of prior experience) and the year re-treatment is offered.

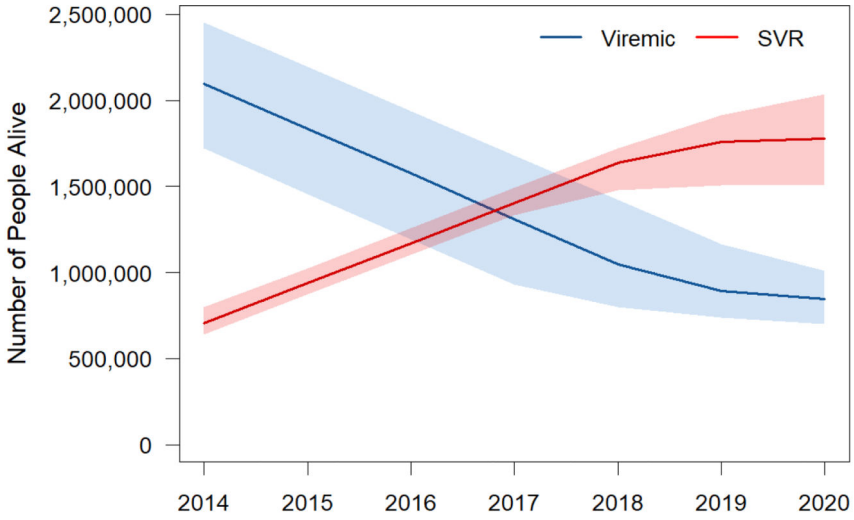
First generation PI (BOC/TEL+PEG+RBV) used for HCV genotype 1 only. Note that the timing of treatment waves is positioned such that the HCV patients will complete treatment in the given year (not necessarily initiate treatment in that year)

DAA1 non-NS5A includes the following drug combinations: SOF+PEG+/−RBV, SOF+/−RBV, SOF+SMV+/−RBV, and SMV+PEG+/−RBV.

DAA1 NS5A includes the following drug combinations: LDV/SOF+/−RBV, SOF+DCV, DCV+PEG+/−RBV, OBV/PTV/r+DSV+/−RBV, OBV/PTV/r+/−RBV, EBR/GZR, and SOF/VEL.

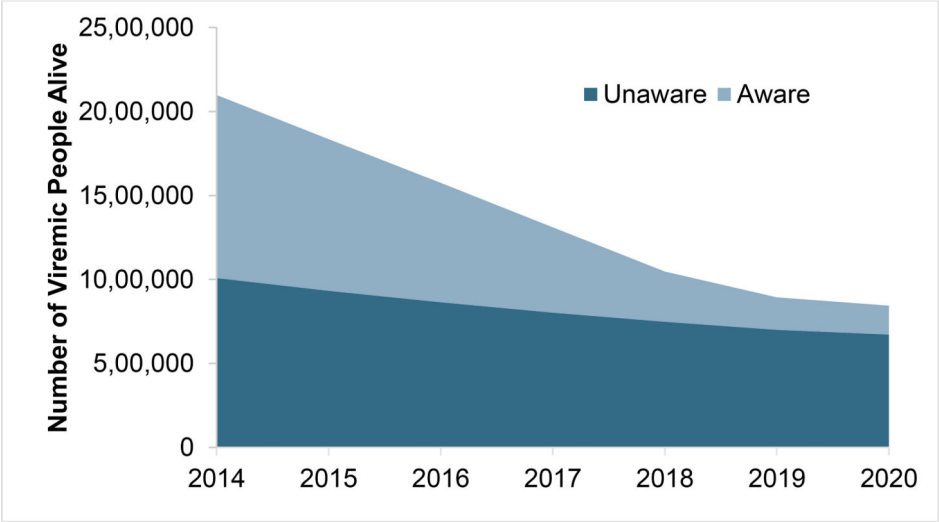
DAA2 NS5A includes the next wave of potential drug combinations such as SOF/VEL/VOX, and glecaprevir/pibrentasivr for selected subgroups. Though these drugs became available in mid 2017, the SVR status of patients receiving them would become available from 2018 onwards; therefore, we noted 2018 as the year for this wave of DAAs.

***Abbreviations***: PEG, peginterferon; RBV, ribavirin; BOC, boceprevir; TEL, telaprevir; DAA, direct-acting antiviral; NS5A, nonstructural protein 5A; SOF, sofosbuvir; SMV, simeprevir; LDV, ledipasvir; DCV, daclatasvir; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; DSV, dasabuvir; EBR, elbasvir; GZR, grazoprevir; VEL, velpatasvir; VOX, voxilaprevir




**A**. Number of patients alive who either are viremic or achieved SVR between 2014 and 2020. Bands show 95% uncertainty intervals generated by probabilistic sensitivity analysis.

*Abbreviation*: SVR, sustained virologic response




**A**. Number of patients alive viremic patients aware and unaware of their infection between 2014 and 2020.

**Figure 2.**

**A.** Number of patients alive viremic patients aware and unaware of their infection between 2014 and 2020. Bands show 95% uncertainty intervals generated by probabilistic sensitivity analysis.

*Abbreviation*: SVR, sustained virologic response

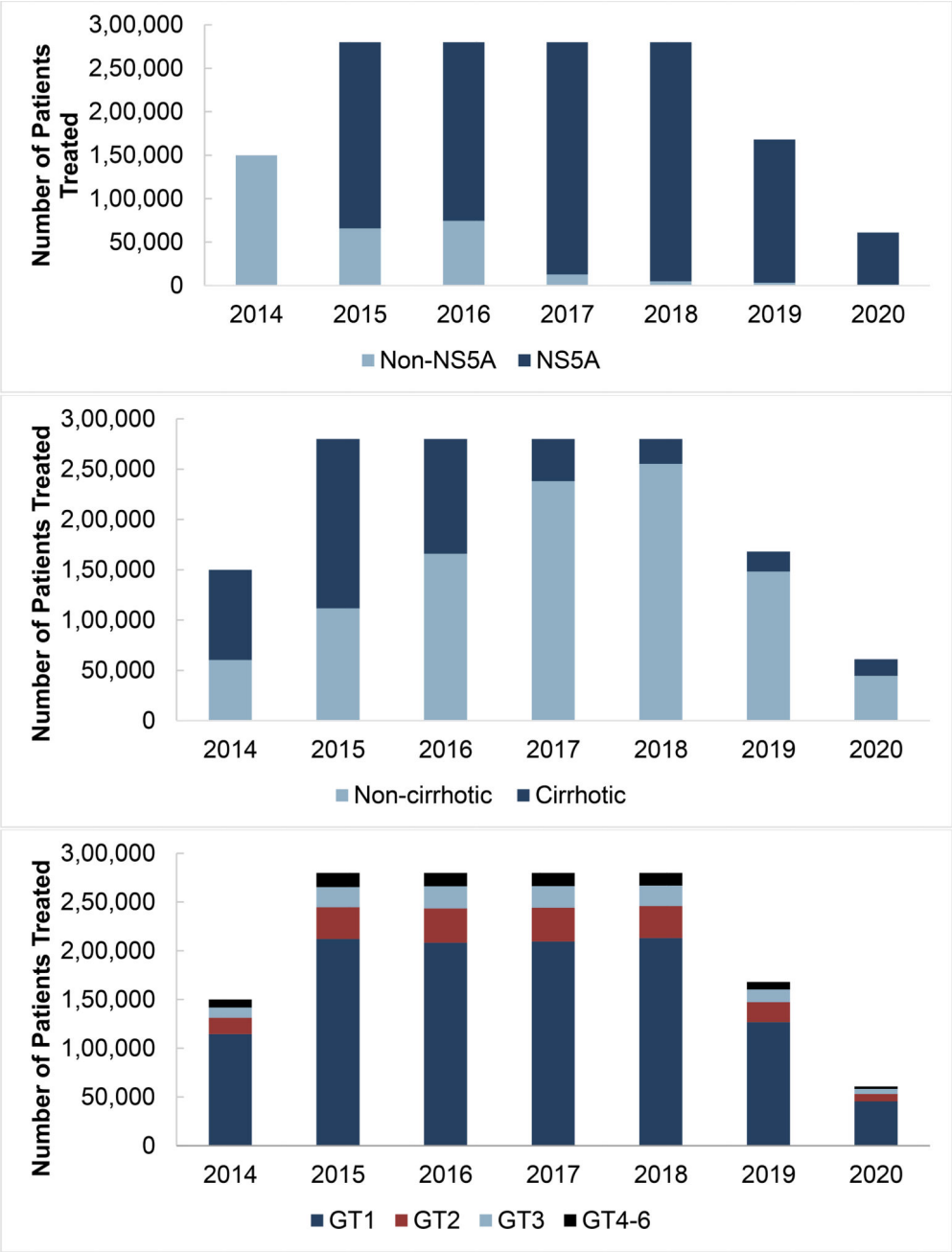
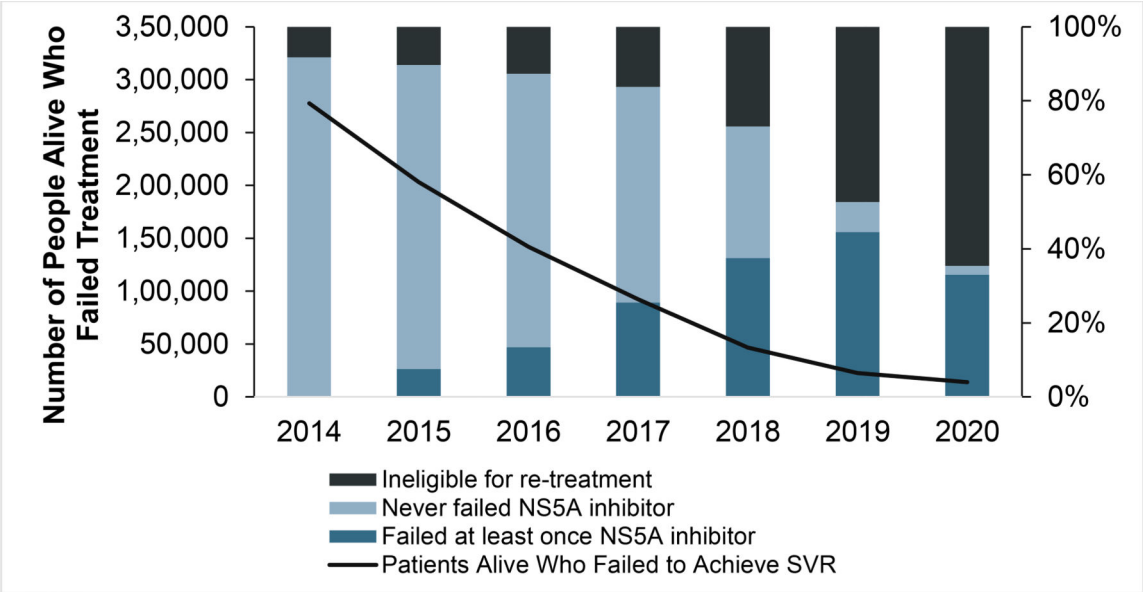
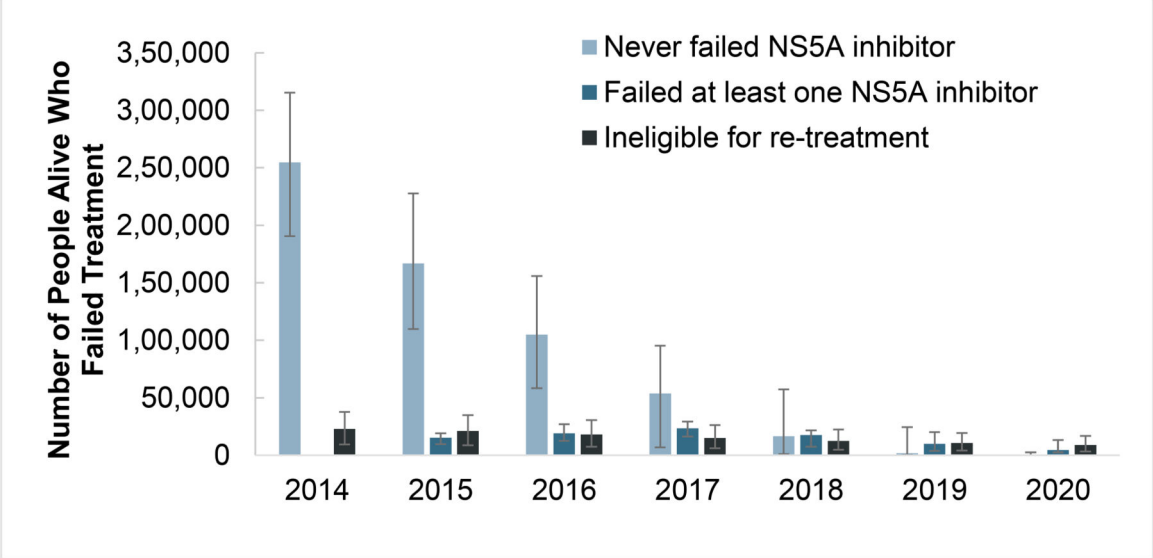



**Figure 3.**

**A–C.** Number of patients treated with DAAs each year from 2014 to 2020 by: (A) NS5A versus non-NS5A inhibitors, (B) presence or absence of cirrhosis, and (C) by HCV genotypes




**A**. Number of patients alive between 2014 and 2020 who failed to achieve SVR after one or more treatments

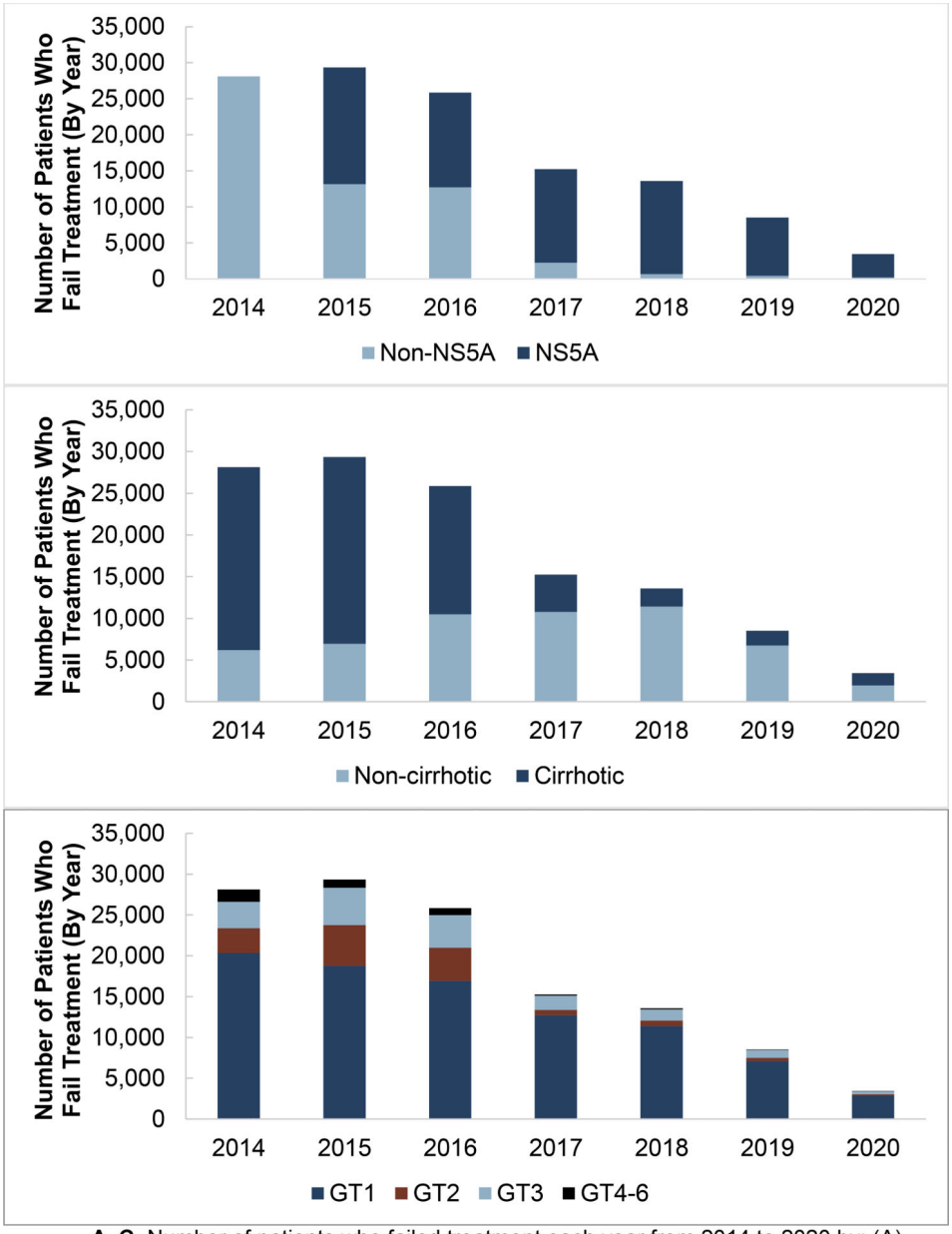



**B**. 95% uncertainty interval of the number of patients alive between 2014 and 2020 who failed to achieve SVR after one or more treatments

**Figure 4.**

**A.** Number of patients alive between 2014 and 2020 who failed to achieve SVR after one or more treatments

**B.** 95% uncertainty interval of the number of patients alive between 2014 and 2020 who failed to achieve SVR after one or more treatments




**A–C.** Number of patients who failed treatment each year from 2014 to 2020 by: (A) NS5A versus non-NS5A inhibitors, (B) presence or absence of cirrhosis, and (C) by HCV genotypes

**Figure 5.**

**A–C.** Number of patients who failed treatment each year from 2014 to 2020 by: (A) NS5A versus non-NS5A inhibitors, (B) presence or absence of cirrhosis, and (C) by HCV genotypes