HHS Public Access

Author manuscript

*J Clin Gastroenterol*. Author manuscript; available in PMC 2019 March 21.

Published in final edited form as:

*J Clin Gastroenterol*. 2018 August ; 52(7): 641–647. doi:10.1097/MCG.0000000000000857.

# Uptake of and Factors Associated With Direct-acting Antiviral Therapy Among Patients in the Chronic Hepatitis Cohort Study, 2014 to 2015

**Philip R. Spradling, MD**[*], **Jian Xing, PhD**[*], **Loralee B. Rupp, MS, MBA**[†], **Anne C. Moorman, MPH**[*], **Stuart C. Gordon, MD**[†], **Mei Lu, PhD**[†], **Eyasu H. Teshale, MD**[*], **Joseph A. Boscarino, PhD**[‡], **Mark A. Schmidt, PhD**[§], **Yihe G. Daida, PhD**[‖], **Scott D. Holmberg, MD, MPH**[*], and **Chronic Hepatitis Cohort Study (CHeCS) Investigators**

[*]National Centers for HIV, Viral Hepatitis, STD, and TB Prevention (NCHHSTP), Centers for Disease Control and Prevention (CDC), Division of Viral Hepatitis, Atlanta, GA

[†]Henry Ford Health System, Detroit, MI

[‡]Center for Health Research, Geisinger Health System, Danville, PA

[§]The Center for Health Research, Kaiser Permanente-Northwest, Portland, OR

[‖]The Center for Health Research, Kaiser Permanente-Hawaii, Honolulu, HI.

## Abstract

**Background:** Limited information is available describing the uptake of direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) infection among patients in general US health care settings. We determined the proportion of HCV-infected patients in the Chronic Hepatitis Cohort Study prescribed DAAs in 2014, who initiated treatment and identified characteristics associated with treatment initiation.

**Methods:** Uptake was defined as the proportion of HCV-infected patients with at least 1 clinical encounter in 2013 who were prescribed a DAA regimen during 2014 and initiated the regimen by August 2015. Using multivariable analysis, we examined demographic and clinical characteristics associated with receipt of DAAs.

**Results:** The cohort comprised 9508 patients; 544 (5.7%) started a DAA regimen. Higher annual income [adjusted odds ratios (aOR) 2.3 for income > $50K vs. <$30K], higher Fibrosis-4 score (aORs, 2.1, 2.0, and 1.4 for Fibrosis-4, >5.88, 3.25 to 5.88, 2.0 to 3.25, respectively, vs. <2.0), genotype 2 infection (aOR 2.2 vs. genotype 1), pre-2014 treatment failure (aOR 2.0 vs. treatment-

Address correspondence to: Philip R. Spradling, MD, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Division of Viral Hepatitis, Mailstop G37, 1600 Clifton Road NE, Atlanta, GA 30333, (pspradling@cdc.gov).

Chronic Hepatitis Cohort Study (CHeCS) Investigators: The CHeCS Investigators include the following investigators and sites: Scott D. Holmberg, Eyasu H. Teshale, Philip R. Spradling, Anne C. Moorman, Jim Xing, and Yuna Zhong, Division of Viral Hepatitis, National Centers for HIV, Viral Hepatitis, STD, and TB Prevention (NCHHSTP), Centers for Disease Control and Prevention (CDC), Atlanta, GA; Stuart C. Gordon, David R. Nerenz, Mei Lu, Lois Lamerato, Jia Li, Loralee B. Rupp, Nonna Akkerman, Nancy Oja-Tebbe, Talan Zhang, Sheri Trudeau, and Yueren Zhou, Henry Ford Health System, Detroit, MI; Joseph A. Boscarino, Zahra S. Daar, and Robert E. Smith, Center for Health Research, Geisinger Health System, Danville, PA; Yihe G. Daida, Connie M. Trinacty, and Carmen P. Wong, The Center for Health Research, Kaiser Permanente-Hawaii, Honolulu, HI; Mark A. Schmidt, Judy L. Donald, and Erin M. Keast, The Center for Health Research, Kaiser Permanente-Northwest, Portland, OR.

naive), and human immunodeficiency virus (HIV) coinfection (aOR 1.8 vs. HCV monoinfection) were associated with DAA initiation. Black race/ethnicity (aOR 0.7 vs. whites) and Medicaid coverage (aOR 0.5 vs. private insurance) were associated with noninitiation. Sex, age, comorbidity, previous liver transplant, and duration of follow-up were not associated with receipt of DAAs.

**Conclusions:** Among patients in these general US health care settings, uptake of DAA therapy was low in 2014, and especially so among minority and Medicaid patients. Systemic efforts to improve access to DAAs for all patients are essential to reduce morbidity and mortality from HCV infection.

### Keywords

direct-acting antivirals; hepatitis C; treatment uptake; chronic hepatitis cohort study

## INTRODUCTION

According to data collected in the National Health and Nutrition Examination Survey (NHANES) during 2003 to 2010, 3.6 million noninstitutionalized persons in the United States had been infected with hepatitis C virus (HCV), of whom approximately 2.7 million had chronic infection[1]; inclusion of populations not sampled in NHANES was later estimated to add at least 800,000 to the total number of persons with chronic infection.[2] However, only a small fraction of HCV-infected persons have been treated and only a modest subset of those, using interferon (IFN)-based therapy, have achieved a sustained viral response, considered a virologic cure. In an analysis of HCV-related clinical care provided during the era before availability of direct-acting antiviral treatment for HCV infection, investigators estimated that as of 2013 only 7% to 11% of all HCV-infected persons in the United States had been treated and only 5% to 6% had achieved sustained viral response.[3]

The approval and release of second generation DAAs in the United States, beginning in late 2013, revolutionized treatment of hepatitis C and offered the potential for widespread reduction in HCV infection prevalence. Compared with earlier, entirely IFN-based regimens, these newer agents are highly efficacious, tolerable, and substantially shorten the duration of treatment, albeit expensive.[4–8] Despite studies attesting to the cost-effectiveness of DAA-based treatment,[9–13] the combination of high price and the large number of infected persons (approximately 800,000 persons in the United States met the criteria for high and highest priority for treatment, according to one estimate[14]) has led private and public sector payers to limit patient access to these drugs.[15–17] Recently, however, a number of payers in rapid succession have eliminated requirements that limit DAAs to patients with advanced fibrosis.[18]

To our knowledge, there are no existing estimates of DAA uptake in US general health care settings. Published assessments have been typically limited to numbers of prescriptions filled, in the absence of an established denominator of eligible HCV-infected patients (eg, pharmacy companies), or confined to payer types (eg, Medicaid) or provider systems (eg, Veterans Administration [VA]).[19–24] Therefore, the objective of this analysis was to determine DAA uptake among HCV-infected patients in the Chronic Hepatitis Cohort Study

(CHeCS), an observational study conducted at 4 geographically and demographically disparate US sites, and to determine patient characteristics associated with receipt of DAAs.

## METHODS

### Study Population

We used data collected from patients with chronic HCV infection enrolled in the CHeCS, a study whose composition and criteria for inclusion have been summarized previously.[25] Briefly, the cohort was created on the basis of analysis of electronic health records and administrative data (supplemented with individual chart review by trained data abstractors) of over 2.7 million patients (18 years or older) who had at least 1 clinical service visit (ie, outpatient or inpatient, emergency department, or laboratory test) between January 1, 2006 and December 31, 2014 at 4 sites: Geisinger Health System in Danville, PA; Henry Ford Health System in Detroit, MI; Kaiser Permanente-Northwest in Portland, OR; and Kaiser Permanente of Honolulu, HI. Complete follow-up observation data were available through August 31, 2015. Chronic HCV infection was confirmed based upon chart review and ≥ 1 positive HCV-RNA tests before antiviral treatment. Data collected included patient demographics, medical encounters, receipt of and response to HCV antiviral therapy, and laboratory and biopsy results. The parent study protocol was reviewed and approved by an institutional review board at each participating site.

For the purposes of this substudy, uptake was defined as the proportion of patients in the chronic hepatitis C cohort still infected with HCV (ie, patients never treated and those who failed previous treatment) as of December 31, 2013 who were prescribed a DAA regimen (with or without IFN) from January 1, 2014 to December 31, 2014 and started the regimen by August 31, 2015. Treatment prescription and initiation was ascertained by electronic prescription and pharmacy records and confirmed by patient chart review (ie, actual physician/nurse notation in clinic notes). To determine the population of persons still infected with HCV and eligible for DAA therapy at the beginning of 2014, we limited the entire CHeCS hepatitis C cohort to patients who had had at least 1 hospital, clinic or emergency department visit, or pharmacy encounter during 2013, and excluded those who died or were treated and achieved a sustained virological response before January 1, 2014.

### Statistical Analysis

After determining uptake, we compared the socio-demographic (ie, study site, age, sex, race/ethnicity, annual income according to census tract geocode, and insurance status) and clinical [ie, pretreatment Fibrosis-4 (FIB4) score among patients who initiated DAAs or most recent score before 2014 among those who did not, pre-2014 treatment status, body mass index, HCV genotype, Charlson comorbidity score, liver transplant history, and hepatitis B virus and human immunodeficiency virus (HIV) coinfection status] characteristics of patients who initiated and those who did not initiate DAA therapy during the study periods using logistic multivariable analysis, controlling for all variables in the model. FIB4 score, a noninvasive marker for hepatic fibrosis calculated using patient age, serum aminotransferase levels, and platelet count, was stratified into 4 categories (< 2.0, 2.0 to 3.25, 3.26 to 5.88, ≥ 5.88), corresponding to progressively higher degrees of fibrosis, the

latter category having been validated as predictive of cirrhosis in this cohort.[26] Three categories were used for the Charlson comorbidity index, corresponding to the number of medical comorbid diagnoses present at the time of HCV infection diagnosis (ie, 0, 1, ≥ 2).[27,28] All statistical analyses were conducted using SAS Enterprise Guide version 5.1.

We plotted the number of patients who initiated a DAA regimen during each month of the study interval (drugs prescribed during 2014 but could be initiated as late as August 31, 2015), according to the agents included in the regimen. The regimens included sofosbuvir (SOF)-based without ledipasvir (LDV) [ie, SOF ± simeprevir or daclatasvir ± ribavirin (RBV)] and SOF with LDV ± RBV. No patients received an ombitasvir-containing regimen during the study period. We also examined the distribution of patients for whom the time interval between DAA prescription and initiation was <1 month, 1 to 3 months, and >3 months, and determined the provider type who prescribed the regimen (ie, gastroenterologist/hepatologist, infectious disease practitioner, primary care, or other).

## RESULTS

The CHeCS chronic hepatitis C cohort during 2006 to 2014 comprised 17,750 patients. After excluding hepatitis C patients who had died (2975 or 17%) or were treated and cured before January 1, 2014 (2238 or 12%), and those without a clinical encounter during 2013 (3029 or 17%), 9508 patients were classified as still HCV-infected and thus potentially eligible to initiate a DAA regimen during the study period (Fig. 1). Among these 9508 patients, 58.7% were male, and 64.6% and 23.1% were non-Hispanic white and black, respectively; 79.8% were aged 41 to 70 years; 46.0% and 12.8% had private insurance and Medicaid, respectively; and 24.4% and 27.3% had an annual income <$30,000 and > $50,000, respectively. With regard to clinical characteristics, 17.5% had failed earlier treatment, 78.4% had HCV genotype 1 infection, 3.3% were HIV coinfected, 4.9% had had a liver transplant, and 13.7% and 13.8% had a pretreatment FIB4 score of 3.25 to 5.88 and >5.88, respectively (Table 1).

Of the 9508 patients with HCV infection at the start of the study period, 544 (5.7%) initiated treatment from January 1, 2014 to August 31, 2015; 31 (5.7% of 544) initiated a DAA regimen that included IFN. Uptake was low even among patients with advanced liver disease, according to FIB4 score: 8.6% among those with a pretreatment score of 3.25 to 5.88 and 11.6% among those with a score >5.88 (Table 1).

Table 1 also shows the results of the multivariable analysis comparing characteristics of patients who initiated and those who did not initiate DAA treatment during the study period. Characteristics associated with receipt of a DAA regimen included higher annual income [adjusted odds ratio (aOR) 1.7; 95% confidence interval (CI), 1.2–2.3 and aOR, 2.3; 95% CI, 1.7–3.2 for income ≥ $30,000 to $50,000 and >$50,000, respectively, compared with < $30,000), higher FIB4 score (aOR, 1.4; 95% CI, 1.1–1.9; aOR, 2.0; 95% CI, 1.5–2.6; and aOR, 2.1; 95% CI, 1.6–2.8 for scores 2.0 to 3.25, 3.25 to 5.88, and >5.88, respectively, compared with a score <2.0), previous failed treatment (aOR, 2.0; 95% CI, 1.6–2.4, compared with no previous treatment), genotype 2 HCV infection (aOR, 2.2; 95% CI, 1.7–3.0, compared with genotype 1 infection), and HIV coinfection (aOR, 1.8; 95% CI, 1.2–2.8,

compared with HCV monoinfection). Characteristics associated with a lower likelihood of DAA initiation included non-Hispanic Black race (aOR, 0.7; 95% CI, 0.5–0.9, compared with non-Hispanic white race), Medicaid coverage (aOR, 0.5; 95% CI, 0.3–0.8, compared with private insurance), and receipt of care at one of the study sites (aOR, 0.3; 95% CI, 0.2–0.5, compared with a study site that offered hepatology referral care).

Figure 2 depicts the treatment initiation date among patients prescribed a DAA regimen in 2014, according to the number of patient regimens and DAA components of the regimen received. Among patients who initiated during the earlier phase of the period (January 2014 to October 2014), SOF-based regimens without LDV ± RBV predominated, whereas during the latter phase, and commensurate with its FDA approval in October 2014, SOF with LDV ± RBV was the principal regimen initiated. Nearly all treatment initiations in 2015 were from prescriptions for SOF with LDV ± RBV written in 2014. The distribution of intervals between prescription and treatment initiation dates are shown in Figure 3: the interval was <1 months among 66% of patients, 1 to 3 months among 17%, and >3 months among 17%. Among provider types who prescribed DAA regimens, 87% were gastroenterologists or hepatologists, 12% were infection disease specialists, <1% were primary care providers, and <2% were “other” providers (Fig. 4).

## DISCUSSION

Our study is the first to estimate treatment uptake in a large cohort of patients with HCV infection in general health care settings during the first year following second generation DAA approval in the United States. A particular advantage of the CHeCS is that data are collected from patients under real-world conditions, in the absence of a study protocol that dictates to providers the type and frequency of clinical assessment and interventions. Furthermore, patients in the CHeCS represent a variety of sociodemographic backgrounds, have access to primary care providers and specialists, and have their clinical care financed through the private and public sector. As the study sites encompass broad catchment areas in their respective regions of the country, we believe our findings are likely representative of HCV care in other general US health care settings. We were also able to establish a denominator of HCV-infected patients who were potentially eligible to receive DAAs in 2014, from which we were able to estimate treatment uptake in the entire cohort.

In this analysis, we found that only 5.7% of HCV-infected patients potentially eligible for treatment in the CHeCS initiated a DAA regimen prescribed in 2014. Reports of DAA uptake in other US settings, which include the VA, are slightly better. A recent report from the VA of nearly 150,000 patients estimated that 10.2% had received treatment during the first 16 months of DAA approval.[24] In 2 separate studies evaluating much smaller cohorts of HIV/HCV coinfected patients, DAA treatment uptake was 14% and 6% over time periods similar to the VA report.[29,30]

We found that receipt of DAAs was associated with sociodemographic and clinical characteristics. Higher annual income, non-Medicaid insurance coverage, and white race were independently associated with receipt of DAAs, as were severe liver disease (ie, higher FIB4 score), genotype 2 infection, previous treatment failure, and HIV coinfection. Patients

affiliated with one of the sites, a staff model health maintenance organization, had a 70% reduced odds of treatment compared with a tertiary hepatology center, suggesting that access to specialty providers or restrictive drug formulary policies may have affected receipt of DAAs. Although American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA) HCV treatment guidelines at the time noted that it was "most appropriate to treat those at greater risk of disease complications before treating those with less advanced disease,"[31] we found that DAA uptake was low even among patients with moderate to severe liver disease (ie, 8.6% among those with a pretreatment FIB4 score of 3.25 to 5.88 and 11.6% among those with a score >5.88). HCV-infected patients with HIV coinfection are at high risk for liver disease progression and, accordingly, were among those groups listed as high priority for DAA treatment in the earlier iteration of HCV treatment guidelines; we found that HIV coinfected patients in our study were nearly twice as likely to receive DAAs compared with those with HCV monoinfection. Patients in our study who had previously failed treatment were twice as likely to receive DAAs as those never treated, which may have reflected more advanced liver disease in the former, and some data suggest that IFN failure may exacerbate the progression of liver disease.[32,33] Although patients with genotype 2 infection constituted only 10% of the cohort, they were twice as likely to receive DAAs compared with patients with genotype 1 infection, perhaps reflecting that genotype 2 infection is easier to cure. In the pre-DAA era, patients with genotype 2 had a relatively high frequency of sustained viral response to IFN-based treatment.[34] In our multivariable analysis, we controlled for study site, race, treatment history, income, and insurance status, so it is not apparent that the frequency of these covariates among patients with genotype 2 infection affected our finding.

Restriction of DAA access among Medicaid beneficiaries has been well-described in the literature and widely reported in the press,[15,16,35] and indeed, Medicaid patients in our study had a 50% reduced odds of receiving DAAs compared with those with private insurance. We also found that black patients had a 30% reduced odds of receiving DAAs compared with whites, and patients with lower annual income less likely to receive DAAs compared with those with higher annual incomes. Similarly, in the aforementioned VA study, black patients had of a 21% reduced odds of DAA treatment compared with whites.[24] As a disproportionate number of persons with HCV infection are black, as are those with low income, our findings highlight the urgent need for targeted efforts to improve access to DAAs.

It is important to be mindful that our uptake estimate is likely high in the context of all patients in these CHeCS-affiliated health care organizations. In an earlier study of CHeCS patients, we estimated that only one-half of HCV infections expected in the study population from which the cohort was drawn had been identified through testing[36]; among these patients, 17% had advanced liver disease at the time of diagnosis, indicating long-term infection despite having had, on average, 6 years in their respective health systems.[37] Therefore, the denominator we used in this study to estimate uptake could likely have been substantially higher if all HCV-infected patients in the CHeCS-affiliated health care organizations had been identified, and thus have resulted in a lower uptake estimate. This underscores the importance of testing and identifying all patients with HCV infection so that access to treatment can be monitored and completely delivered.

It is also important to note that what we estimated was *effective* uptake, in the sense that our measurement was dependent purely on the number of patients who actually started DAA treatment, and not on the basis of what uptake might have been if all DAA prescriptions written by providers in 2014 had been filled and consumed. It is certainly possible that some providers, after failed attempts to gain approval for prescriptions for some patients on the basis of insurance or liver fibrosis status, may have decided not to attempt prescribing for other such patients. Thus, our estimate of uptake was unlikely to be reflective of provider preferences, prescription practices, or awareness of DAA treatment indications; on the contrary, it was more likely shaped by systemic factors affiliated with drug costs and payer policies. As our study interval coincided with the period immediately after approval and release of the second generation DAAs, it is quite possible that estimates of DAA uptake in subsequent years may reveal improvement, in some degree stemming from decreasing drug costs and more permissive prescription policies from payers and drug benefit managers. In this respect, this study will serve as a baseline against which estimates of uptake during future periods can be compared.

There are several limitations to this analysis. As mentioned, our period of study encompassed the first calendar year after approval of the second generation DAAs. Since then, reduction in systems barriers, drug costs, and availability of newer agents may have improved uptake. Although our study cohort is large and reflective of real-life clinical care at 4 sites across the United States with broad catchment areas, these results may not be generalizable to other settings or cohorts with different characteristics. Also, having to rely primarily on electronic health data made it difficult to discern and quantify the effect of other factors potentially associated with uptake; these could include other patient-related (eg, drug/alcohol use, mental health issues, awareness of disease severity/treatment options), provider-related (eg, awareness of and futility related to known systems barriers to treatment approval), and systems-related (eg, limited availability of DAAs on formularies, eligibility restrictions imposed by payers) factors. It is possible, too, that some patients could have been prescribed a regimen in 2014 but left the CHeCS before initiating the regimen, thus falsely lowering our estimate of uptake. Although we reviewed electronic prescription records and fill orders, supplemented by patient medical chart review, it is possible that we missed a small number of patients who were prescribed DAAs in 2014 and initiated by August 2015. Such an oversight, too, would have led to our providing a falsely low uptake estimate.

Current HCV treatment guidelines state “treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy.”[31] In that respect, with an annual uptake of 5.7%, which amounted to 544 patients treated per year, it would take 17.5 years to treat our entire HCV-infected cohort, and in the meantime those left untreated would experience progressive liver injury and accrue greater health care costs. According to model-based predictions, even if annual treatment capacity (with highly efficacious antiviral agents) was unlimited beginning in 2014, by 2050 the cumulative incidence of decompensated cirrhosis cases, hepatocellular carcinoma cases, liver-related deaths, and liver transplants in the United States would be 165,100, 149,200, 280,400, and 24,500, respectively.[38]

Aside from improving DAA access by dramatically reducing the price of drugs, which has begun to occur as the result of market forces[39] increasing treatment capacity will entail increasing the number of providers who are trained (and permitted by payers) to administer them. As our study revealed, approximately 99% of prescribing providers were medical subspecialists; most of these were gastroenterologists or hepatologists, and only a small fraction overall (12%) were infectious disease physicians. Expansion of the number of treating providers will need to involve the inclusion of primary care clinicians, as there insufficient numbers of subspecialists (gastroenterologists, hepatologists, and infectious disease specialists) in the United States to be the sole DAA prescribers.[40–42] To this end, the advent of pan-genotypic DAAs and shorter-course regimens should reduce the complexity of treatment, enabling more clinicians to be involved in the treatment of HCV-infected patients.

## Acknowledgments

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

The CHeCS investigation follows the guidelines of the US Department of Health and Human Services regarding the protection of human subjects.

Henry Ford Health System receives funding for CHeCS from the Centers for Disease Control and Prevention and from Gilead Sciences. CHeCS was previously funded through May 2016 by the CDC Foundation, which received grants from AbbVie; Genentech, A Member of the Roche Group; Gilead Sciences; Janssen Pharmaceuticals, Inc. and Vertex Pharmaceuticals; past partial funders include Bristol-Myers Squibb. Granting corporations do not have access to CHeCS data and do not contribute to data analysis or writing of manuscripts.

S.C.G. receives grant/research support from AbbVie Pharmaceuticals, Bristol-Myers Squibb, Conatus, CymaBay, Exalenz BioScience, Gilead Pharmaceuticals, Intercept Pharmaceuticals, and Merck. He is also a consultant/advisor for Abbvie, Bristol-Myers Squibb, CVS Caremark, Gilead, Intercept, and Merck, and serves as a speaker/ teacher in programs sponsored by Gilead Pharmaceuticals and Intercept Pharmaceuticals. The remaining authors declare that they have nothing to disclose.

## REFERENCES

1. Denniston MM, Jiles RB, Drobeniuc J, 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. [PubMed: 24737271]
2. Edlin BR, Eckhardt BJ, Shu MA, et al. Toward a more accurate estimate of the prevalence of hepatitis C in the United States. Hepatology 2015;62:1353–1363. [PubMed: 26171595]
3. Holmberg SD, Spradling PR, Moorman AC, et al. Hepatitis C in the United States. N Engl J Med 2013;368:1859–1861. [PubMed: 23675657]
4. Brennan T, Shrank W. New expensive treatments for hepatitis C infection. JAMA 2014;312:593–594. [PubMed: 25038617]
5. Chung RT, Baumert TF. Curing chronic hepatitis C—the arc of a medical triumph. New Engl J Med 2014;370:1576–1578. [PubMed: 24720678]
6. Ornstein C New hepatitis C drugs are costing Medicare billions. Washington Post 3 29, 2015 Available at: https://www.washingtonpost.com/national/health-science/medicare-spent-45-billion-on-new-hepatitis-c-drugs-last-year-data-shows/2015/03/29/66952dde-d32a-11e4-a62f-ee745911a4ff_story.html. Accessed June 30, 2016.
7. Walker J Expensive hepatitis C medications drive prescription-drug spending. Wall Street Journal 3 10, 2015 Available at: http://www.wsj.com/articles/expensive-hepatits-c-medication-drive-prescription-drug-spending-1425960214. Accessed June 30, 2016.

8. Barker T CMS enters the hepatitis C drug pricing debate. Medicaid and the Law 11 9, 2015 Available at: http://www.medicaidandthelaw.com/2015/11/09/cms-enters-the-hepatitis-c-drug-pricing-debate/. Accessed June 30, 2016.
9. Najafzadeh M, Anderson K, Shrank WH, et al. Cost-effectiveness of novel regimens for the treatment of hepatitis C virus. Ann Intern Med 2015;162:407–419. [PubMed: 25775313]
10. Leidner AJ, Chesson HW, Xu F, et al. Cost-effectiveness of hepatitis C treatment for patients in early stages of liver disease. Hepatology 2015;61:1860–1869. [PubMed: 25677072]
11. Rein DB, Wittenborn JS, Smith BD, et al. The cost-effectiveness, health benefits, and financial costs of new antiviral treatments for hepatitis C virus. Clin Infect Dis 2015; 61:157–168. [PubMed: 25778747]
12. Linas BP, Barter DM, Morgan JR, et al. The cost-effectiveness of sofosbuvir-based regimens for treatment of hepatitis C virus genotype 2 or 3 infection. Ann Intern Med 2015;162:619–629. [PubMed: 25820703]
13. Younossi ZM, Singer ME, Mir HM, et al. Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. J Hepatol 2014;60:530–537. [PubMed: 24269472]
14. Xu F, Leidner AJ, Tong X, et al. Estimating the number of patients infected with chronic hepatitis C virus meeting 'highest' or 'high' priority treatment criteria in the United States. Am J Public Health 2015;105:1285–1289. [PubMed: 25973816]
15. Barua S, Greenwald R, Grebely J, et al. Restrictions for Medicaid reimbursement of sofosbuvir for the treatment of hepatitis C virus infection in the United States. Ann Intern Med 2015;163:215–224. [PubMed: 26120969]
16. Canary LA, Klevens RM, Holmberg SD. Limited access to new hepatitis C virus treatment under state Medicaid programs. Ann Intern Med 2015;163:226–228. [PubMed: 26121095]
17. Chidi AP, Bryce CL, Donohue JM, et al. Economic and public health impacts of policies restricting access to hepatitis C treatment for Medicaid patients. Value Health 2016;19: 326–334. [PubMed: 27325324]
18. Jacobson IM. Watching the dominoes of restriction begin to fall. HCV Next; 7 2016 Available at: http://www.healio.com/hepatology/hepatitis-c/news. Accessed July 29, 2016.
19. Brennan TA, Lotvin A, Shrank W. Analysis of "real world" Solvaldis (sofosbuvir) use and discontinuation rates. CVS Health 2014 Available at: https://cvshealth.com/sites/default/files/styles/SovaldiUseAndDiscontinuation_ResearchArticle_PDF.pdf. Accessed on July 1, 2016.
20. Lotvin A, Shrank W, Chang A, et al. Harvoni utilization in the weeks after launch: patterns and implications. CVS Health 2014 Available at: https://cvshealth.com/sites/default/files/styles/CVS_Health_Harvoni_Utilization_Post_Launch.pdf. Accessed on July 1, 2016.
21. Clements KM, Clark RE, Lavitas P, et al. Access to new medications for hepatitis C for Medicaid members: a retrospective cohort study. J Manag Care Spec Pharm 2016; 22:714–722. [PubMed: 27231798]
22. Veterans Administration. State of care for veterans with hepatitis C 2014 9 2014 Available at: http://www.hepatitis.va.gov/pdf/HCV-State-of-Care-2014.pdf. Accessed July 1, 2016.
23. Gidwani R, Barnett PG, Goldhaber-Fiebert JD, et al. Uptake and utilization of directly-acting antiviral medications for hepatitis C infection in U.S. veterans. J Viral Hepat 2015;22:489–495. [PubMed: 25417805]
24. Kanwal F, Kramer JR, El-Serag HB, et al. Race and gender differences in the use of direct acting antiviral agents for hepatitis C virus. Clin Infect Dis 2016;63:291–299. [PubMed: 27131869]
25. Moorman AC, Gordon S, Rupp L, et al. Baseline characteristics and mortality among people in care for chronic viral hepatitis: the chronic hepatitis cohort study. Clin Infect Dis 2013;56:40–50. [PubMed: 22990852]
26. Li J, Gordon SC, Rupp LB, et al. The validity of serum markers for fibrosis staging in chronic hepatitis B and C. J Viral Hepatitis 2014;21:930–937.
27. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383. [PubMed: 3558716]

28. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–619. [PubMed: 1607900]
29. Cope R, Glowa T, Faulds S, et al. Treating hepatitis C in a Ryan White-funded HIV clinic: has the treatment uptake improved in the interferon-free directly active antiviral era? AID patient care STDs 2016;30:51–55.
30. Kuniholm MH, Leach T, Lunievicz J, et al. Hepatitis C direct acting antiviral therapies in a New York City HIV/AIDS special needs plan: uptake and barriers. AIDS Patient Care STDs 2015;29:643–645. [PubMed: 26669792]
31. American Association for the Study of Liver Diseases/ Infectious Diseases Society of America. Recommendations for Testing, Managing, and Treating Hepatitis C Available at: http://www.hcvguidelines.org/. Accessed June 22, 2016.
32. Lu M, Li J, Rupp LB, et al. Hepatitis C treatment failure is associated with increased risk of hepatocellular cancer. J Viral Hepat 2016;23:718–729. [PubMed: 27028626]
33. Baran B, Gulluoglu M, Soyer OM, et al. Treatment failure may lead to accelerated fibrosis progression in patients with chronic hepatitis C. J Viral Hepatitis 2014;21:111–120.
34. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335–1374. [PubMed: 19330875]
35. ReV Lo, Gowda C, Urick PN, et al. Disparities in absolute denial of modern hepatitis C therapy by type of insurance. Clin Gastroenterol Hepatol 2016;14:1035–1043. [PubMed: 27062903]
36. Spradling PR, Rupp L, Moorman AC, et al. Hepatitis B and C virus infection among 1.2 million persons with access to care: factors associated with testing and infection prevalence. Clin Infect Dis 2012;55:1047–1055. [PubMed: 22875876]
37. Moorman AC, Xing J, Ko S, et al. Late diagnosis of hepatitis C virus infection in the Chronic Hepatitis Cohort Study (CHeCS): missed opportunities for intervention. Hepatology 2015;61:1479–1484. [PubMed: 25131217]
38. Kabiri M, Jazwinski AB, Roberts MS, et al. The changing burden of hepatitis C virus infection in the United States: model-based predictions. Ann Intern Med 2014;161:170–180. [PubMed: 25089861]
39. Pezalla E Pricing pressures: how the business of medicine affects the price of therapy. HCV Next; 11 2015 Available at: http://www.healio.com/hepatology/hepatitis-c/news. Accessed on July 29, 2016.
40. Kottilil S, Wright M, Polis MA, et al. Treatment of hepatitis C virus infection: is it time for the internist to take the reins? Ann Intern Med 2014;161:443–444. [PubMed: 25222390]
41. Arora S, Thornton K, Murata G, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. N Engl J Med 2011;364:2199–2207. [PubMed: 21631316]
42. Mitruka K, Thornton K, Cusick S, et al. Expanding primary care capacity to treat hepatitis C virus infection through an evidence-based care model—Arizona and Utah, 2012–2014. MMWR 2015;63:393–398.

## KEY POINTS

In a large cohort of hepatitis C patients with access to integrated health care in the United States, only 5.7% of patients prescribed direct-acting antiviral (DAA) therapy in 2014 initiated treatment by September 2015. Note: The data included in this manuscript were delivered as an oral presentation at the American Association for the Study of Liver Diseases annual meeting “The Liver Meeting” in Boston, MA, on November 13, 2016.

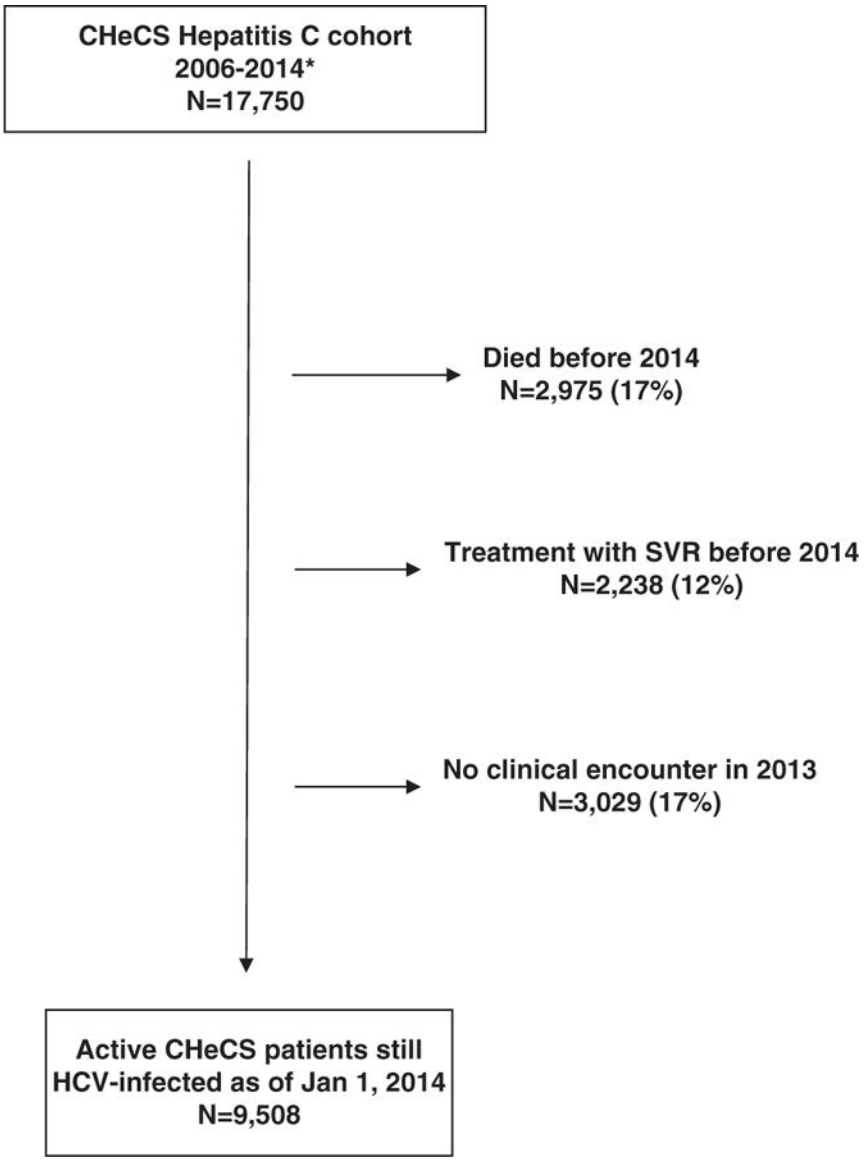


**FIGURE 1.**

Flow-chart depicting derivation of the study cohort. *Observation data available through August 31, 2015. CHeCS indicates Chronic Hepatitis Cohort Study; HCV, hepatitis C virus; SVR, sustained viral response.

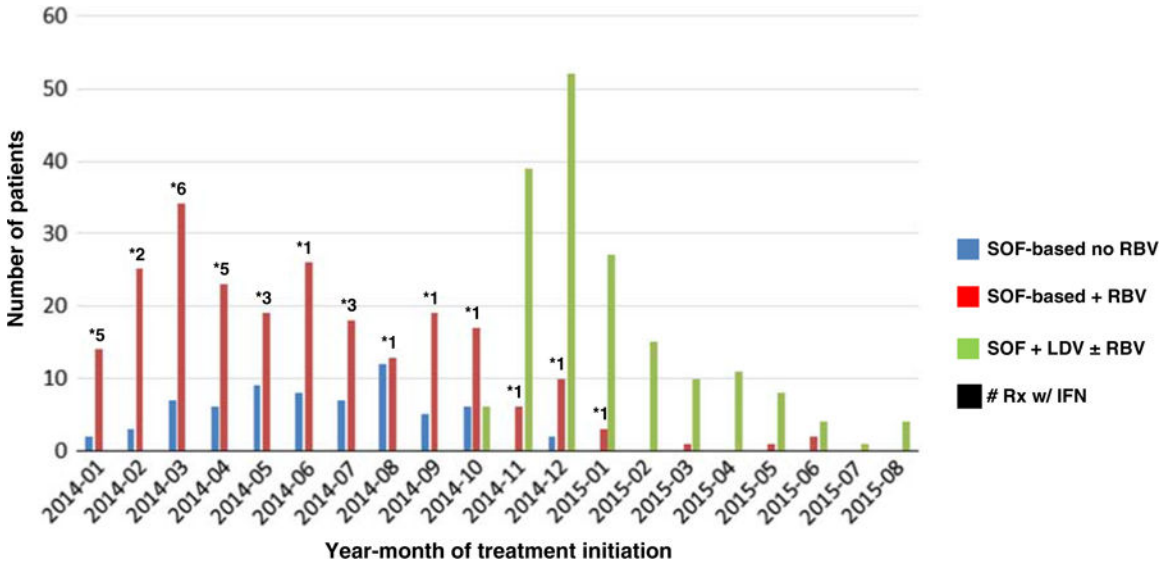


**FIGURE 2.**

Number of hepatitis C virus-infected patients initiating direct-acting antiviral therapy (*y*-axis) by month (*x*-axis), according to regimen, January 2014 to August 2015, Chronic Hepatitis Cohort Study. All treatment initiations were on the basis of prescription of drugs during 2014; initiation dates of regimens prescribed in 2015 are not shown. IFN indicates interferon; LDV, ledipasvir.

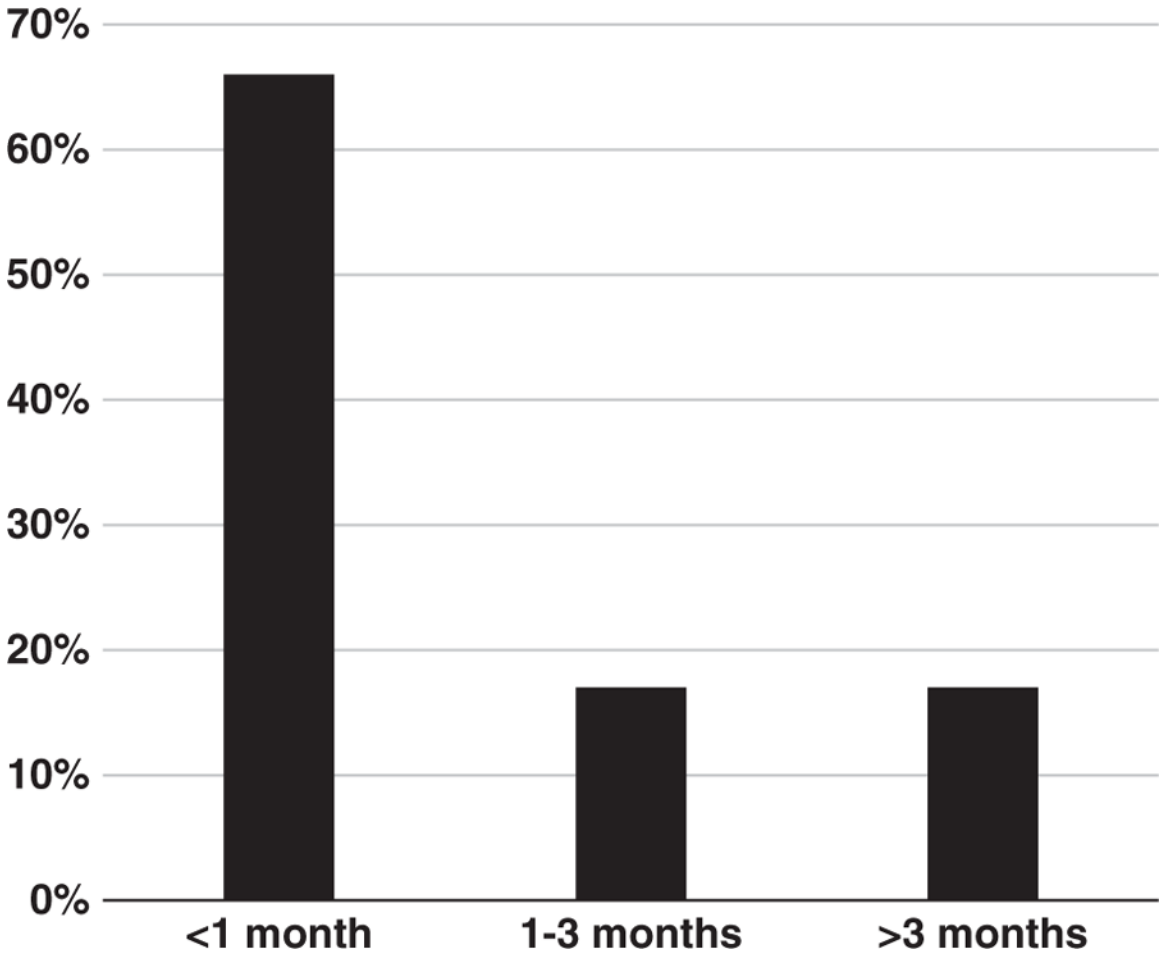


**FIGURE 3.**
Time interval between prescription and initiation of direct-acting antiviral regimens among patients with hepatitis C, Chronic Hepatitis Cohort Study, 2014 to 2015.

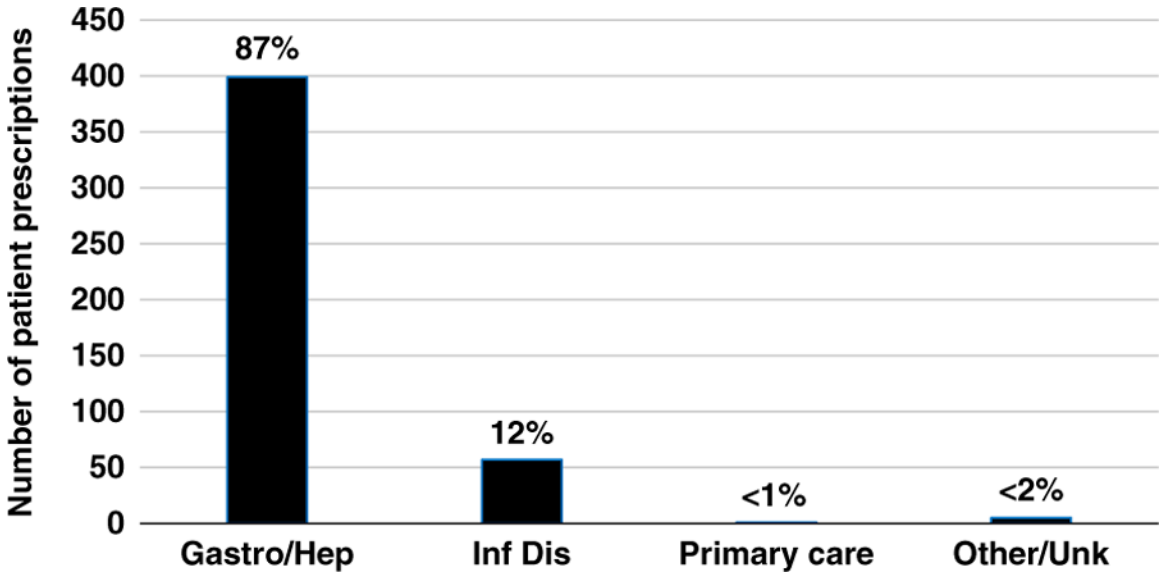


**FIGURE 4.**

Types of providers who prescribed direct-acting antiviral regimens for patients with hepatitis C, Chronic hepatitis Cohort Study, 2014 to 2015.

**TABLE 1.**

Characteristics of HCV-infected Patients Who Did and Did Not Initiate Direct-acting Antiviral Therapy, Chronic Hepatitis Cohort Study

| | n (%) | | | | |
|---|---|---|---|---|---|
| **Characteristics** | **Overall** | **Initiated Therapy by August 31, 2015** | **Did Not Initiate Therapy** | **Adjusted Odds Ratio (95% Confidence Interval)** | ***P*** |
| Total | 9508 | 544 (5.7) | 8964 (94.3) | — | — |
| Sex | | | | | |
| Male | 5581 (58.7) | 357 (6.4) | 5224 (93.6) | 1.1 (0.9–1.4) | 0.25 |
| Female | 3927 (41.3) | 187 (4.8) | 3740 (95.2) | ref | — |
| Race/ethnicity | | | | | |
| Non-Hispanic white | 6140 (64.6) | 364 (5.9) | 5776 (94.1) | Ref | — |
| Non-Hispanic black | 2193 (23.1) | 106 (4.8) | 2087 (95.2) | 0.7 (0.5–0.9) | 0.005 |
| Other | 1175 (12.4) | 74 (6.3) | 1101 (93.7) | 0.9 (0.7–1.2) | 0.48 |
| Age group (y) | | | | | |
| ≤30 | 642 (6.8) | 14 (2.2) | 628 (97.8) | Ref | — |
| 31–40 | 758 (8.0) | 19 (2.5) | 739 (97.5) | 1.1 (0.5–2.6) | 0.79 |
| 41–50 | 1186 (12.5) | 58 (4.9) | 1128 (95.1) | 1.6 (0.7–3.4) | 0.24 |
| 51–60 | 3735 (39.3) | 221 (5.9) | 3514 (94.1) | 1.4 (0.7–2.8) | 0.38 |
| 61–70 | 2658 (28.0) | 206 (7.8) | 2452 (92.2) | 1.6 (0.8–3.3) | 0.22 |
| ≥71 | 529 (5.6) | 26 (4.9) | 503 (95.1) | 1.0 (0.4–2.3) | 0.93 |
| Insurance status | | | | | |
| Private | 4371 (46.0) | 260 (5.9) | 4111 (94.1) | Ref | — |
| Medicaid | 1215 (12.8) | 34 (2.8) | 1181 (97.2) | 0.5 (0.3–0.8) | 0.003 |
| Medicare | 3004 (31.6) | 220 (7.3) | 2784 (92.7) | 1.0 (0.8–1.2) | 0.85 |
| Other/unknown | 918 (9.7) | 30 (3.3) | 888 (96.7) | 0.6 (0.4–1.1) | 0.085 |
| Annual income (by census tract geocode) | | | | | |
| < $30K | 2321 (24.4) | 77 (3.3) | 2244 (96.7) | Ref | — |
| ≥$30–50K | 4336 (45.6) | 243 (5.6) | 4093 (94.4) | 1.7 (1.2–2.3) | < 0.001 |
| > $50K | 2594 (27.3) | 210 (8.1) | 2384 (91.9) | 2.3 (1.7–3.2) | < 0.001 |
| Not available | 257 (2.7) | 14 (5.4) | 243 (94.6) | 1.6 (0.8–3.2) | 0.175 |
| Study site | | | | | |
| Portland, OR | 2547 (26.8) | 70 (2.7) | 2477 (97.3) | 0.3 (0.2–0.5) | < 0.001 |

| Characteristics | n (%) Overall | Initiated Therapy by August 31, 2015 | Did Not Initiate Therapy | Adjusted Odds Ratio (95% Confidence Interval) | *P* |
|---|---|---|---|---|---|
| Honolulu, HI | 745 (7.8) | 58 (7.8) | 687 (92.2) | 0.8 (0.6–1.1) | 0.21 |
| Detroit, MI | 3587 (37.7) | 286 (8.0) | 3301 (92.0) | Ref | — |
| Danville, PA | 2629 (27.7) | 130 (4.9) | 2499 (95.1) | 1.1 (0.8–1.5) | 0.70 |
| Genotype (3657 missing) | | | | | |
| Genotype 1 | 4587 (78.4) | 340 (7.4) | 4247 (92.6) | Ref | — |
| Genotype 2 | 609 (10.4) | 76 (12.5) | 533 (87.5) | 2.2 (1.7–3.0) | < 0.001 |
| Genotype 3 | 522 (8.9) | 49 (9.4) | 473 (90.6) | 1.2 (0.9–1.7) | 0.25 |
| Genotype 4,5, or 6 | 104 (1.8) | 9 (8.7) | 95 (91.3) | 1.3 (0.6–2.7) | 0.47 |
| Genotype mixed | 29 (0.5) | 4 (13.8) | 25 (86.2) | 1.5 (0.5–4.6) | 0.48 |
| FIB4 (510 missing) | | | | | |
| < 2.0 | 4865 (54.1) | 172 (3.5) | 4693 (96.5) | Ref | — |
| 2.0–3.25 | 1659 (18.4) | 102 (6.1) | 1557 (93.9) | 1.4 (1.1–1.9) | 0.012 |
| 3.26–5.88 | 1232 (13.7) | 106 (8.6) | 1126 (91.4) | 2.0 (1.5–2.6) | < 0.001 |
| > 5.88 | 1242 (13.8) | 144 (11.6) | 1098 (88.4) | 2.1 (1.6–2.8) | < 0.001 |
| Charlson Comorbidity Score | | | | | |
| 0 | 5792 (60.9) | 298 (5.1) | 5494 (94.9) | Ref | — |
| 1 | 1557 (16.4) | 89 (5.7) | 1468 (94.3) | 1.3 (1.0–1.7) | 0.081 |
| ≥2 | 2159 (22.7) | 157 (7.3) | 2002 (92.7) | 1.2 (1.0–1.6) | 0.103 |
| Continuous follow-up (y) | | | | | |
| < 3 | 1899 (20.0) | 84 (4.4) | 1815 (95.6) | Ref | — |
| ≥3 | 7609 (80.0) | 460 (6.0) | 7149 (94.0) | 0.8 (0.6–1.1) | 0.21 |
| Previous treatment | | | | | |
| Yes | 1667 (17.5) | 218 (13.1) | 1449 (86.9) | 2.0 (1.6–2.4) | < 0.001 |
| No | 7841 (82.5) | 326 (4.2) | 7515 (95.8) | Ref | — |
| HIV coinfection | | | | | |
| Yes | 318 (3.3) | 32 (10.1) | 286 (89.9) | 1.8 (1.2–2.8) | 0.008 |
| No | 9190 (96.7) | 512 (5.6) | 8678 (94.4) | Ref | — |
| HBV coinfection | | | | | |
| Yes | 101 (1.1) | 12 (11.9) | 89 (88.1) | 1.2 (0.6–2.4) | 0.54 |
| No | 9407 (98.9) | 532 (5.7) | 8875 (94.3) | Ref | — |

*J Clin Gastroenterol*. Author manuscript; available in PMC 2019 March 21.

| Characteristics | n (%) | | | | |
|---|---|---|---|---|---|
| | Overall | Initiated Therapy by August 31, 2015 | Did Not Initiate Therapy | Adjusted Odds Ratio (95% Confidence Interval) | *P* |
| Previous liver transplant | | | | | |
| Yes | 468 (4.9) | 68 (14.5) | 400 (85.5) | 1.1 (0.8–1.6) | 0.46 |
| No | 9040 (95.1) | 476 (5.3) | 8564 (94.7) | Ref | — |

Treatment initiations were on the basis of prescription of drugs in 2014.

CHeCS indicates Chronic Hepatitis Cohort Study; FIB4, Fibrosis-4; HBV, hepatitis B virus; HIV, human immunodeficiency virus; Ref, reference.