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Low uptake of direct-acting antiviral therapy among hepatitis C patients with advanced liver disease and access to care, 2014–2017

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Abstract

Goals: To determine the proportion and characteristics of adults with hepatitis C at healthcare organizations in four U.S. states who initiated direct-acting antivirals (DAAs).

Background: There are almost no data to assess the penetrance of treatment of the hepatitis C population in general U.S. healthcare settings.

Study: We conducted a prospective observational study using electronic clinical, pharmacy, and mortality data to determine the fraction of patients who initiated DAAs between January 2014 and December 2017, by start date and regimen. We used stepwise multivariate logistic regression analysis to identify sociodemographic and clinical characteristics associated with receipt of DAAs.

Results: Of 8,823 patients, 2,887 (32.7%) received DAAs. Quarterly (Q) uptake ranged from 1.1% in Q3 2014 to a high of 5.6% in Q2 2015. Characteristics associated with receipt of DAAs included age 51–70 years, higher income, pre-2014 treatment failure, and higher non-invasive

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Ethical Considerations: The CHeCS investigation follows the guidelines of the US Department of Health and Human Services regarding the protection of human subjects. The institutional review board at each participating site approved the study protocol.

fibrosis score (FIB4); however, over one-half of patients with FIB4 scores >3.25, consistent with severe liver disease, were not treated. A lower likelihood of initiation was associated with Medicaid coverage. Of 5,936 patients who did not initiate treatment, 911 (15.3%) had died and 2,774 (46.7%) had not had a clinical encounter in ≥12 months by the end of the study. Fewer than 1% of DAA prescriptions originated from non-specialty providers.

Conclusion: During four calendar years of follow-up, one-third of patients initiated DAAs. Large fractions of untreated patients had advanced liver disease, died, or were lost to follow-up. Even among patients in integrated healthcare systems, receipt of DAAs was limited.

Keywords

direct-acting antivirals; hepatitis C; treatment uptake; Chronic Hepatitis Cohort Study

Introduction

New cases of acute hepatitis C have increased rapidly in the United States in the past decade, particularly among young adults, and have most often been associated with injection drug use [1]. As a result, there now exists a bimodal distribution of prevalent hepatitis C virus (HCV) infections in a number of states; one peak encompassing older adults infected decades ago and a second involving younger persons infected recently [2]. Critical to interrupting HCV transmission is the identification and treatment of this younger population; however, persons with longstanding infection are at higher near-term risk of developing end-stage liver disease, including hepatocellular carcinoma [3,4]. Those recently infected may propagate the epidemic, but persons infected long ago suffer the burden of decades of liver injury. Treatment of persons with long-standing infection is therefore crucial to the reduction of hepatitis C-related morbidity and mortality, as the benefits of curative treatment may be realized even among persons with advanced disease [5,6]. As outlined in The U.S. National Viral Hepatitis Action Plan for 2017–2020, reduction in the number of viral hepatitis-related deaths will depend upon increased disease awareness, diagnosis, access to care, and curative treatment [5].

Efficacious and well-tolerated 2nd generation direct-acting antiviral (DAA) drugs for HCV infection were first approved in late 2013. Despite relatively early recommendations for nearly universal treatment, private and public sector payers in the United States have restricted coverage to persons with severe liver disease and sustained drug and alcohol abstinence [6–9]. In recent years, government-affiliated healthcare systems, such as in the U.S. Department of Veterans Affairs, Cherokee Nation, and Alaskan Native Tribal Health Consortium, have demonstrated remarkable improvements in DAA access and uptake [10–13]. In contrast, in private sector health systems, uptake of DAAs has lagged [14]. Even among persons already diagnosed with HCV infection and with apparent access to an array of services within private sector integrated healthcare organizations, receipt of potentially curative treatment may be limited. In a previous analysis of HCV-infected patients in the Chronic Hepatitis Cohort Study (CHeCS) prescribed DAAs during 2014, we found that uptake, or the proportion of actively-infected patients who started DAAs, was only 5.7% [15].

The objective of this analysis was to determine to what degree DAA uptake had changed in this cohort since then and to determine patient characteristics associated with initiation.

Materials and Methods

Study population and determinations of uptake

We analyzed data collected from adults with chronic HCV infection in the CHeCS, an observational study of patients who receive integrated healthcare services at four sites: Geisinger Health System in Danville, Pennsylvania; Henry Ford Health System in Detroit, Michigan; Kaiser Permanente-Northwest in Portland, Oregon; and Kaiser Permanente of Honolulu, Hawaii. The criteria for cohort inclusion and analytic methods involved in its derivation have been described extensively [16,17]. Briefly, the cohort was created based on analysis of electronic health records (EHR) and administrative data (supplemented with individual chart review of a subset of records, as funding permitted, by trained data abstractors) of over 2.7 million patients aged ≥18 years who had at least one clinical service visit (i.e., outpatient or inpatient, emergency department, or laboratory test) from January 1, 2006 to December 31, 2013. Patients who met a combination of laboratory-based and International Classification of Disease, Ninth Revision-based criteria identifying them as having chronic HCV infection were included [16]. Among these patients, prospective follow-up data were available through December 31, 2017. Patient information collected from EHR included demographics, clinical encounters, pharmacy records, laboratory results, and mortality data. An institutional review board at each participating site reviewed and approved the study protocol.

We defined overall uptake as the proportion of patients in the cohort with active HCV infection (i.e., including those who failed previous treatment), as of January 1, 2014, who initiated a 2nd generation DAA-containing regimen by December 31, 2017. DAA initiation was ascertained using pharmacy order and prescription fill data. To identify patients with active HCV infection potentially eligible for DAA therapy at the beginning of 2014 (“the study population”), we excluded from the overall cohort the following patients: 1) those who died before 2014, 2) those who initiated treatment before 2014 and achieved sustained viral response (SVR), 3) those who did not have a clinical encounter in 2013, 4) patients who received DAAs during the study period by clinical trial only, and 5) those who underwent liver transplantation. We excluded the latter group because, given the volume of electronic data post-transplant, CHeCS study sites right censor patient follow-up at the point of transplant.

To examine changes in uptake throughout the study period, we first ascertained the number of patients who initiated a DAA regimen during each quarter of the study interval, according to the antiviral agents included in the regimen, and determined the type of provider who prescribed the regimen. We then calculated the % uptake for each quarter by dividing the number of DAA initiations in the quarter (numerator) by the number of patients with active HCV infection in the quarter who remained eligible for treatment (denominator). The denominator for each successive quarter was reduced by: 1) the number of patients who started DAAs in the preceding quarter, 2) the number of deaths among untreated patients during the preceding quarter, and (3) the number of untreated patients whose

last encounter (outpatient, emergency department, inpatient, or laboratory visit) in their respective healthcare organization was >12 months in the past. We also calculated the mean of Fibrosis-4 ('FIB4', an indicator of liver disease severity) scores of patients at DAA initiation by quarter during the study period.

Statistical analysis

We compared sociodemographic and clinical characteristics of patients who initiated with those who did not initiate DAA therapy. The sociodemographic variables were sex, race/ethnicity, age, health insurance status, annual income according to census tract geocode, and study site. Clinical variables included HCV genotype, FIB4 score, Charlson comorbidity score (modified to exclude liver-related morbidity components) [18], duration of continuous follow-up (<3 vs. ≥3 years), pre-2014 treatment status (i.e., never treated versus treatment failure), HIV/HCV coinfection, and HBV/HCV coinfection. FIB4 scores were calculated based on laboratory results collected closest to the DAA start date or, among patients who did not initiate treatment, the latest results available through December 2017.

For the multivariate analysis, we applied the stepwise selection procedure with a cutoff Wald chi-square p-value of .10 to determine the demographic and clinical characteristics for model inclusion. To determine adjusted odds ratios (aOR) for DAA initiation, we generated one model that adjusted for all included factors from stepwise selection (age, insurance, annual income, genotype, FIB4, Charlson comorbidity score, duration of continuous follow-up, pre-2014 treatment). Additional models were generated for each excluded factor from stepwise selection (i.e., had a p-value above specified threshold/tolerance level). Each model controlled for an excluded factor and all included factors. The potential for multicollinearity was examined and ruled out for annual income and health insurance status using Pearson correlation coefficients and variance inflation factors. All statistical analyses were conducted using SAS Enterprise Guide v. 7.11 (SAS Institute, Cary, NC).

Results

The CHeCS chronic hepatitis C cohort numbered 17,750 patients. After excluding patients who died (2,998 or 16.9%) or were treated before January 1, 2014 and achieved SVR (2,482 or 14.0%), who did not have a clinical encounter during 2013 (3,029 or 17.1%), six patients treated exclusively in a clinical trial during the study period, and 412 (2.3%) who underwent liver transplantation, 8,823 remained as the study population (Figure 1). Of these 8,823 patients, 57.8% were male, 66.1% were white, and 66.0% were aged 51–70 years. Patients with private insurance constituted 50.7%, those on Medicare 32.2%, and those on Medicaid 11.2% of the total (Table).

From January 1, 2014 through December 31, 2017, 2,887 (32.7%) patients initiated DAA treatment (Table). Demographic groups for which uptake exceeded the overall frequency included males (34.4%), non-Hispanic blacks (36.8%), patients aged 51–60 (36.6%) and 61–70 years (40.6%), Medicare recipients (37.9%) and privately insured patients (34.1%), those with annual income ≥$30K-$50K (33.0%) and >$50K (38.1%), and patients from two of the study sites (Honolulu, 44.6% and Detroit, 36.7%). Patients who initiated DAAs had more clinical service encounters per calendar year than did patients who were not treated (Means:

17 vs. 13 in 2014, 22 vs. 14 in 2015, 22 vs. 14 in 2016, and 22 vs. 15 in 2017, respectively; all p<0.001). Patients who initiated DAAs also had longer overall CHeCS follow-up than patients who did not (11.1 vs. 8.9 years, respectively; p<0.001).

The Table also shows the complete results of the multivariable analysis (only significant adjusted Odds Ratios (aOR) to two decimal places, without the corresponding 95% Confidence Intervals, are shown below) comparing characteristics of patients who initiated with those who did not initiate DAA treatment. Characteristics associated with receipt of DAAs included certain older age groups (aOR 1.51 for ages 51–61 years, and 1.38 for ages 61–70 years, compared with age ≤30 years), higher annual income (aOR 1.22 and 1.45 for income ≥$30,000-$50,000 and >$50,000, respectively, compared with <$30,000), higher FIB4 score (aOR 1.29, 1.48, and 1.39 for scores 2.0–3.25, 3.25–5.88, and >5.88, respectively, compared with a score <2.0), higher Charlson comorbidity score (aOR 4.17 and 2.60, for scores of 1 and ≥2, respectively, compared with a score of 0), having had ≥3 years of continuous follow-up in CHeCS (aOR 12.02, compared with <3 years), and pre-2014 treatment failure (aOR 1.63, compared with no previous treatment). Characteristics associated with a lower likelihood of DAA initiation included the oldest age group of ≥71 years (aOR 0.65, compared with age ≤30 years); and Medicaid, Medicare, and Other/Unknown coverage (aOR 0.46, 0.86, and 0.59, respectively, compared to private insurance). Receipt of DAAs was also associated with study site. Compared with the Detroit site, which is a tertiary hepatitis referral center, patients at the staff model health maintenance organization (HMO) site in Hawaii had higher odds of initiating DAAs (aOR 1.29), while those at the Oregon site, affiliated with the same HMO, had lesser odds (aOR 0.85).

Figure 2 (**intended for reproduction in color**) depicts the number of patients who initiated DAAs, by quarter and regimen, and the percent uptake of DAAs, by quarter, during 2014–2017. During 2014, 473 patients were treated. In 2015, 1,246 patients initiated DAAs; in the second quarter (Q2) alone, 404 started treatment. Thereafter, the number of patients who initiated per quarter decreased, stabilizing after Q1 2016. During 2016 and 2017, 638 and 530 patients started treatment, respectively. In Q4 2017, initiations decreased to 98 patients, the lowest quarterly total since the approval of sofosbuvir-ledipasvir. Sofosbuvir-ledipasvir remained the predominant regimen received until Q3 2017, after which initiations of sofosbuvir-velpatasvir, elbasvir-grazoprevir, and glecaprevir-pibrentasvir predominated.

While the number of patients initiating DAAs per quarter varied considerably and, as the study period progressed, decreased relative to the peak in Q2 2015, the rate of uptake by quarter during 2014–2017 was comparably less volatile (Figure 2). Quarterly uptake increased from 1.6% in Q4 2014 to 5.0% in Q1 2015. Uptake peaked in Q2 2015 to 5.6% and ranged thereafter from 2.8% (Q2 2016) to 4.6% (Q3 2017). In the final quarter of the study interval (Q4 2017), when the number of initiations was the lowest of the entire study period (N=98), the uptake rate was 3.3%, still higher than in any quarter in 2014. The relative consistency of quarterly uptake compared with the progressive decrease in the number of DAA initiations after mid-2015 was the result of substantial decreases in the denominator of actively infected patients still available for treatment. Of the 5,936 patients from the initial study population who did not initiate treatment during 2014 through 2017,

911 (15.3%) died and 2,774 (46.7%) had not had a health system encounter in more than 12 months.

The mean of FIB4 scores of patients at DAA initiation by quarter was highest during 2014, peaking at 5.24 during Q3. Thereafter, mean scores decreased and were the lowest in 2017, averaging 2.55 among those treated. Among patients with FIB4 scores ≥3.25, however, 58.5% (n=1,380, Table) did not initiate treatment during the study period; among those with scores <2.0, 72.6% did not receive DAAs. Study funding permitted individual chart abstraction for 906 (65.7%) of the 1,380 patients with higher FIB4 scores. Trained abstractors determined for these 906 patients that, based on provider notes, 225 (24.8%) did not initiate treatment because “current medical condition(s) contraindicated treatment”. For example, of these 225 patients, 68 (30.2%) had decompensated cirrhosis, hepatocellular carcinoma, or some other malignancy. Depending on the timeframe within the study period (2014–2017), available regimens and patient life expectancy may have limited treatment options.

Information on the type of provider who prescribed DAAs was available for 2,522 (87.4%) of 2,887 treated patients. Among providers who prescribed DAAs, 85.9% were gastroenterologists or hepatologists, 13.2% were infectious disease specialists, 0.4% were primary care providers, and 0.5% were “other or unknown” providers.

Discussion

In this cohort of patients with active HCV infection on January 1, 2014 who received integrated services from four healthcare organizations in the United States, approximately one-third initiated DAA treatment during the ensuing four calendar years, an increase from our first assessment, when uptake was approximately 6% in 2014 alone [15]. In the present analysis, we observed an increase in the number of DAA initiations at the close of 2014, which promptly peaked in Q2 2015. This escalation immediately followed the release of sofosbuvir-ledipasvir in October 2014 and may have reflected the effects of targeting and first treating patients who had been “warehoused,” awaiting shorter, tolerable interferon-free regimens. Indeed, the approval of sofosbuvir-ledipasvir profoundly affected overall uptake; during the study period approximately 65% of all DAA-treated patients received sofosbuvir-ledipasvir. It was not until Q3 2017 that initiations with sofosbuvir-ledipasvir were surpassed (in total) by more recently approved, largely pangenotypic regimens.

We also calculated the rate of initiations per quarter by dividing the number of DAA initiations in the quarter by the number of patients in the quarter who had not yet initiated DAAs, had not died, and had not been lost to follow-up. Quarterly uptake rate ranged from 1.1% in Q3 of 2014 to a high of 5.6% in Q2 2015 and thereafter ranged from 2.8% to 4.6% (average 3.5%) per quarter. Except for ombitasvir-containing regimens, there was a relative increase in uptake in the quarters immediately following Federal Drug Administration approval of new DAA regimens (Figure 2). In general, these new regimens successively expanded genotype coverage, reduced the need for ribavirin, lowered the daily pill burden, shortened the course of treatment, or provided retreatment options for persons who failed an earlier DAA regimen [19]. Our uptake findings over this period largely parallel those

of another study by Wong et al. involving four U.S. healthcare systems during the same timeframe, in which uptake was 4.8% in 2014 (vs. 5.9% in CHeCS) and increased to 16.9% in 2017 (vs. 3.9%, 3.5%, 4.6%, and 3.3% in the four quarters of 2017 in CHeCS) [14].

Consistent with our previous findings and those of other investigators [6,7,14], we found that patients with lower income and those on Medicaid were less likely to receive DAAs. Although there is evidence to suggest improvement in access to DAAs among Medicaid recipients [20], such patients in the CHeCS had 50% lesser odds of receiving DAAs compared with those with private insurance. Our finding may have reflected the status of uneven Medicaid coverage for DAAs among U.S. states at that time; two CHeCS study sites were in states that received “D” grades by the National Viral Hepatitis Roundtable [21] because of Medicaid restrictions on DAAs coverage. It is worth noting, however, that the proportion of patients with private insurance who initiated treatment was only 34.1%, compared with 20.2% of patients with Medicaid coverage (Table).

Patients from the Hawaii site had 29% higher odds of initiating DAAs compared with the referent site (Michigan), which was a study site that offered tertiary hepatology referral care. In contrast, patients from the Oregon site had 15% reduced odds of receiving DAAs compared with the referent site. The difference in DAA uptake between the Hawaii and Oregon sites was especially notable as both were affiliated with the Kaiser Permanente health system, and both states were the two already mentioned with “D” grades by the National Viral Hepatitis Roundtable [21]. In 2003, the Hawaii site established a dedicated hepatitis C clinic and began taking a proactive approach to hepatitis C management, using a framework to prompt primary care providers to consider specialty care referral for assessment and treatment of HCV-infected patients at the time of diagnosis [22]. This effort was made simpler perhaps by the relatively small number of hepatitis C patients at the Hawaii site (n=699) compared with the Michigan referent site (n=3,151) and the Oregon site (n=2,434).

Clinical factors that increased the odds of DAA initiation were higher FIB4 score, previous treatment failure, higher Charlson comorbidity score, and having three or more years of continuous follow-up in the cohort. American Association for the Study of Liver Disease/ Infectious Disease Society of America hepatitis C treatment guidelines operative in the early phase of the study period prioritized DAA treatment for those patients with advanced liver disease, previous treatment failure, HIV infection, and severe extrahepatic manifestations of HCV infection [19]. These treatment recommendations were soon expanded to include all HCV-infected persons, irrespective of the degree of fibrosis, except for those with limited life expectancy [19]. In this cohort, the mean FIB4 score among patients who initiated DAAs per quarter decreased from 2014 to 2017, indicating that patients with less advanced liver disease were indeed initiating treatment as time went on. Although most patients with advanced liver disease (i.e., FIB4 score ≥3.25) never initiated treatment during CHeCS follow-up, further review indicated that approximately 25% had medical conditions that contraindicated treatment; thus, many of these patients were not suitable treatment candidates, depending on the regimens available during the timeframe and patient life expectancy.

That patients with longer continuous follow-up (≥3 vs. <3 years) and those with higher Charlson comorbidity scores (>0 vs. 0) were at higher odds of initiating DAAs may highlight the importance of sustained and direct engagement with healthcare services. As Charlson comorbidity scores in our cohort were based on the presence in the EHR of non-hepatic diagnostic codes, non-zero scores indicated at least some diagnosis-related engagement with the healthcare system. Patients with zero scores either had clinical encounters without diagnoses of comorbid illnesses or few, if any, encounters during which any comorbid diagnosis could be made. Indeed, patients who initiated DAAs had significantly more clinical service encounters (e.g., inpatient, outpatient, emergency department, or laboratory visits) per year and longer CHeCS follow-up than patients not treated.

Among CHeCS patients who initiated DAAs, we found that nearly all DAAs prescribed in the CHeCS originated from gastroenterologists/hepatologists (85.9%) and infectious disease (13.2%) specialists. In contrast, non-physician clinicians in the Department of Veterans Affairs accounted for 22.2%, infectious disease specialists for 14.9%, and gastroenterologists/hepatologists for 10.3% of DAA prescriptions in 2017 [23].

A distinguishing feature of our study is that we used serially-adjusted patient denominator data, rather than numerator data only, to estimate the fraction of treated patients in the cohort. Other analyses of uptake have encompassed longer follow-up periods and included interferon-based treatment [23]; our study population was limited deliberately to an established cohort with active infection and engaged in care at the beginning of 2014. Therefore, our finding of 32.7% overall uptake did not include the totality of hepatitis C treatment in CHeCS during the pre-DAA and DAA treatment eras. As our data were derived from EHRs, we were limited in our capacity to identify several possible patient, provider, and system-related factors associated with receipt of DAAs. These might include the competing burden of other, more acutely demanding daily living or comorbid issues, provider concerns regarding adherence, lack of patient understanding of hepatitis C and the potential for successful treatment, and the major challenges in navigating the healthcare system and securing payer approval for DAAs [9]. Another limitation is that we could not be certain that patients without a clinical encounter for more than 12 months were indeed lost to follow-up, but rather had been unable or had chosen not to access care for which they were eligible. It is possible, too, that some untreated patients could have left their CHeCS-affiliated healthcare organizations to receive care (and treatment) from non-CHeCS healthcare organizations. As our analysis focused on treatment uptake among already identified hepatitis C patients, we did not attempt to account for, in the denominator of patients “eligible” for treatment, the estimated fraction of persons in the four healthcare organizations with unidentified HCV infection. From an earlier CHeCS publication, however, we estimated that approximately 43% of HCV infections based on the expected age- and race-adjusted prevalence in the healthcare organizations remained undiagnosed [24]. Lastly, although our study cohort was large and reflective of real-life clinical care at these four sites in the U.S. with broad catchment areas, our results may not be generalizable to other settings or cohorts with different characteristics.

In summary, among patients with active HCV infection in the CHeCS at the beginning of 2014, one-third initiated DAA therapy during 2014–2017. The number of initiations decreased among these patients after a brief surge in DAA starts following approval of sofosbuvir-ledipasvir. Uptake per quarter also peaked early in the study period; its subsequent decline was mitigated by large fractions of the initial study population who either had died or had not had recent follow-up by the close of the study period. Patients with severe liver disease had higher odds of starting treatment compared with those with lesser degrees of fibrosis; however, over one-half of patients with FIB4 scores >3.25, presumably not subject to payer fibrosis restrictions, never received DAAs. Thus, even among these patients with access to integrated healthcare systems, receipt of DAAs remained limited. In favorable terms, patients with evidence of more frequent and sustained clinical engagement had higher odds of treatment. At one study site, despite Medicaid restrictions, the establishment of a dedicated hepatitis C clinic and a proactive framework to prompt specialty care referral after HCV infection diagnosis increased the odds of DAA initiation compared with other CHeCS sites. At all sites, expansion of hepatitis C treatment capacity to non-specialty providers could improve access to treatment, and patient navigation programs could help ensure that all steps for medication approval are properly completed [25,26]. Additional research exploring the barriers to DAA initiation (including psychosocial and quality of life issues) among patients already identified with HCV infection and linked to care, particularly those with advanced liver disease, is warranted.

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Conflict of interest:

Stuart C. Gordon receives grant/research support from AbbVie Pharmaceuticals, Conatus, CymaBay, Gilead Sciences, Intercept Pharmaceuticals, and Merck. He is also a consultant/advisor for Dova Pharmaceticals and Intercept and serves as a speaker/teacher in programs sponsored by Dova. Mei Lu, Joseph A. Boscarino, Mark A. Schmidt, Yihe G. Daida, Jia Li, and Loralee B. Rupp, receive research grant support from Gilead Sciences and Intercept Pharmaceuticals.

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References

[1]. CDC. Surveillance for Viral Hepatitis – United States, 2017. https://www.cdc.gov/hepatitis/statistics/2017surveillance/index.htm. Accessed

[2]. Morse A, Barritt AS, Jhaveri R. Individual state hepatitis C data supports expanding beyond baby boomers to all adults. Gastroenterol 2018;154:1850–1851.

[3]. Seefe LB. Natural History of Chronic Hepatitis C. Hepatology 2002;36:S35–S46. [PubMed: 12407575]

[4]. Bruden D, McMahon BJ, Townshend-Bulson L, et al. Risk of end stage liver disease, hepatocellular carcinoma and liver-related death in the Hepatitis C Alaska Cohort. Hepatology 2017;66:37–45. [PubMed: 28195349]

[5]. Ioannou GN, Feld JJ. What are the benefits of a sustained virologic response to direct-acting antiviral therapy for HCV infection? Gastroenterol 2019;156:446–460.

[6]. Backus LI, Belpeiro PS, Shahoumian TA, et al. Impact of sustained virologic response with direct-acting antiviral treatment on mortality in patients with advanced liver disease. Hepatology 2019;69:487–497. [PubMed: 28749564]

[7]. Canary LA, Klevens RM, Holmberg SD. Limited access to new hepatitis C virus treatment under state Medicaid programs. Ann Intern Med 2015; 163:226–8. [PubMed: 26121095]

[8]. Gowda C, Lott S, Grigorian M, et al. Absolute insurer denial of direct-acting antiviral therapy for hepatitis C: a national specialty pharmacy cohort study. Open Forum Infect Dis. 2018 Jun 7;5(6):ofy076. doi: 10.1093/ofid/ofy076. eCollection 2018 Jun.

[9]. Mera J, Reilley B, Leston J, et al. In a Critical State: Ongoing barriers to treatment for hepatitis C virus (HCV). Am J Med 2019;132:547–549. [PubMed: 30476467]

[10]. Belperio PS, Chartier M, Ross DB, et al. Curing hepatitis C virus infection: best practices from the U.S. Department of Veterans Affairs. Ann Intern Med 2017;167:499–504. [PubMed: 28973196]

[11]. U.S. Department of Veterans Affairs, Office of Public and Intergovernmental Affairs. VA on path to cure 100,000 Veterans of hepatitis C. March 18, 2019. https://www.va.gov/opa/pressrel/pressrelease.cfm?id=5219. Accessed November 5, 2019.

[12]. US News and World Report, Associated Press. Cherokee Nation Lauded for Hepatitis C Elimination Effort. May 16, 2018. https://www.usnews.com/news/healthiest-communities/articles/2018-05-16/cherokee-nation-lauded-for-hepatitis-c-elimination-effort.

[13]. McMahon BJ, Townshend-Bulson L, Homan C, et al. Cascade of care for Alaska Native People with chronic hepatitis C virus infection: statewide program with high linkage to care. Clin Infect Dis 2019; ciz832, 10.1093/cid/ciz832.

[14]. Wong RJ, Jain MK, Therapondos G, et al. Race/ethnicity and insurance status disparities in access to direct acting antivirals for hepatitis V virus treatment. Am J Gastroenterol 2018;113:1329–1338. [PubMed: 29523864]

[15]. Spradling PR, Xing J, Rupp L, et al. Uptake of and factors associated with direct-acting antiviral therapy among patients in the Chronic Hepatitis Cohort Study, 2014–2015. J Clin Gastroenterol 2018;52:641–647. [PubMed: 28590325]

[16]. Moorman A, Gordon S, Rupp L, et al. Baseline characteristics and mortality among people in care for chronic viral hepatitis: The Chronic Hepatitis Cohort Study (CHeCS). Clin Infect Dis 2013; 56: 40–50. [PubMed: 22990852]

[17]. Moorman AC, Rupp LB, Gordon SC, et al. Long-term liver disease, treatment, and mortality outcomes among 17,000 persons diagnosed with chronic hepatitis C virus infection: current Chronic Hepatitis Cohort Study status and review of findings. Infect Dis Clin North Am 2018;32:253–268. [PubMed: 29778254]

[18]. 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]

[19]. American Association for the Study of Liver Diseases/Infectious Diseases Society of America. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. https://www.hcvguidelines.org. Accessed April 2, 2019.

[20]. Kapadia SN, Jeng PJ, Schackman BR, et al. State Medicaid hepatitis C treatment eligibility criteria and use of direct-acting antivirals. Clin Infect Dis 2018;66:1618–1620. [PubMed: 29206910]

[21]. National Viral Hepatitis Roundtable. Hepatitis C: state of Medicaid access, 2017. https://stateofhepc.org. Accessed December 7, 2018.

[22]. Foster MA, Xing J, Moorman AC, et al. Frequency of and factors associated with receipt of liver-related specialty care among patients with hepatitis C in the Chronic Hepatitis Cohort Study. Dig Dis Sci 2016;61:3469–3477. [PubMed: 27510752]

[23]. Butt AA, Yan P, Lo Re V, et al. Trends in treatment uptake and provider specialty for hepatitis C virus (HCV) infection in the Veterans Affairs Healthcare System: results from the Electronically Retrieved Cohort of HCV-Infected Veterans (ERCHIVES). Clin Infect Dis 2019;68:857–859. [PubMed: 30137251]

[24]. 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 Oct;55:1047–55. [PubMed: 22875876]

[25]. Gaudino A, Gay B, Garmon C, et al. Localized US efforts to eliminate hepatitis C. Infect Dis Clin N Am 2018;32:293–311.

[26]. Zuckerman A, Carver A, Chastain CA. Building a hepatitis C clinical program: strategies to optimize outcomes. Curr Treat Options Infect Dis 2018;10:431–446. [PubMed: 30524209]

[27]. U.S. Department of Health and Human Services. National Viral Hepatitis Action Plan, 2017–2020. https://www.hhs.gov/hepatitis/viral-hepatitis-action-plan/index.html. Accessed April 2, 2019.

[28]. 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]

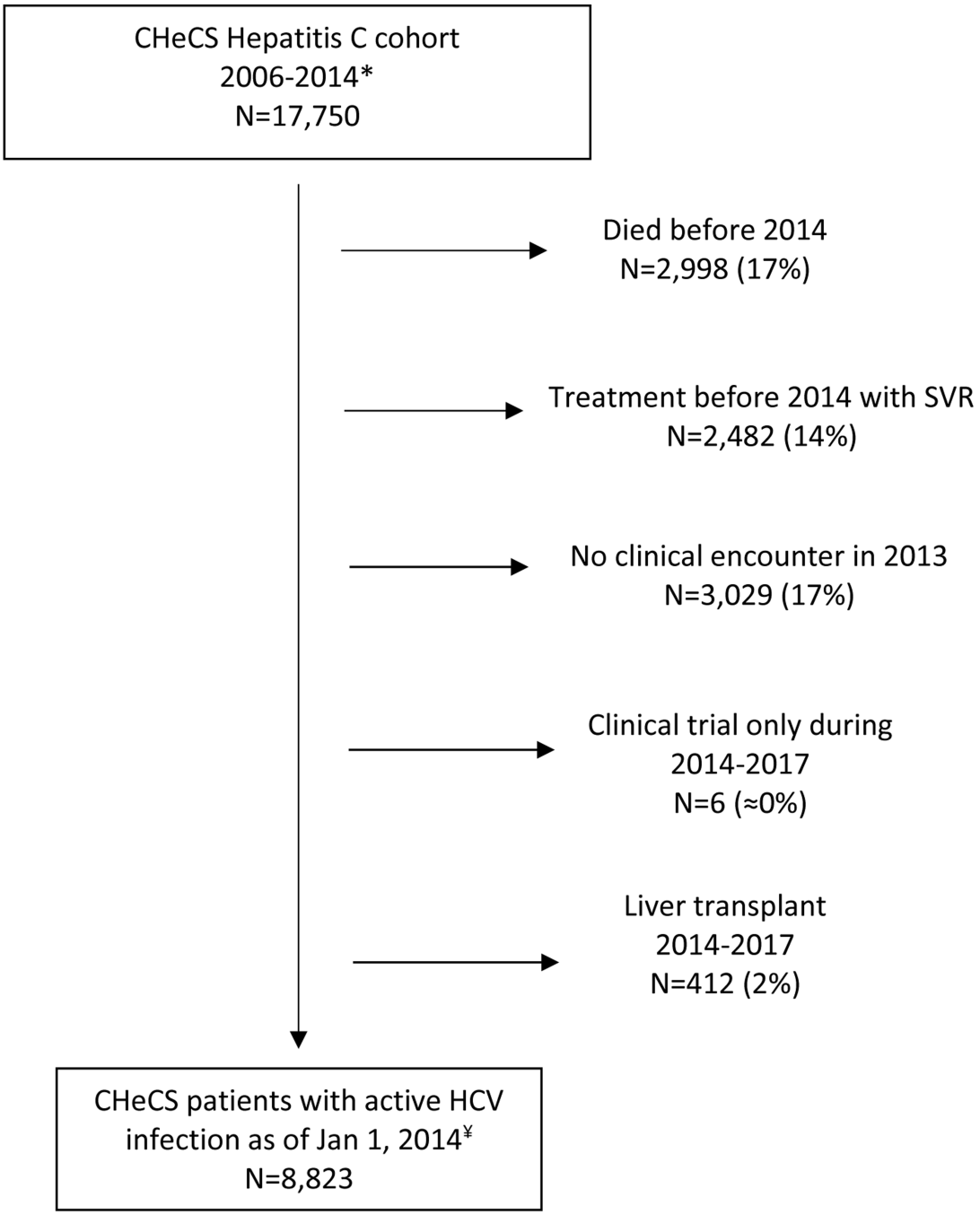

Figure 1.

Derivation of the study population.

*Source population for the study.

¥Prospective data were available through December 31, 2017.

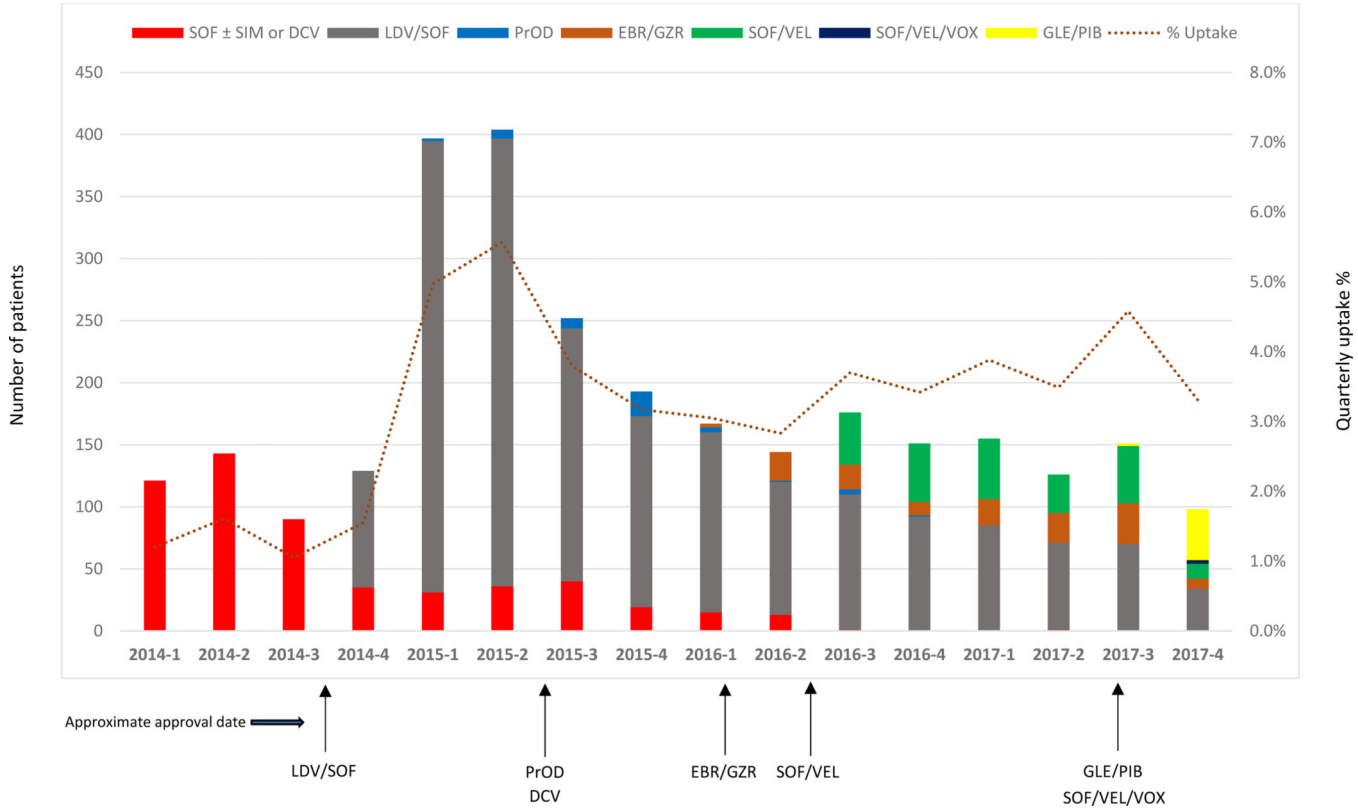

Figure 2.

Stacked bars: Number of patients with HCV infection who initiated direct-acting antiviral therapy, by year-quarter and regimen (in color). Dotted line: Percent uptake of direct-acting antiviral therapy, by year-quarter. Chronic Hepatitis Cohort Study, 2014–2017. SOF, sofosbuvir; SIM, simeprevir; DCV, daclatasvir; LDV, ledipasvir; PrOD, ombitasvir/paritaprevir/ritonavir/dasabuvir; EBR, elbasvir; GZR, grazoprevir; VEL, velpatasvir; VOX, voxilaprevir; GLE, glecaprevir; PIB, pibrentasvir.

Table.

Characteristics of HCV-infected patients who initiated and did not initiate direct-acting antiviral therapy, January 2014-December 2017, Chronic Hepatitis Cohort Study.

Characteristics	Overall n (%)	Initiated n (%)	Did NOT initiate n (%)	Adjusted Odds Ratio[a] (95% Confidence Interval)
Total	8823	2887 (32.7)	5936 (67.3)	
Sex				
Male	5099 (57.8)	1752 (34.4)	3347 (65.6)	1.01 (0.90–1.13)
Female	3724 (42.2)	1135 (30.5)	2589 (69.5)	Ref
Race/ethnicity				
Non-Hispanic White	5833 (66.1)	1826 (31.3)	4007 (68.7)	Ref
Non-Hispanic Black	2096 (23.8)	771 (36.8)	1325 (63.2)	1.04 (0.90–1.20)
Other	894 (10.1)	290 (32.4)	604 (67.6)	0.94 (0.78–1.14)
Age group (years)				
≤30	628 (7.1)	92 (14.6)	536 (85.4)	Ref
31–40	737 (8.4)	141 (19.1)	596 (80.9)	1.1 (0.76–1.59)
41–50	1137 (12.9)	300 (26.4)	837 (73.6)	1.31 (0.94–1.83)
51–60	3445 (39.0)	1262 (36.6)	2183 (63.4)	1.51 (1.11–2.05)
61–70	2380 (27.0)	967 (40.6)	1413 (59.4)	1.38 (1.00–1.91)
≥71	496 (5.6)	125 (25.2)	371 (74.8)	0.65 (0.43–0.97)
Insurance status				
Private	4475 (50.7)	1525 (34.1)	2950 (65.9)	Ref
Medicaid	986 (11.2)	199 (20.2)	787 (79.8)	0.46 (0.37–0.56)
Medicare	2841 (32.2)	1077 (37.9)	1764 (62.1)	0.86 (0.75–0.99)
Other/Unknown	521 (5.9)	86 (16.5)	435 (83.5)	0.59 (0.43–0.81)
Annual income (by census tract geocode)				
<$30K	2211 (25.1)	598 (27.0)	1613 (73.0)	Ref
≥$30-<50K	4043 (45.8)	1336 (33.0)	2707 (67.0)	1.22 (1.06–1.41)
>$50K	2336 (26.5)	890 (38.1)	1446 (61.9)	1.45 (1.24–1.70)
Not available	233 (2.6)	63 (27.0)	170 (73.0)	1.45 (0.98–2.15)
Study site				
Portland, OR	2434 (27.6)	725 (29.8)	1709 (70.2)	0.85 (0.73–0.98)
Honolulu, HI	699 (7.9)	312 (44.6)	387 (55.4)	1.29 (1.06–1.58)
Detroit, MI	3151 (35.7)	1157 (36.7)	1994 (63.3)	Ref
Danville, PA	2539 (28.8)	693 (27.3)	1846 (72.7)	0.93 (0.79–1.11)
Genotype (2938 missing)				
Genotype 1	4642 (78.3)	2121 (45.7)	2521 (54.3)	Ref
Genotype 2	637 (10.8)	280 (44.0)	357 (56.0)	0.93 (0.78–1.11)
Genotype 3	510 (8.6)	200 (39.2)	310 (60.8)	0.83 (0.67–1.02)
Genotype 4,5, or 6	102 (1.7)	48 (47.1)	54 (52.9)	1.15 (0.75–1.75)

Characteristics	Overall n (%)	Initiated n (%)	Did NOT initiate n (%)	Adjusted Odds Ratio[a] (95% Confidence Interval)
Genotype Mixed	34 (0.6)	15 (44.1)	19 (55.9)	0.82 (0.40–1.70)
FIB4 (273 missing)				
<2.0	4575 (53.3)	1255 (27.4)	3320 (72.6)	Ref
2.0-<3.25	1647 (19.2)	626 (38.0)	1021 (62.0)	1.29 (1.11–1.50)
3.25-<5.88	1250 (14.6)	509 (40.7)	741 (59.3)	1.48 (1.25–1.75)
≥5.88	1109 (12.9)	470 (42.4)	639 (57.6)	1.39 (1.17–1.65)
Charlson Score				
0	6533 (74.0)	1687 (25.8)	4846 (74.2)	Ref
1	837 (9.5)	496 (59.3)	341 (40.7)	4.17 (3.46–5.03)
2 or more	1453 (16.5)	704 (48.5)	749 (51.5)	2.60 (2.22–3.03)
Continuous follow-up				
<3yr	605 (6.9)	22 (3.6)	583 (96.4)	ref
≥3yr	8218 (93.1)	2865 (34.9)	5353 (65.1)	12.02 (6.97–20.75)
Pre-2014 treatment failure				
Yes	1558 (17.7)	838 (53.8)	720 (46.2)	1.63 (1.43–1.86)
No	7265 (82.3)	2049 (28.2)	5216 (71.8)	ref
HIV/HCV Coinfection				
Yes	249 (2.8)	98 (39.4)	151 (60.6)	1.27 (0.93–1.74)
No	8574 (97.2)	2789 (32.5)	5785 (67.5)	ref
HBV/HCV Coinfection				
Yes	100 (1.1)	35 (35.0)	65 (65.0)	1.12 (0.66–1.91)
No	8723 (98.9)	2852 (32.7)	5871 (67.3)	ref

[a]Note: Adjusted by age, insurance, income, genotype, FIB4, Charlson Score, duration of continuous follow-up, pre-2014 treatment.

Abbreviations: HBV, hepatitis B virus; HIV, human immunodeficiency virus