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Colin Waters

Anya Cutler

Kinna Thakarar

Kathleen Fairfield

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ORIGINAL RESEARCH

Analysis of Claims Data Reveals Clinical and Social Factors Associated With Hepatitis C Direct-Acting Antiviral Prescriptions in Maine

Colin T. Waters, MD, PhD [a,*], Anya Cutler, MS, MPH [b], Kinna Thakarar, DO, MPH [c,d], Kathleen Fairfield, MD, MPH, DrPH [c,d]

[a] University of Vermont Larner College of Medicine, Department of Emergency Medicine, Burlington, Vermont
[b] MaineHealth Institute for Research, Center for Interdisciplinary and Population Health Research, Westbrook, Maine
[c] MaineHealth Maine Medical Center, Portland, Maine
[d] Tufts University School of Medicine, Boston, Massachusetts

ABSTRACT

Introduction: Several curative options for chronic hepatitis C virus (HCV) infection exist. We investigated factors associated with prescriptions for HCV direct-acting antiviral (DAA) therapy to inform improved access to HCV treatment.

Methods: We conducted a cross-sectional analysis of all-payer claims data for the state of Maine to identify patients with diagnosis codes for chronic HCV. Prescription claims were analyzed to determine which patients were prescribed a DAA for HCV treatment. Univariate analysis identified factors associated with prescription status, which were incorporated into a multivariable logistic regression model to identify factors associated with DAA prescribing.

Results: Insurance status was significantly associated with DAA prescribing status, with Maine Medicaid recipients more likely to be prescribed, whereas those with Medicare or dually eligible less likely. Male sex was associated with a DAA prescription, whereas patients with a diagnosis of HIV coinfection were less likely to have a prescription.

Discussion: In light of studies conducted in other states and over different time frames, we hypothesize that DAA-prescribing rates were subject to changes in reimbursement rates over time. Additionally, access to DAAs is likely state-dependent, reflecting a patchwork of availability across the United States. DAA prescribing rates in the setting of different comorbidities may reflect a preference to prescribe DAAs to people with more advanced liver disease.

Conclusions: Our study suggests that there are likely many avenues for increasing access to DAAs from the level of health systems to individual prescribers.

Keywords: Chronic hepatitis C, Human viral hepatitis, Antiviral agents, Health services accessibility, Claims analysis

1. Introduction

Acute infection with hepatitis C virus (HCV) is typically asymptomatic. Most patients with acute HCV will be unable to clear the virus and will progress to chronic infection over several months.[1] Chronic HCV infection affects approximately 2.5 to 4 million residents of the United States[1,2] and is associated with substantial morbidity and mortality when untreated. In the 2010s, direct-acting antivirals (DAAs) enabled curative HCV treatment, defined as an undetectable serum HCV viral load 12 or more weeks after treatment completion [ie, sustained virologic response (SVR)]. SVR rates of 99% have been described

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* Corresponding author.
E-mail address: colin.waters@uvmhealth.org (C. T. Waters).

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in patients without cirrhosis who were treated for 4 or more weeks, and rates of nearly 95% have been described in patients with cirrhosis treated for 8 or more weeks.[3]

Treatment with DAA and subsequent SVR is linked to fewer complications of chronic HCV, including hepatocellular carcinoma[4] and the need for liver transplantation. The benefits of this treatment have been demonstrated in patients without cirrhosis, supporting early treatment initiation, and in patients with more advanced disease.[5] In addition to the benefit to individual patients, DAA therapy reduces all-cause health care costs among patients with cirrhosis.[6] The Infectious Disease Society of America and the American Association for the Study of Liver Diseases has recommended that all patients with chronic HCV be treated with DAA therapy.[7] Furthermore, the WHO has established a goal of eliminating HCV infection by 2030 via a targeted 80% treatment rate.[8] Meeting these goals requires redoubled screening efforts,[9] especially with 2020 guidelines from the Centers for Disease Control and Prevention recommending that all individuals 18 years and older be screened once in their lifetime.[10]

Despite benefit to individual patients and cost-savings to society, many patients with chronic HCV have not been treated.[11,12] Patient-specific factors, such as prior treatment experience, comorbidities, co-prescriptions, degree of liver disease, and HCV genotype,[13] may influence individualized treatment decisions. Structural disparities in DAA-prescribing rates have also been identified and include age, insurance status, urban-rural area of residence, and history of substance use disorder. These disparities indicate systemic failures to provide appropriate therapy.[12]

Considerations of patient-specific factors have evolved as new DAAs are introduced. Before the introduction of pan-genotypic combinations, HCV genotyping was a crucial step, and although still an important factor, SVR rates of 95% are seen independent of viral genotype with newer DAAs.[13]? Comorbid diagnoses and complications of chronic HCV, such as hepatic fibrosis[15] and chronic kidney disease,[13] have impacted treatment decisions according to guidelines and insurer reimbursement practices.[16]

Insurance status among patients with chronic HCV is a known determinant of DAA therapy. In a study from 2011 to early 2017 of 29 544 patients across 4 states, patients treated with DAA therapy were more likely to have Medicare or commercial insurance versus Medicaid or indigent care.[15] This study also found a significant effect of age on treatment status, with the lowest treatment rate among patients younger than 45 years.[15]

Relatively few studies have explored state-wide populations for factors associated with DAA prescriptions among people with chronic HCV. However, a state-wide approach enables analysis of a large population across insurers and rural-urban settings. Furthermore, this approach captures patients who may be lost to follow-up within a single health system. We analyzed a database of all-payer insurance claims in Maine to identify factors associated with DAA prescribing to identify strengths and shortcomings in providing DAA therapy. Prior work identified a greater incidence of acute hepatitis C infection in nonurban and rural areas in central Appalachian states and in Indiana.[17,18] However, to our knowledge, our study reflects the first assessment of DAA prescribing in a rural New England state.

2. Methods

We conducted a retrospective, cross-sectional analysis of medical and prescription claims data for patients with a diagnosis of chronic HCV available in the Maine Health Data Organization All Payer Claims Database. Patient data were available for patients with any commercial insurance, Medicare, and Maine Medicaid during this study period. Commercial insurers with less than $2 million in annual premiums are not required to report claims. Also, self-funded Employee Retirement Income Security Act plans are likewise exempt, although some do voluntarily submit data. Overall, approximately 90% of the insured population is estimated to be included in the database. The database does not include patients who self-pay, or claims paid by the Veterans Administration health care system. However, Veterans Administration claims paid for by a separate commercial insurer would be included. The database also does not include claims associated with substance use disorder based on payor interpretation of 42 CFR Part 2, which has been previously assessed to result in a loss of approximately 11.7% of HCV-related claims.[19]

Patients were included if they had a claim with a primary or secondary ICD10 code for chronic viral hepatitis C (B18.2). Of note, ICD10 codes were introduced on October 1, 2015. Although we included claims data collected from Q1 of 2015 to Q3 of 2019, October 1, 2015, was the effective start date of our review. ICD9 codes were not included in our analysis. Demographic data, prescription claims for DAA medications of interest (Supplementary Table 1),[5] comorbidities (Supplementary Table 2),[20] and prescribed medications of interest (Supplementary Table 3)[21] were collected for these patients. Comorbidities were included if they could influence the decision to initiate DAA therapy and/or the

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Table 1. Demographic characteristics of patients with chronic hepatitis C (N = 6161).

Characteristic	Not prescribed DAA, No. (%) (n = 4152)	Prescribed DAA, No. (%) (n = 2009)	*P* value*	Adjusted *P* value†
Age, y			<.001	<.001
<35	552 (13)	276 (14)		
35–49	886 (21)	558 (28)		
50–64	1432 (34)	751 (37)		
65+	1282 (31)	424 (21)		
Sex				
Female	1820 (44)	829 (41)		
Male	2332 (56)	1180 (59)	.056	>.9
Rurality			.8	>.9
Metropolitan	2182 (53)	1081 (54)		
Micropolitan	713 (17)	327 (16)		
Rural	707 (17)	339 (17)		
Small town	537 (13)	260 (13)		
Unknown	13 (0.3)	2 (0.1)		
Insurance			<.001	<.001
Any commercial	1231 (30)	603 (30)		
Medicaid	1546 (37)	1062 (53)		
Medicaid, Medicare	827 (20)	297 (15)		
Medicare	548 (13)	47 (2.3)		

Abbreviations: DAA, direct-acting antiviral.
*Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank-sum test.
†Bonferroni correction for multiple testing.

choice of DAA.[13] These comorbidities were related to disease severity (eg, hepatic fibrosis, hepatic encephalopathy, ascites), potential complications (eg, cryoglobulinemia, chronic kidney disease), and co-infections (eg, HIV, hepatitis B virus).[13] Charlson comorbidity indices[22,23] were calculated with the R package "comorbidity"[24] using all diagnosis claims available during the study period. Federal Rural-Urban Commuting Area (RUCA) codes were used to define rurality. RUCA codes incorporate factors such as urbanicity, population density, and commuting patterns.[25] We assigned a RUCA code for each patient by using a RUCA ZIP code approximation file to crosswalk census tracts to ZIP codes.[26] We then created 5 groups from the 10 RUCA codes: metropolitan, micropolitan, rural, small town, and unknown.

Univariate statistical comparisons of DAA-prescribed and no-DAA-prescribed groups were performed using Pearson's chi-squared test or Fisher's exact test for categorical variables, and analysis of variance and Wilcoxon rank-sum test for continuous variables. Bonferroni multiple-testing correction was performed for univariate comparisons. A significance level (α) of 0.05 was used. A multivariable logistic regression model was run with all covariates that had a statistical association with DAA prescription status during univariate regression analysis. All analyses were conducted in R v3.6.2.

This study does not include factors requiring patient consent. The Maine Medical Center Institutional Review Board approved this study.

3. Results

We identified 6161 patients across the state of Maine who had a diagnosis of chronic HCV during our study period. Of these patients, 3512 (57%) were male and 2649 (43%) were female (Table 1). There were 828 patients younger than 35 years old, and 1706 older than 65.

A total of 2009 (33%) patients had at least 1 DAA prescription during the study period (Table 2). No difference by sex was observed. Patient age significantly differed (adjusted $P < .001$) between those with and without a prescription. This difference was most marked in patients older than 65 years, with 25% (n = 424) prescribed a DAA versus 75% (n = 1282) not prescribed a DAA. For patients 50 to 64 years old, 34% were prescribed a DAA; for patients 35 to 49 years old, 39% were prescribed a DAA; and for patients younger than 35 years, 33% were prescribed a DAA.

Among included patients, 33% with commercial insurance, 41% with Maine Medicaid alone, 26% with a combination of Medicaid and Medicare, and 8% with Medicare alone were prescribed a DAA (adjusted $P <$ .001). We found no significant difference (adjusted $P > .9$) in RUCA categories of residence between patients with and without prescriptions.

Comorbidities and complications differed significantly between groups (Table 2). Patients prescribed a DAA were significantly less likely to be diagnosed with renal impairment (adjusted $P < .001$), HIV

Table 2. Comorbidities and Co-prescriptions of patients with chronic hepatitis C (N = 6161).

Characteristic	Not prescribed DAA, No. (%)* (n = 4152)	Prescribed DAA, No. (%)* (n = 2009)	*P* value†	Adjusted *P* value‡
Hepatic fibrosis	1005 (24)	536 (27)	.036	.7
Renal impairment	336 (8.1)	91 (4.5)	<.001	<.001
HBV coinfection	1 (<0.1)	1 (<0.1)	.5	>.9
HIV coinfection	673 (16)	243 (12)	<.001	<.001
Jaundice	76 (1.8)	27 (1.3)	.2	>.9
Peritonitis	45 (1.1)	11 (0.5)	.038	.7
Hepatic encephalopathy	275 (6.6)	70 (3.5)	<.001	<.001
Ascites	300 (7.2)	95 (4.7)	<.001	.003
Nephritic syndrome	7 (0.2)	1 (<0.1)	.5	>.9
Charlson Comorbidity Score, median (IQR)	2.00 (1.00, 4.00)	2.00 (1.00, 3.00)	<.001	<.001
Prescription				
Proton-pump inhibitor	891 (21)	552 (27)	<.001	<.001
Antiplatelet	114 (2.7)	56 (2.8)	>.9	>.9
Lipid-lowering agent	243 (5.9)	95 (4.7)	.069	>.9
Antiarrhythmic	25 (0.6)	11 (0.5)	.8	>.9
Antiepileptic	112 (2.7)	52 (2.6)	.8	>.9

Abbreviations: DAA, direct-acting antiviral; HBV, hepatitis B virus; IQR, interquartile range.
*Unless otherwise indicated.
†Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank-sum test.
‡Bonferroni correction for multiple testing.

Table 3. Odds of receiving a DAA prescription for chronic hepatitis C.

Variable	OR (2.5%–97.2% CI)	*P* value
Age 35–49 y*	1.33 (1.11–1.6)	.002
Age 50–64 y*	1.32 (1.1–1.6)	.004
Age 65≤ y*	1.19 (0.96–1.48)	.11
Medicaid†	1.44 (1.25–1.65)	<.001
Medicaid, Medicare†	0.76 (0.64–0.91)	.002
Medicare†	0.19 (0.14–0.26)	<.001
Male sex	1.17 (1.04–1.31)	.008
Hepatic fibrosis	1.42 (1.24–1.63)	<.001
Renal impairment	0.84 (0.63–1.1)	.2
HIV coinfection	0.81 (0.68–0.97)	.021
Charlson Comorbidity Index	0.90 (0.86–0.93)	<.001
Proton-pump inhibitor prescription	1.36 (1.19–1.55)	<.001

Abbreviations: OR, odds ratio.
*Relative to younger than 35 years group (referent).
†Relative to commercial insurance ± Medicaid or Medicare (referent).

coinfection (adjusted $P < .001$), ascites (adjusted $P = .003$), or hepatic encephalopathy (adjusted $P < .001$).

As drug-drug interactions are a potential factor in DAA prescribing, we assessed differences in co-prescriptions as well. Among antiarrhythmics, lipid-lowering agents, antiplatelet agents, antiepileptics, and proton-pump inhibitors, DAA prescription was only significantly different among patients prescribed proton-pump inhibitors (27% with versus 21% without a DAA prescription; adjusted $P < .001$).

Our final regression model (Table 3) found that several factors were associated with a higher odds of receiving a DAA prescription in the fully adjusted model. These factors included an age of 35 to 49 years [odds ratio (OR 1.33; 95% CI, 1.11–1.6; $P = .002$)] or 50 to 64 years (OR, 1.32; 95% CI, 1.1–1.6; $P = .004$), an insurance status of Medicaid alone (OR, 1.44; 95% CI, 1.25–1.65; $P < .001$), male sex (OR, 1.17; 95% CI, 1.04–1.31; $P = .008$), a diagnosis of hepatic fibrosis (OR, 1.42; 95% CI, 1.24–1.63; $P < .001$), and proton-pump inhibitor co-prescription (OR, 1.36; 95% CI, 1.19–1.54; $P < .001$). Conversely, after adjustments for all other variables, several factors were associated with a lower odds of receiving a DAA prescription. These factors included insurance status of Medicaid and Medicare (OR, 0.76; 95% CI, 0.64–0.91; $P = .002$) or of Medicare alone (OR, 0.19; 95% CI, 0.14–0.26, $P < .001$) versus private insurance, or a diagnosis of HIV (OR, 0.81; 95% CI, 0.68–0.97; $P = .021$).

4. Discussion

In this study of adults with HCV, we found that only one-third of patients received a prescription for DAA therapy. Factors associated with DAA prescribing included male sex, age 35 to 49 or 50 to 64 years, a diagnosis of hepatic fibrosis, and having Medicaid.

Although state-specific prescribing rates are limited, prior single-center studies found similar prescribing rates. For example, a study in North Carolina found an approximate 35% treatment rate,[11] and a study in Florida found a 27% DAA-treatment rate.[12] Additionally, a recent nationwide study of

commercially insured patients identified a DAA-dispensing rate of 34.2%.[27]

Insurance status was an important factor associated with DAA prescription status, with substantially more patients with Medicaid than commercial insurance prescribed a DAA. This relatively high percentage is striking, given prior work demonstrating that Medicaid frequently denied DAA coverage for patients across several different states.[28] Our finding of greater coverage for patients with Maine Medicaid contrasts to findings in Florida from 2014 to 2017, where 18.5% of patients with Medicaid received DAA prescriptions.[12] An additional study of 4 states from 2011 to 2017 found comparatively low prescribing rates for patients with Medicaid versus Medicare or commercial insurance.[15] State-to-state variation in Medicaid reimbursement for DAA therapy has been well-documented,[29,30] and has changed over time as clinical guidelines are revised.[31] Reimbursement practices have also changed as legal challenges to restrictions on reimbursement for DAAs[32] and guidance from The Centers for Medicare and Medicaid Services[33] led to greater coverage of DAAs. Interestingly, there is some evidence that although denials of DAA coverage by Medicaid appears to have declined between 2014 and 2015 and between 2016 and 2017, denials by commercial insurance and Medicare appear to be rising.[28,34] However, these rates were obtained in different studies and with different sample compositions. Consistent with our relatively low prescribing rate among patients with Medicare alone, a prior analysis found lower prescribing rates among people with Medicare versus those with commercial insurance.[15] Prior work also identified different approval times among insurance providers, with North Carolina Medicaid significantly longer than both private insurers and Medicare, and private insurers significantly longer than Medicare.[11]

The higher DAA-prescribing rate we observed may reflect an evolution in Medicaid coverage over time.[35] This hypothesis is supported by a summary published by the National Viral Hepatitis Roundtable and the Harvard Law School Center for Health Law and Policy Innovation. This summary described per-state Medicaid requirements for DAA prescribing between 2014 and 2016,[16] and reported that Maine Medicaid reduced its fibrosis restrictions and provider requirements during this period. However, Maine also increased its sobriety requirements, with subsequent relaxation in 2018.[36]

A prior analysis of administrative claims, electronic health record review, and prescription records covering more than 785 000 individuals from 2013 to 2016 found a diagnosis of substance use disorder was a predictor of lower prescribing likelihood. This finding suggests that although people with substance use disorder may be at higher risk for HCV acquisition and transmission, they may face additional barriers to care.[37] Unfortunately, due to known data sequestration of substance use disorder claims in all-payer claims databases,[19] we are unable to further investigate co-occurring substance use disorder among our study population.

Notably, Maine underwent Medicaid expansion during our study period, with retroactive coverage to July 2, 2018.[38] Further assessment of the impact of Maine Medicaid expansion on DAA coverage would be an interesting follow-up to our study.

We found that patients with both chronic HCV and HIV infections are relatively less likely to be prescribed a DAA. Because we were unable to capture if patients had received prior DAA treatment, and given that most patients living with HIV in Maine are older than 55 years and engaged in HIV care, these patients were likely treated for HCV before the DAA era.[39] Importantly, co-infected patients not receiving DAA therapy are significantly more likely to experience mortality than co-infected patients receiving therapy,[11] suggesting an important connection between HCV treatment and lower mortality in HIV co-infected patients.

Our work found additional significant associations between comorbidities and DAA prescribing status. Notably, patients with a diagnosis of hepatic fibrosis were more likely to be prescribed a DAA. Our results are consistent with prior work that found that patients with greater severity of fibrosis or with cirrhosis are more likely to receive DAA therapy.[15] These findings may reflect a combination of prescribing practices and trends in reimbursement during our study period. For instance, Maine Medicaid initially required a fibrosis score of F1 or greater in 2014, but it removed any fibrosis requirement in 2016.[16]

Our initial analysis found that individuals with renal impairment were less likely to be prescribed a DAA. However, there was no significant difference between these 2 populations in the logistic regression model, possibly because of limited power. Prior authors have discussed potential hesitation in prescribing DAAs that are renally cleared (eg, sofosbuvir) in patients with chronic kidney disease and/or concern for progression of renal disease due to treatment.[13] As chronic HCV itself is linked to the development of chronic kidney disease, more education about the long-term impact of curative DAA therapy and the safety of prescribing DAAs without requiring renal adjustment should be a priority.

Interestingly, we find no difference in RUCA codes among patients with and without a DAA prescription. Recent work examining DAA prescribing among people with Medicare found similar rates of DAA prescribing between rural and urban residents after adjusting for ZIP-code level socioeconomic status, county-level primary care provider density, and patient characteristics.[40] This work did find evidence that uptake rates differed between rural and urban areas, with patients in urban areas experiencing a greater rate than those in rural areas. Given similar DAA-prescribing rates between rural and urban patients, future work could assess potential differences in diagnosis rates of chronic HCV among rural and urban populations in Maine, as has been done in other rural states.[17]

Our study has several limitations, including a known issue of sequestration of claims data related to substance use from 2013 to 2017, covering approximately half of our study period. Prior assessments of the impact of this redaction have estimated a loss of 11.7% of eligible patients with HCV.[19] It is unclear how this may impact the results of our study, although this impact was estimated to more significantly affect patients younger than 65 years, possibly influencing the age distribution of DAA-prescribing rates that we observed. Although race was not captured in the dataset used in this study, Maine census data estimates that 94.4% of the population is White, versus 76.3% of the United States population. Thus, our study population may not generalize to other regions of the United States.[41] Prior work found differences in DAA-prescribing rates associated with race and ethnicity, including a multicenter study demonstrating lower prescribing rates among Hispanic versus non-Hispanic White people.[15] Also, in a single-center study from 2011 to 2015 exploring DAA-prescribing for patients with HIV and HCV coinfection, self-reported race was associated with lower prescribing rates among African American versus Caucasian patients.[11] The all-payer claims dataset only captures data for insured patients, and we were therefore unable to report prescribing rates in uninsured populations. Although our data benefit from a multi-year time-scale, we did not analyze elements of heterogeneity that may have important structural and clinical outcomes, including effects of introducing new DAA therapies into the market, changes in prescribing guidelines and reimbursement rates, and Maine Medicaid expansion. Due to the limitations of our data, we were unable to account for prior treatment and could not determine the presence or absence of active disease. Finally, due to the scope of our study, we were unable to capture patient perspectives on barriers to accessing DAA treatment, such as stigma or mistrust of the health care system.[42]

5. Conclusions

We found that despite the availability of a potentially curative treatment for a disease with significant morbidity and mortality, most patients with diagnosed chronic HCV do not have evidence of a DAA prescription. Addressing this undertreatment requires engagement with communities that are at risk for chronic HCV to encourage testing and follow-up, as well as education of clinicians on indications for chronic HCV testing and removal of sobriety requirements. Outpatient treatment should be facilitated through not only dedicated clinics, but also nontraditional settings (eg, syringe service programs, mobile clinics), and primary care providers. These facilitators have previously been shown to be safe and effective through the Extension for Community Healthcare Outcomes model in New Mexico[43] and by general practitioners in Australia.[44] Finally, policy efforts should focus on reimbursement and removal of prior authorization and sobriety requirements.

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