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MAJOR ARTICLE

Absolute Insurer Denial of Direct-Acting Antiviral Therapy for Hepatitis C: A National Specialty Pharmacy Cohort Study

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Background. Despite the availability of new direct-acting antiviral (DAA) regimens, changes in DAA reimbursement criteria, and a public health focus on hepatitis C virus (HCV) elimination, it remains unclear if public and private insurers have increased access to these therapies over time. We evaluated changes in the incidence of absolute denial of DAA therapy over time and by insurance type.

Methods. We conducted a prospective cohort study among patients who had a DAA prescription submitted from January 2016 to April 2017 to Diplomat Pharmacy, Inc., which provides HCV pharmacy services across the United States. The main outcome was absolute denial of DAA prescription, defined as lack of fill approval by the insurer. We calculated the incidence of absolute denial, overall and by insurance type (Medicaid, Medicare, commercial), for the 16-month study period and each quarter.

Results. Among 9025 patients from 45 states prescribed a DAA regimen (4702 covered by Medicaid, 1821 Medicare, 2502 commercial insurance), 3200 (35.5%; 95% confidence interval, 34.5%–36.5%) were absolutely denied treatment. Absolute denial was more common among patients covered by commercial insurance (52.4%) than Medicaid (34.5%, $P < .001$) or Medicare (14.7%, $P < .001$). The incidence of absolute denial increased across each quarter of the study period, overall (27.7% in first quarter to 43.8% in last quarter; test for trend, $P < .001$) and for each insurance type (test for trend, $P < .001$ for each type).

Conclusions. Despite the availability of new DAA regimens and changes in restrictions of these therapies, absolute denials of DAA regimens by insurers have remained high and increased over time, regardless of insurance type.

Keywords. direct-acting antiviral; hepatitis C virus; insurance.

INTRODUCTION

All-oral, direct-acting antiviral (DAA) regimens for the treatment of chronic hepatitis C virus (HCV) infection have been available since 2014 [1]. These regimens result in high (≥94%) rates of cure and have been associated with few adverse effects [2]. Viral eradication can help to eliminate HCV transmission [3, 4], reduce the risk of liver complications [5], decrease extrahepatic manifestations of disease [6], and prolong survival [7]. As a result, HCV management guidelines from the American Association for the Study of Liver Diseases/Infectious Diseases Society of America have recommended DAA treatment for all chronic HCV-infected patients [8]. The ability to cure chronic HCV in nearly all infected people makes the prospect of eliminating HCV in the United States possible [9].

Despite the acknowledged benefits of HCV therapy [10], the high costs of DAAs have led public and private insurers in the United States to restrict access to these medications [11]. Insurers established varying criteria for reimbursement of DAAs, such as evidence of advanced liver fibrosis, consultation with a specialist, and/or abstinence from alcohol or illicit drug use [12, 13]. Restrictions for reimbursement of DAAs have been shown to be common across state Medicaid programs [14–16]. Analyses conducted shortly after the release of DAAs into the market showed that the downstream effect of these restrictions, absolute denial by insurers, was common overall, but more frequent among patients covered by Medicaid than Medicare or commercial insurance [17, 18]. However, these studies were not nationally representative and evaluated access to DAAs during their initial availability only.

Over the last 2 years, advocacy efforts by stakeholders, class action lawsuits, threats of legal action, and greater price competition due to the availability of new DAAs have led to relaxations

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of restrictions in DAA reimbursement within a variety of settings [19–21]. Consequently, it is important to examine how access to DAAs has changed since their initial release.

We determined the incidence of absolute denial of DAA therapy by type of insurance in a national sample of chronic HCV-infected patients prescribed DAA therapy between January 2016 and April 2017. Given the relaxation of restrictions in DAA reimbursements across a number of settings, we hypothesized that the overall incidence of absolute denial was lower than in initial reports [17, 18] and has declined over time.

METHODS

Study Design and Data Source

We conducted a prospective cohort study using data from Diplomat Pharmacy, Inc., which provides specialty pharmaceuticals, including DAAs, to patients across the United States. DAAs are often dispensed by specialty pharmacies because of their high costs and requirements for special handling and delivery [22]. For each DAA prescription, Diplomat contacts the prescribing clinician, obtains information required by the insurer to determine medical need for DAA treatment, and submits this to the insurer for review. Final decision on DAA fill (approval or denial) is provided to the pharmacy from the insurer, typically within 30 days. Diplomat uses an electronic record system to record data on demographics, health insurance, and prescribed medications. HCV-related clinical data, such as HCV genotype, stage of hepatic fibrosis, alcohol consumption, and HIV status, are not electronically available for all patients with a submitted DAA prescription. The study was approved by the University of Pennsylvania Institutional Review Board.

Study Patients

Chronic HCV-infected patients with health insurance were included if they had a DAA prescription submitted to Diplomat between January 1, 2016, and April 30, 2017. If a patient had multiple DAA treatment courses prescribed during the period of interest, only the first regimen was included. Follow-up began on the date that the DAA prescription was received by Diplomat. Observation continued until the pharmacy ascertained the final outcome for the prescription (ie, absolute denial or DAA prescription fill).

Main Study Outcome

The primary outcome was absolute denial of DAA prescription, defined as lack of approval of DAA fill by the insurer. The status of all prescriptions with insurers was ascertained through August 31, 2017. Insurers' requests for alternative DAA regimens due to formulary restrictions were not recorded as absolute denials.

Data Collection

Demographic and pharmacy data collected from Diplomat's electronic records at the time the DAA prescription was received by the pharmacy included age, sex, state of residence, type of insurance, and DAA regimen prescribed. Type of insurance was determined based on the insurance plan to which the DAA prescription was submitted and was classified as Medicaid (joint federal- and state-funded programs for medical care and drug benefits for low-income and special needs individuals [23]), Medicare (federal health insurance program available to Americans aged ≥65 years and to some <65 years with certain disabilities or chronic health conditions [24]), or commercial insurance (health benefits that are employer sponsored, privately purchased, or obtained via health exchange through the Affordable Care Act [25]). For patients covered by Medicaid, we also determined enrollment in a fee-for-service or managed care plan.

Statistical Analysis

Differences in patients' characteristics by type of insurance (Medicaid, Medicare, or commercial insurance) were assessed using chi-square tests for categorical data and Kruskal-Wallis tests for continuous data.

We calculated the incidence and 95% confidence intervals (CIs) of absolute denial of DAA prescription, overall and by type of insurance, for the total 16-month study period and for each quarter. We included April 2017 within the final quarter (January–April 2017) for these analyses. We determined tests for trend to assess the significance of changes in the incidence of absolute DAA denial over time. In addition, we calculated the proportion of absolute denials within each state, overall and by insurance type. Data were analyzed using Stata 12.1 (Stata Corporation, College Station, TX).

RESULTS

Between January 1, 2016, and April 30, 2017, Diplomat received DAA prescriptions for 9025 patients from 45 US states (4702 covered by Medicaid; 1821 by Medicare; 2502 by commercial insurance). Medicaid patients were younger than those with Medicare or commercial insurance (Table 1).

Among these 9025 patients, 3200 (35.5%; 95% CI, 34.5%–36.5%) received an absolute denial of their treatment (Figure 1; Supplementary Table 1). Throughout the observation period, the incidence of absolute denial was more common among patients covered by commercial insurance (52.4%) than by Medicaid (34.5%, $P < .001$) or Medicare (14.7%, $P < .001$). Among Medicaid beneficiaries, the overall incidence of absolute denial was higher among those with fee-for-service (47.5%) than managed care plans (32.6%, $P < .001$).

The incidence of absolute denial increased across each quarter of the 16-month study period when examined overall (27.7% in the first quarter to 43.8% in the last quarter; test for trend, $P < .001$) and for each type of insurance (test for trend, $P < .001$ for each type) (Figure 1). Among Medicaid beneficiaries, patients enrolled in managed care plans experienced an increase in the incidence of absolute denial over time (test for trend, $P < .001$); however, no change over time was observed for

Table 1. Characteristics of Chronic Hepatitis C Virus–Infected Patients for Whom a Direct-Acting Antiviral Prescription Was Received by the Specialty Pharmacy Between January 2016 and April 2017, Overall and by Type of Insurance

Characteristic	Overall	Medicaid	Medicare	Commercial Insurance	*P* Value
No. (%) with DAA prescription submitted to pharmacy	9025	4702 (52.1)	1821 (20.2)	2502 (27.7)	
Median age (IQR), y	57 (49–62)	55 (45–60)	64 (58–68)	58 (49–62)	<.001
Female sex, No. (%)	3463 (38.4)	1834 (39.0)	714 (39.2)	915 (36.6)	.200
DAA regimen prescribed, No. (%)					<.001
Sofosbuvir/velpatasvir +/- ribavirin	1726 (19.1)	1026 (21.8)	213 (11.7)	487 (19.5)	
Sofosbuvir/ledipasvir +/- ribavirin	4662 (51.7)	1957 (41.6)	1213 (66.6)	1492 (59.6)	
Sofosbuvir + ribavirin	392 (4.3)	212 (4.5)	79 (4.3)	101 (4.0)	
Sofosbuvir + simeprevir +/- ribavirin	9 (0.1)	4 (0.1)	3 (0.2)	2 (0.1)	
Paritaprevir/ritonavir/ombitasvir + dasabuvir +/- ribavirin	402 (4.5)	217 (4.6)	30 (1.7)	155 (6.2)	
Paritaprevir/ritonavir/ombitasvir +/- ribavirin	9 (0.1)	6 (0.1)	2 (0.1)	1 (0.04)	
Elbasvir/grazoprevir +/- ribavirin	1316 (14.6)	994 (21.1)	177 (9.7)	145 (5.8)	
Daclatasvir + sofosbuvir +/- ribavirin	495 (5.5)	279 (5.9)	100 (5.5)	116 (4.6)	
Pegylated interferon alfa + sofosbuvir + ribavirin	14 (0.2)	7 (0.2)	4 (0.2)	3 (0.1)	

Abbreviations: DAA, direct-acting antiretroviral; IQR, interquartile range.

those enrolled in fee-for-service plans (test for trend, $P = .34$) (Supplementary Table 1).

Among the 45 states from which a DAA prescription was submitted during the observation period, 8 states contributed 90% of prescriptions: Pennsylvania (2839 [31.5%]), California (2133 [23.6%]), Michigan (1292 [14.3%]), Massachusetts (557 [6.2%]), New Jersey (553 [6.1%]), Delaware (316 [3.5%]), Oregon (231 [2.6%]), and Maryland (167 [1.9%]) (Table 2). The overall incidence of absolute DAA denial varied by type of insurance within and across states (Figure 2; Table 2). Among prescriptions submitted from these 8 states, the overall incidence of absolute denial was higher in Maryland (86/167 [51.5%]), Delaware (155/316 [49.1%]), New Jersey (261/553 [47.2%]), and Pennsylvania (1297/2839 [45.7%]) than those in the other 4 states.

DISCUSSION

For DAA prescriptions submitted to a national specialty pharmacy between January 2016 and April 2017, 35.5% were absolutely denied by the insurance carrier. The incidence of absolute

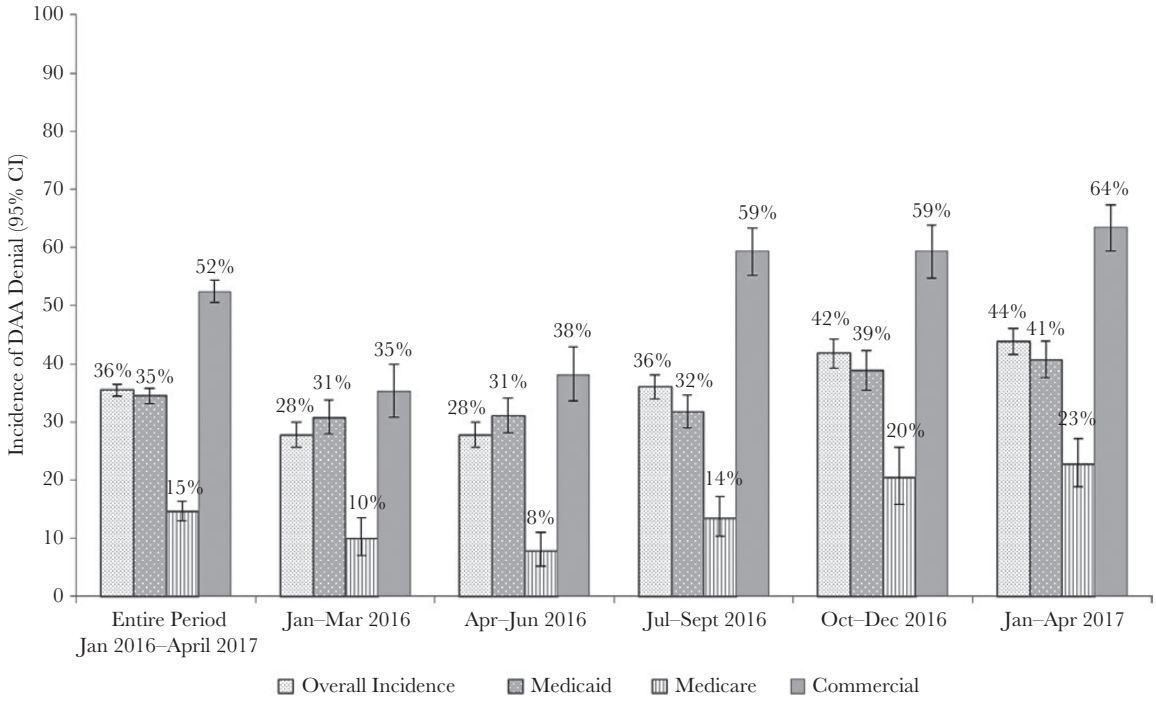

Figure 1. Incidence of absolute denial of direct-acting antiviral regimen documented by the specialty pharmacy over the specified time period according to type of insurance, overall and by quarter of calendar year. Abbreviation: CI, confidence interval.

Table 2. Incidence of Absolute Denial of Direct-Acting Antiviral Regimen Documented by the Specialty Pharmacy Between January 2016 and April 2017, According to Patient's Insurance and State of Residence

	Overall		Medicaid		Medicare		Commercial Insurance	
State	No. Submitted (% of Total)	No. Denied (% of Submitted)	No. Submitted	No. Denied (% of Submitted)	No. Submitted	No. Denied (% of Submitted)	No. Submitted	No. Denied (% of Submitted)
Overall	9025	3200 (35.5)	4702	1620 (34.5)	1821	268 (14.7)	2502	1312 (52.4)
AL	17 (0.2)	3 (17.7)	0	0	13	1 (7.7)	4	2 (50.0)
AK	2 (0.02)	1 (50.0)	0	0	0	0	2	1 (50.0)
AZ	44 (0.5)	22 (50.0)	14	13 (92.9)	9	0 (0.0)	21	9 (42.9)
AR	0 (0)	0	0	0	0	0	0	0
CA	2133 (23.6)	360 (16.9)	1780	247 (13.9)	183	35 (19.1)	170	78 (45.9)
CO	31 (0.3)	22 (71.0)	1	1 (100.0)	6	2 (33.3)	24	19 (79.2)
CT	20 (0.2)	9 (45.0)	3	1 (33.3)	6	0 (0.0)	11	8 (72.7)
DE	316 (3.5)	155 (49.1)	110	74 (67.3)	76	8 (10.5)	130	73 (56.2)
FL	45 (0.5)	23 (51.1)	8	6 (75.0)	17	4 (23.5)	20	13 (65.0)
GA	23 (0.3)	10 (43.5)	5	4 (80.0)	8	0 (0.0)	10	6 (60.0)
HI	0 (0)	0	0	0	0	0	0	0
ID	17 (0.2)	3 (17.7)	2	1 (50.0)	8	0 (0.0)	7	2 (28.6)
IL	107 (1.2)	50 (46.7)	17	16 (94.1)	33	4 (12.1)	57	30 (52.6)
IA	1 (0.01)	1 (100.0)	0	0	0	0	1	1 (100.0)
IN	16 (0.2)	7 (43.8)	4	3 (75.0)	3	0 (0.0)	9	4 (44.4)
KS	4 (0.04)	0 (0.0)	0	0	1	0 (0.0)	3	0 (0.0)
KY	25 (0.3)	5 (20.0)	3	3 (100.0)	15	0 (0.0)	7	2 (28.6)
LA	3 (0.03)	1 (33.3)	0	0	0	0	3	1 (33.3)
ME	0 (0)	0	0	0	0	0	0	0
MD	167 (1.9)	86 (51.5)	46	32 (69.6)	52	7 (13.5)	69	47 (68.1)
MA	557 (6.2)	110 (19.8)	466	78 (16.7)	16	3 (18.8)	75	29 (38.7)
MI	1292 (14.3)	477 (36.9)	462	232 (50.2)	379	41 (10.8)	451	204 (45.2)
MN	9 (0.1)	6 (66.7)	3	3 (100.0)	1	1 (100.0)	5	2 (40.0)
MS	0 (0)	0	0	0	0	0	0	0
MO	14 (0.2)	0 (0.0)	1	0 (0.0)	1	0 (0.0)	12	0 (0.0)
MT	21 ().2)	9 (42.9)	0	0	1	1 (100.0)	20	8 (40.0)
NE	1 (0.01)	1 (100.0)	0	0	0	0	1	1 (100.0)
NV	75 (0.8)	25 (33.3)	2	2 (100.0)	24	3 (12.5)	49	20 (40.8)
NH	9 (0.1)	4 (44.4)	3	3 (100.0)	1	0 (0.0)	5	1 (20.0)
NJ	553 (6.1)	261 (47.2)	199	129 (64.8)	148	14 (9.5)	206	118 (57.3)
NM	2 (0.02)	0 (0.0)	0	0	2	0 (0.0)	0	0
NY	6 (0.07)	5 (83.3)	0	0	0	0	6	5 (83.3)
NC	118 (1.3)	44 (37.3)	25	12 (48.0)	58	8 (13.8)	35	24 (68.6)
ND	4 (0.04)	1 (25.0)	0	0	0	0	4	1 (25.0)
OH	26 (0.3)	8 (30.8)	4	3 (75.0)	11	1 (9.1)	11	4 (36.4)
OK	4 (0.04)	3 (75.0)	1	0 (0.0)	0	0	3	3 (100.0)
OR	231 (2.6)	46 (19.9)	186	32 (17.2)	13	1 (7.7)	32	13 (40.6)
PA	2839 (31.5)	1297 (45.7)	1294	676 (52.2)	662	124 (18.7)	883	497 (56.3)
RI	4 (0.04)	4 (100.0)	3	3 (100.0)	1	1 (100.0)	0	0
SC	23 (0.3)	5 (21.7)	1	1 (100.0)	19	1 (5.3)	3	3 (100.0)
SD	1 (0.01)	1 (100.0)	0	0	0	0	1	1 (100.0)
TN	9 (0.1)	2 (22.2)	0	0	0	0	9	2 (22.2)
TX	89 (1.0)	47 (52.8)	3	3 (100.0)	28	6 (21.4)	58	38 (65.5)
UT	10 (0.1)	9 (90.0)	4	4 (100.0)	0	0	6	5 (83.3)
VT	0 (0)	0	0	0	0	0	0	0
VA	13 (0.1)	6 (46.2)	3	3 (100.0)	3	0 (0.0)	7	3 (42.9)
WA	61 (0.7)	27 (44.3)	19	13 (68.4)	3	0 (0.0)	39	14 (35.9)
WV	8 (0.09)	6 (75.0)	3	2 (66.7)	1	1 (100.0)	4	3 (75.0)
WI	70 (0.8)	36 (51.4)	27	20 (74.1)	19	1 (5.3)	24	15 (62.5)
WY	5 (0.06)	2 (40.0)	0	0	0	0	5	2 (40.0)

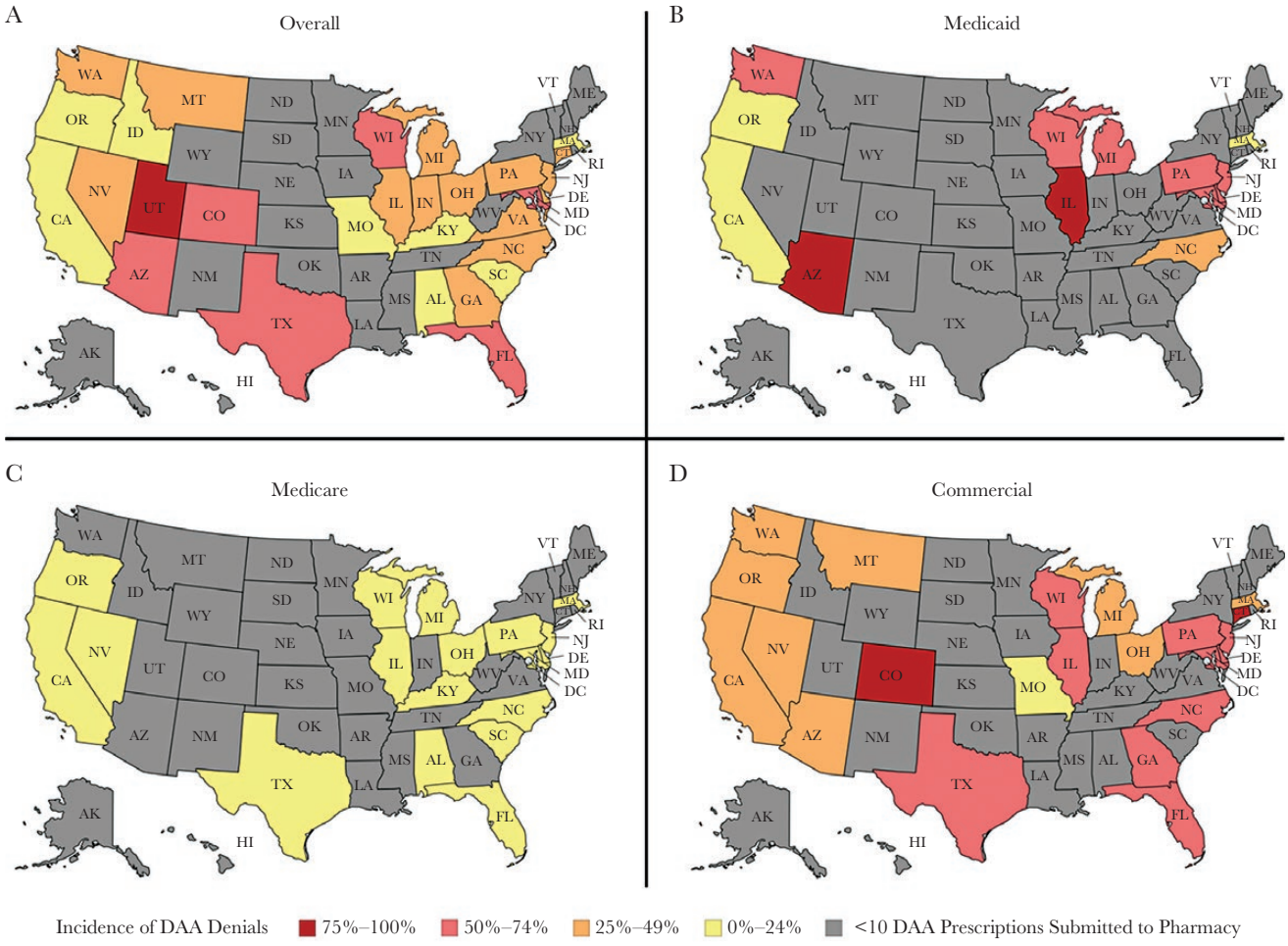

Figure 2. Incidence of absolute denial of direct-acting antiviral regimen documented by the specialty pharmacy between January 2016 and April 2017 according to patient's state of residence, overall (A) and by type of insurance (B: Medicaid; C: Medicare; D: commercial insurance).

denial was higher among commercially insured (52.4%) and Medicaid (34.5%) beneficiaries compared with Medicare beneficiaries (14.7%). Notably, the incidence of denial increased for all insurance types over subsequent quarters during the observation period. Finally, the incidence of absolute DAA denial varied by type of insurance within and across states.

Contrary to our hypothesis, the overall incidence of absolute denial in this study (35.5%) was substantially higher in magnitude than that observed in 2 prior analyses conducted shortly after the release of all-oral DAA regimens (absolute denial range, 8.2%–16.2%) [17, 18]. The reason for this higher-than-expected denial rate is unclear, but may be due to attempts to treat chronic HCV-infected patients who have less advanced liver fibrosis, have not met sobriety restrictions, or have not had consultation with a specialist.

In prior studies, denial of DAA therapy was reported to occur in as high as 46.3% of Medicaid beneficiaries [17, 18]. In contrast, the results of the present study indicate that the overall incidence of absolute denial of DAAs is now lower in magnitude for Medicaid beneficiaries (34.5%). The lower overall absolute denial rate of DAAs among Medicaid beneficiaries is likely a consequence of the statement by the Centers for Medicare and Medicaid Services that restriction of access to DAAs based on cost containment violates federal law [26], following reports highlighting restrictions on reimbursement of DAAs across state Medicaid programs [14, 15]. This notification prompted class action lawsuits and threats of legal action against some state Medicaid programs in response to the rationing of DAA therapies [27–29]. These efforts contributed to changes in the criteria for reimbursement of DAAs across a number of Medicaid programs [16]. There have been several notable trends in Medicaid HCV treatment criteria in recent years, including more transparency in treatment restrictions, decreased restrictions particularly for the degree of liver fibrosis, and more information on restrictions imposed by managed care organizations [19]. However, as Table 2 and Figure 2 demonstrate, there remains considerable heterogeneity in the incidence of absolute denial across state Medicaid programs, presumably due to the varying criteria for reimbursement across these programs [14–16].

We found that among Medicaid beneficiaries, the overall incidence of absolute denial was higher among those with fee-for-service than managed care plans. However, Medicaid patients enrolled in managed care plans experienced an increase in the incidence of absolute denial over time, while no change was observed for those enrolled in fee-for-service plans. The increase in denial for Medicaid patients in managed care plans is concerning since Medicaid programs, by law, must ensure that their managed care organizations offer either similar or less restrictive coverage than the fee-for-service plans in the same state [30]. Regulators should ensure that parity in access to DAA treatments between Medicaid fee-for-service and managed care programs is monitored and enforced.

Our study found a substantially higher incidence of absolute denial for patients covered by Medicare (14.7%) and commercial insurance (52.4%) than that reported in prior studies [17, 18]. Those reports showed that 2.5%–5.0% of Medicare beneficiaries and 5.9%–10.2% of commercially insured individuals had their DAA regimens absolutely denied. Little is known about restrictions to HCV treatment among Medicare and commercial insurance beneficiaries. It is possible that these plans were less restrictive shortly after the release of DAAs but became more restrictive in their reimbursement policy over time. Our data highlight the need for transparency in defining criteria for restriction by all insurers, including commercial insurance and Medicare Part D plans.

Also contrary to our hypothesis, we observed that the incidence of absolute denial increased over time, regardless of insurance type. The reasons for this increase remain unclear. The combination of cost and demand for DAA treatments has strained the budgets of many payers since these drugs became available [12]. As a result, insurers may be electing to prioritize certain patient populations, such as those who have advanced hepatic fibrosis/cirrhosis or who abstain from alcohol and injection drug use, when deciding whether to allocate DAA treatments [11–13]. Future studies should evaluate the reasons for the increasing denials across insurance plans as well as denial rates in specific patient groups.

The high incidence of absolute denial of DAA therapy has important implications. From a clinical standpoint, patients denied access to HCV therapy remain at risk for the development of hepatic fibrosis, cirrhosis, liver decompensation, and hepatocellular carcinoma. Denial of DAA treatment can also lead to ongoing HCV-associated inflammation, which might increase the risk of extrahepatic complications. Further, failure to treat and cure chronic HCV maintains a reservoir of HCV transmission. From a public health standpoint, the high incidence of absolute denial of DAA treatment represents a major barrier to the goal of HCV elimination. A recent report by the National Academies of Sciences, Engineering, and Medicine determined that at least 260 000 chronic HCV-infected patients must be treated yearly to achieve elimination of HCV in the United States by 2030 [9]. Given the clinical benefits of curing chronic HCV infection [10], cost-effectiveness of DAA treatment [31–33], and importance of antiviral therapy to HCV elimination efforts, the National Academies' report recommended that public and private insurers should remove restrictions to DAAs that are not medically indicated and offer treatment to all chronic HCV-infected patients [9]. This recommendation is consistent with guidelines from the American Association for the Study of Liver Diseases/Infectious Diseases Society of America that recommend DAA treatment for all patients with chronic HCV infection [8]. The high incidence of denial of HCV therapy adversely impacts strategies for HCV elimination.

This study had several potential limitations. First, the specialty pharmacy did not electronically record certain data elements in a manner that could be obtained for the purpose of this study. The pharmacy did not record the date of the final disposition of the DAA prescription as a distinct data field, preventing us from calculating the median time to DAA fill or denial. Extractable HCV-related data were not available for all patients with a submitted DAA prescription. As a result, we were unable to identify factors that were independently associated with absolute DAA denial. Data on interim denials and appeals were also not electronically recorded. Second, insurers did not provide the specialty pharmacy with their reasons for denial, which were only submitted to the patients. We therefore were unable to confirm the precise reasons for the high incidence of absolute denial within and across insurance types. Finally, while our analysis was nationally representative, 8 states constituted the majority of the data, and data on 5 states were not available at all because the specialty pharmacy did not service those regions.

In conclusion, despite the availability of new DAA regimens and changes in restrictions to these therapies, absolute denials of DAA regimens by insurers have remained high and increased over time, regardless of type of insurance. These data provide evidence of a continued lack of access to HCV therapy across insurance types. To achieve the goal of HCV elimination [9], access to antiviral treatment must be improved.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. S.L. and M.G. are employees of EnvoyHealth. S.T. has received investigator-initiated research grant support (to the Philadelphia Field Initiating Group for HIV Trials) from Gilead Sciences and has served on an advisory board for Gilead Sciences. J.R.K. has served on an advisory board for Gilead Sciences. All other authors report no relevant conflicts of interest. All authors have submitted the ICMJE

Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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