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Compliance and Treatment Failure of Hepatitis C with Direct-acting Antivirals: A 2-Year Retrospective, Observational Study in Kentucky Medicaid Patients

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ABSTRACT

Background: New generation Direct-acting antivirals (DAAs) for the treatment of chronic hepatitis C infection have been on the market for more than 3 years since late 2013. Whether these medications cure patients at the rates claimed in clinical trials is not clear. Furthermore, as compliance is known to affect treatment outcomes, DAAs compliance rate is worth studying.

Methods: We analyzed the association of social-demographic, DAA use, enrollment with Kentucky Medicaid Managed Care Organizations (MCOs) and comorbidities, and DAA compliance in 1128 Kentucky Medicaid members treated with DAAs between August 07, 2014 and August 06, 2016.

Results: Age, MCOs, liver fibrosis or cirrhosis, the use of ribavirin as supportive treatment of DAAs and taking more than one DAA were significant determinants of patient compliance. Age above 60 and being enrolled with Wellcare were associated with an increase in hepatitis C medications adherence after adjusting for all other risk factors (1.434 [1.045, 1.968] for age >=60 in comparison to age between 50-59, 0.58 [95% CI: (0.37, 0.89)], 0.35 [95% CI: (0.21, 0.58)], 0.64 [95% CI: (0.42, 0.99)] and 0.55 [95% CI: (0.40, 0.76)] respectively for Aetna, Anthem, Humana and Passport compared with Wellcare). In contrast, being comorbid with liver fibrosis/cirrhosis, taking ribavirin or more than one DAA were significantly related to decreased adherence (0.74 [0.57, 0.96], 61.6% [0.26, 0.58], 0.50 [0.29, 0.86 respectively]. Use of Sovaldi and being comorbid with rheumatoid arthritis also had an impact without achieving significance.

Conclusion: The findings of this study can be a useful screening tool for patients with factors that have predispositions for noncompliance. However, more studies in this area should be done to endorse these findings before they can be translated into clinical practice.

INTRODUCTION

It is estimated that 3.5 million persons are living with hepatitis C virus (HCV) infection in the United States (Edlin et al, 2015). The state of Kentucky saw the highest incidence (4 per 100,000 population) of acute hepatitis C infection in US from 2010 through 2014 (Center for Disease Control, 2014). During this time, Women of childbearing age between 15-44 who tested positive for HCV increased by 22% nationally and greater than 200% for Kentucky (Koneru et al, 2016). Among those acutely infected, chronic HCV (CHC) infection develops in 50-85% of the patients, posing great challenge and pressure to the medical and public health community (Lauer et al, 2001).

Before the development of oral, direct-acting antivirals (DAAs), the backbone of chronic hepatitis C infection was the combination of pegylated interferon and ribavirin, which can eradicate the virus in more than 50% of patients (Poynard et al, 2003). Interferon induces host antiviral gene expression to inhibit virus replication, protein synthesis and assembly, along with enhancing immune response (Feld & Hoofnagle, 2003). As a guanosine analogue, ribavirin directly inhibits HCV replication and was found to potentiate the antiviral activity of interferon (Feld & Hoofnagle, 2003). They affect non-specific intracellular singling pathways of HCV replication. HCV treatment took a major step forward at the end of 2013 with the approvals of the second-generation protease inhibitor simeprevir (Olysio) and the nucleotide polymerase inhibitor sofosbuvir (Sovaldi). Both are DAAs and target only specific molecules and enzymes involved in various stages of the HCV life cycle. Ever since then, concerns have been raised by the states about the budgetary impact on Medicaid programs and beneficiary access to needed care (CMS, 2015). As much as the Center for Medicare and Medicaid Services (CMS) is trying to remain committed to Medicaid beneficiaries continuing to have access to needed prescribed

medications, they also recognize the challenges that have risen with DAA HCV drugs (CMS, 2015). Limitations on treatment capacity makes it difficult to eliminate the hepatitis C virus in the United States (Brawley et al, 2016). Currently, less than 3 percent of the state's Medicaid beneficiaries with the disease receive treatment (Patrick 2016). For Harvoni alone, Medicaid spending nationwide on this medication soared 22-fold in one year, from just 95 million in 2014 to $2.2 billion in year 2015 (5CMS 2016). In Kentucky, spending on Harvoni and Sovaldi in the first two quarters of fiscal year 2016 exceeded $25 million (Medicaid.org, 2017).

For over a decade, the standard-of-care treatment for CHC has been interferon/ribavirin combination therapy, which has a 40-50% response rate in genotype 1 CHC patients and a response of up to 70-80% in genotype 2/3 CHC patients (Umar et al, 2013). With CHC infection cure rates between 90%-100% using the new generation oral medications in just 12 weeks' time (US FDA, 2016), non-adherence is the most important risk factor for hepatitis C virus treatment failure (Sarpel et al, 2016; American Association for the Study of Liver Diseases, 2017). Although extensive studies have related poor adherence and outcomes with interferon and ribavirin-based therapy (Davis et al, 2003; McHutchison et al, 2002; Younossi et al, 2015), few studies, however, have evaluated the compliance rate of these highly effective direct-acting antivirals (DAAs) since their approval in late 2013 in non-controlled environments. A review published in 2014 analyzed the factors that modulate patient-driven adherence to the treatment of HCV infection with first generation protease inhibitors telaprevir (TVR) and boceprevir (BOC). It suggested that treatment complexity and side effects were key points for the adherence and success of the therapy (Larrey et al, 2014). A multicenter multinational phase 3 clinical trial discovered that a high overall adherence rate of 96.2% was achieved in 1483 patients treated with interferon- and ribavirin-free sofosbuvir (SOF) and ledipasvir (LED) in a fixed dose

combination therapy (Younossi et al 2016). Up to now, the magnitude of the association of non-compliance with treatment failure in patients with CHC infection is unclear, but any factors that may potentially reduce sustained virologic response can impede the hard-earned progress the Center for Medicare and Medicaid Services and state Medicaid agencies have made expanding access to this expensive cure regimen (Center for Disease Control (CDC), 2012; CMS, 2016; Gensen et al, 2014).

We performed a case control study in CHC patients enrolled in Kentucky Medicaid population to evaluate the compliance to new DAAs and the factors associated with high compliance. Subgroup analysis was also conducted to evaluate laboratory features and patient characteristics associated with treatment failure. This study aimed to bridge the gap in current hepatitis C treatment by exploring the compliance pattern in a state severely impacted by the hepatitis C epidemic.

METHODS

Dataset

This retrospective observational study was carried out on hepatitis C patients enrolled with Kentucky Medicaid who were treated with the new generation antiviral therapies in 114 counties in Kentucky between August 07, 2014 and August 06, 2016. Outpatient prescriptions covered through Kentucky Medicaid were managed either with Kentucky Medicaid's Fee for Service (FFS) program through Magellan Health, a Pharmacy Benefit Manager, or carved out to the Medicaid Managed Care Organizations (MCOs), including Aetna Better Health (Aetna), Anthem Blue Cross Blue Shield (Anthem), Humana CareSource (Humana), Passport Health Plan (Passport) and Wellcare of Kentucky (Wellcare). All 1128 patients were identified from the Kentucky Medicaid Database by searching 11 DAA medications approved by the Food and Drug

Administration (FDA) for use in CHC treatment: Daklinza (Daclatasvir), Epclusa (Sofosbuvir/Velpatasvir), Harvoni (Ledipasvir/Sofosbuvir), Inciviek (Telaprevir), Olysio (Simeprevir), Sovaldi (sofosbuvir), Technivie (Paritaprevir/Ombitasvir/Ritonavir), Viekira Pak (Dasabuvir/Paritaprevir/Ombitasvir/Ritonavir) and Zepatier (Elbasvir/Grazoprevir). All 5613 hepatitis C related prescriptions including add-on ribavirin and interferon alpha prescriptions were examined.

Compliance in our study was defined by the formulary metric Proportion of Days Covered (PDC). Reported as a percentage, it measured the number of days covered by prescriptions and divided by the number of days in the measurement period for that medication. It is usually preferred over the use of the Medication Possession Ratio (MPR) for a more conservative estimate of adherence (Nau, 2012). The PDC value for each member was the average PDC value of all hepatitis C medications reimbursed through Kentucky Medicaid during the study period. A patient was defined as "compliant" with hepatitis C treatment when the average PDC for all medications was 100%.

The covariates obtained through each prescription entry included age (year), sex, race, county of residence, MCO/PBM, medication, medication National Drug Code (NDC), dispensed quantity, days of supply (days) and comorbidities. The corresponding comorbidities associated with each member on DAA were extracted as well for risk stratification. Age was categorized into 4 groups: ≤40, 40~49, 50~59 and ≥60. To better investigate the relationship of geographic location and compliance, counties were rearranged into new categories based on county Beale Code Urban-Rural Classification Scheme and Rural-Urban Continuum Codes (National Cancer Institute (NCI), n.d.). They are relabeled as "Metro county" if Beale Codes are between 1~3,

"Urban county" if between 4-6 and "Rural county" if between 7-9. Metro status is "1" if counties are grouped as "Metro county" and "0" if otherwise.

All antiviral medications for hepatitis C were evaluated to investigate patient-specific adherence. Antiviral regimen may change, therefore an additional variable called "multiple treatment" was added to account for the variance in compliance, with a value of "1" if a member had received more than 1 DAAs in the designated time and "0" if otherwise. As patients can be on interferon alpha 2a and ribavirin for supportive therapy of DAAs, the use of either or both medications were added as covariates as well.

A total of 31 types of comorbidities were captured by submission of out-patient prescription medication claims. included cancer, cardiovascular disease and respiratory disease among others. To make more general predictions on the impact of certain diseases on treatment compliance, two new composite comorbidity variables were created: "cardiovascular disease (CVD)" and "cancer". The number and types of comorbidities related to members were compared in two groups: compliant members and non-compliant members.

Statistical Analysis

Statistical analysis was conducted with SAS 9.4 for Windows V6.1. Comparisons were performed using the Student t test, the Mann-Whitney-Wilcoxon test and Chi-square test in two compliance groups. To identify the factors shaping compliance with CHC treatment, bivariate relationships between compliance and the covariates described earlier were assessed. Covariates with a p-value of less than 0.05, together with covariates that have been identified to impact treatment adherence rate in previous studies, were selected into a backward stepwise multi-variate logistic analysis.

Exploratory analyses included the use of descriptive statistics. Specifically, frequencies and percentages were examined for categorical variables-beale codes, DAAs, metro status, gender, race, MCOs and supportive therapy, and means, standard deviations and ranges were examined for continuous variables-age, PDC (%), number of comorbidities.

The bivariate relationship between compliance and selected patient parameters were assessed to determine unadjusted associations. Rather than using age as an ordinal predictor, age categories are used as the predictor of interest to add clinical importance. The same applies for the variable "county", as they are re-adapted based on Beale Codes and Metro Status.

Multi-variate logistic regression was used for the final model, with the possibility of 100% compliance with hepatitis C treatment as the outcome of interest. Backward elimination with a significance level of 0.1 was carried out for this model, starting with the main effects for all potential predictors mentioned in the Methods section.

RESULTS

A total of 1531 Medicaid members on hepatitis C treatment were identified between August 07, 2014 and August 06, 2016. Of these patients, 395 members were excluded from the study because they had a gap of 45 days or greater in coverage per year (n=302) (National Committee for Quality Assurance (NCQA), 2008), died (n=8), or were only on ribavirin, interferon alfa-2a or both (n=93), leaving 1128 active members enrolled contiguously using DAAs.

The descriptive statistics for the members enrolled in this study are provided in Table 1. Of the 1128 patients, 682 (60.3) had a 100% compliance rate by PDC. Comorbidities were common with an average number of 6 for each member. The majority of patients were white

(41.4%) male (62.5%), came from metro areas (58.7%) and used passport (40.5%) as their PBM. They were mostly treated with Harvoni (58.6%) or Sovaldi (37.3%), together with ribavirin or ribavirin plus interferon for supportive care.

Table 1. Summary of Descriptive Statistics for Medicaid Members Treated with DAAs between August 07, 2014 and August 06, 2016

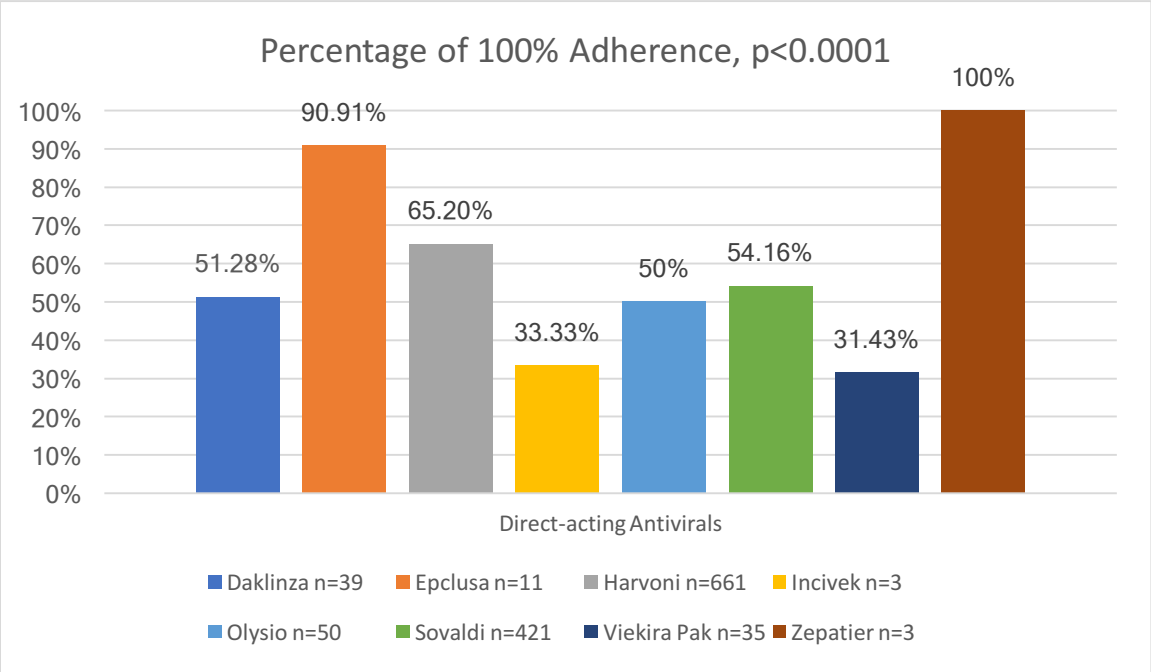
Variable	Pertinent Statistics
Age (years)	
n	1128
Mean (SD)	52.4 (9.3)
Median (Q1, Q3)	55 (47, 59)
(Min, Max)	(19, 71)
PDC (%)	
n	1128
Mean (SD)	95.7 (8.4)
Median (Q1, Q3)	1 (94.4, 100)
(Min, Max)	(21.4, 100)
Number of comorbidities (n)	
n	1128
Mean (SD)	5.6 (2.8)
Median (Q1, Q3)	5 (3, 7)
(Min, Max)	(0, 17)
Beale code [n (%)]	
1	450 (39.9)
2	131 (11.6)
3	81 (7.2)
4	35 (3.1)
5	21 (1.9)
6	116 (10.3)
7	175 (15.5)
8	38 (3.4)
9	81 (7.2)
Direct-acting Antivirals	
Daklinza	39 (3.5)
Epclusa	11 (0.1)
Harvoni	661 (58.6)
Incivek	3 (0.0)
Olysio	50 (4.4)
Sovaldi	421 (37.3)
Viekira Pak	35 (3.1)
Zepatier	3 (0.0)
Gender [n (%)]	

Female	423 (37.5)
Male	705 (62.5)
Metro status [n (%)]	
0	466 (41.31)
1	662 (58.7)
Managed care organization [n (%)]	
Aetna	130 (11.5)
Anthem	83 (7.4)
Humana	141 (12.5)
Magellan	12 (1.06)
Passport	457 (40.5)
Wellcare	305 (27.0)
Race [n (%)]	
White	463 (41.0)
Black	89 (7.9)
Other races or ethnicity	278 (24.6)
Not provided	198 (17.6)
Supportive care	
Interferon	62 (5.5)
Ribavirin	442 (39.2)
Interferon or ribavirin	442 (39.2)

Eight DAAs were used in the study population. Although all DAAs have similar safety and efficacy data in randomized controlled trials (Muir, 2014), compliance can be drastically lower than in a closely monitored environment, denoting potentially substantial deviance of outcome in actual clinical settings. The compliance statistics by DAA in Kentucky Medicaid population are illustrated in Figure 1. Epclusa and Zepatier were used in 11 and 3 patients respectively, but had the highest compliance rate at 90.9% and 100%. Both has similar dosing schedules and can be used with or without ribavirin and peginterferin, just like other DAAs used in this population. Thus, it is very likely that the high compliance presented in the population was due to coincidence. Harvoni and Sosaldi, both of which are mainstream treatments for chronic HCV infection, were the most heavily prescribed antivirals in Kentucky Medicaid beneficiaries. The percentage of patients with 100% compliance with Harvoni and Sovaldi

regimens ranges from 54%- 66%. The other DAAs were all less frequently used and poorly managed.

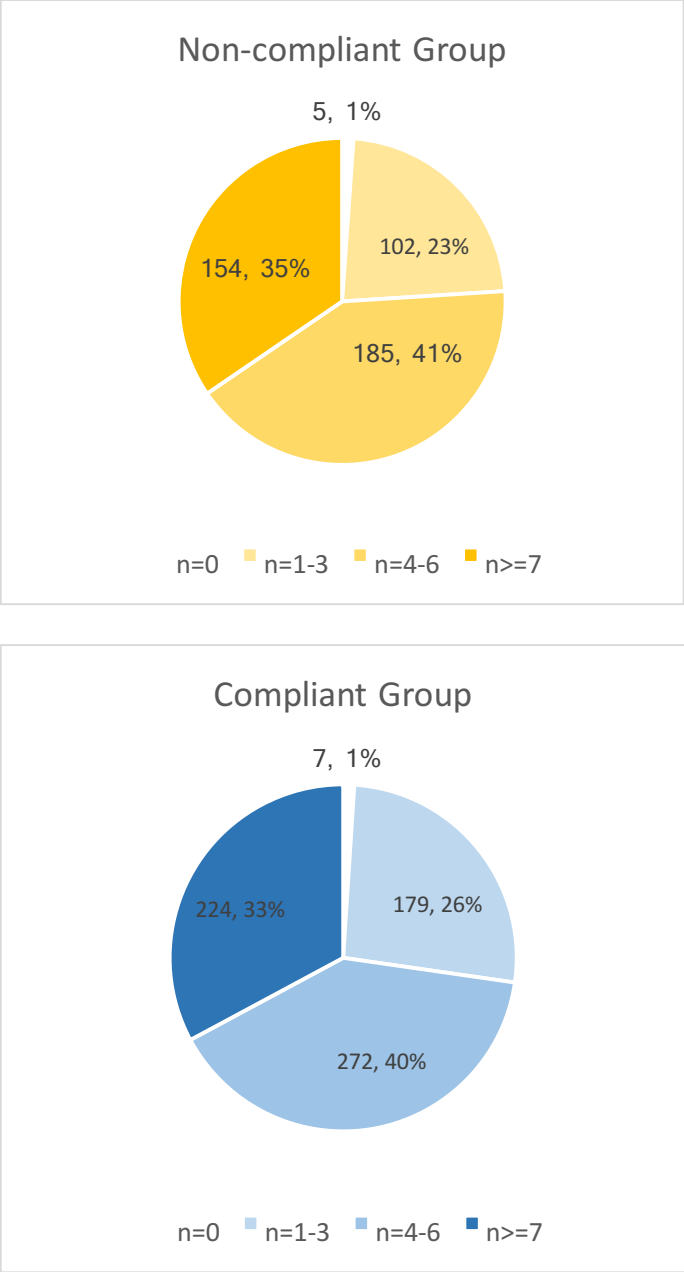
Figure 1. Percentage Compliance in Kentucky Medicaid Population by DAA



It has been demonstrated in multiple studies that comorbidities have a major influence on the outcome of antiviral therapy of hepatitis C (El-Zayadi, 2009; Louie, 2012). They may exert effects through altering the course, on response of DAA, or on ribavirin/peginterferon treatment (EL-Zayadi, 2009). No statistical significance was established in the number of comorbidities, however, a trend towards a higher number of comorbidities among non-compliant group can be inferred from the pie charts below in Figure 2. About 24% of members in the non-compliant group had less than 3 comorbidities vs. 27% of compliant group. At the other end of the spectrum are the extremely comorbid patients with 4-17 concurrent diseases. In the non-

compliant group, 41% and 35% of the patients had 4-6 or greater than 7 comorbidities, respectively, in comparison with 40% and 33% in the compliant group.

Figure 2. Distribution of Comorbidities in Kentucky Medicaid Population with Hepatitis C



Bivariate comparisons of socio-demographic and other covariates are presented in Table 2. Patients who were 100% compliant with hepatitis C therapy were compared to those who were

not; 682 of the 1128 patients (60.4%) were found to be compliant. This allows for the assessment of unadjusted associations of potential factors with compliance. Age (as a categorical variable), race, MCO, DAAs used in the therapy and whether patient got multiple DAA treatments were found to be significantly associated with medication compliance. Members in the less-than-49 age group had a considerably lower compliance than those that were 50 and above. Most patients in the compliance group were white (42.1%) and resided metro areas (56.6%). Passport had the greatest number of patients in the compliance group while patients with Wellcare were better managed and more adherent (58.0% of Passport vs. 70.5% of Wellcare). To avoid uneven sample size in the DAA category where the majority (88.5%) of scripts were in only two drug categories (Faber & Fonseca, 2014), 8 DAA groups were downsized to 3: Harvoni, Sovaldi and other DAAs. As anticipated, patients on 1 DAA were 1.59 times more likely to adhere to therapy than those on 2 or more. The use of ribavirin for supportive care was also shown to have an impact, with non-compliance group having 15.3% more patients on ribavirin than compliance group.

Table 2. Univariate Analysis of Hepatitis C Treatment Compliance

	Non-compliant Patients (n = 446)	**Compliant Patients (n=682)**	**P value**
Age [n (%)]			
<40	47 (10.5)	80 (11.7)	0.03
40-49	71 (15.9)	144 (21.1)	
50-59	226 (50.7)	287 (42.1)	
>=60	102 (22.9)	171 (25.1)	
Male gender [n (%)]	275 (61.7)	430 (63.1)	0.64
Race [n (%)]			
White	176 (39.5)	287 (42.1)	0.003
Black	43 (9.6)	46 (6.7)	
Other	167 (37.4)	211 (30.9)	
Not Provided	60 (13.5)	138 (20.2)	
Beale code [n (%)]			
1-3	276 (61.2)	386 (56.6)	0.06
4-6	71 (15.9)	101 (14.8)	

7-9	99 (22.2)	195 (28.6)	
Metro status [n (%)]			
0	170 (38.1)	296 (43.4)	0.08
1	276 (61.9)	386 (56.6)	
MCO [n (%)]			
Aetna	55 (12.3)	75 (11.0)	0.0002
Anthem	44 (9.9)	39 (5.7)	
Humana	57 (12.8)	84 (12.3)	
Magellan	8 (1.8)	4 (0.6)	
Passport	192 (43.1)	265 (38.9)	
Wellcare	90 (20.2)	215 (31.5)	
Comorbidities (n)	5.7 ± 2.9	5.5 ± 2.8	0.36
Direct-acting Antivirals			
Harvoni	230 (46.6)	431 (59.1)	0.0001
Sovaldi	193 (39.1)	228 (31.3)	
Other DAAs	71 (14.4)	70 (9.6)	
Multiple Treatment			
0	399	635	0.0303
1	47	47	
Supportive Care			
Ribavirin	216 (48.4)	226 (33.1)	<.0001
Interferon	27 (6.1)	35 (5.1)	0.5068
Ribavirin or Interferon	216 (48.4)	226 (33.1)	<.0001

Data are expressed as frequencies (column percentage) of patients.

The bivariate analysis between 31 comorbidities and compliance, arranged from the highest to the lowest frequency, is reported in Table 3. Patients with chronic kidney disease (CKD), depression and substance use disorder (SUD) were linked to the highest rate of compliance. This finding in patients with SUD is not unexpected, given that opioid treatment programs are structured to provide medical supervision over opioid detoxication and the administration of all other prescribed medications, including antivirals for hepatitis C (McCance-Katz & Valdiserri, 2015). None of the disease states but liver fibrosis/cirrhosis was found to be statistically significant in relation to compliance. Although myocardial infarction, liver cancer, colorectal cancer, prostate cancer, osteoporosis and liver transplant were marginally significant

(p-value <=0.1), they were excluded from the final multi-variate logistic regression model because of their tendency to lead to inaccurate conclusions (King & Zeng, 2001).

Table 3. Bivariate Associations Between Comorbidities with Hepatitis C Therapy Compliance

Comorbidity	Frequency	Percentage compliant (%)	Odds Ratio	P value
Cardiovascular disease	869	60.1	0.93	0.62
Hypertension	800	60.1	0.95	0.72
Hyperlipidemia	399	59.4	0.93	0.59
Ischemic heart disease	171	57.9	0.88	0.46
Heart failure	79	60.8	1.01	0.96
Stroke/Transient heart attack	59	57.6	0.88	0.65
Atrial fibrillation	28	53.6	0.75	0.45
Myocardial infarction	26	42.3	0.47	0.06
Substance use disorder	836	61.1	1.46	0.44
Liver fibrosis/cirrhosis	637	57.3	0.74	0.01
Rheumatoid arthritis	543	57.8	0.81	0.08
Depression	511	61.3	1.06	0.62
COPD/Bronchiectasis	480	61.0	1.04	0.73
Asthma	374	60.7	1.01	0.91
Anemia	274	57.7	0.86	0.28
Chronic kidney disease	273	61.5	1.06	0.68
Diabetes	268	60.1	0.98	0.88
Hyperthyroidism	117	56.4	0.83	0.34
Cataract	106	60.4	1.00	0.99
Benign prostatic hyperplasia	80	58.8	0.93	0.75
Cancer	72	51.4	0.67	0.10
Liver cancer	41	46.3	0.55	0.06
Breast cancer	9	44.4	0.52	0.32
Colorectal cancer	9	88.9	5.28	0.08
Lung cancer	9	55.6	0.82	0.76
Prostate cancer	7	28.6	0.26	0.08
Endometrial cancer	1	100.0	/	0.42
Osteoporosis	46	73.9	1.90	0.06
Glaucoma	41	70.7	1.61	0.17
Liver transplant	22	40.9	0.45	0.06
Alzheimer's and related diseases	18	61.1	1.02	0.95
Hip/Pelvic fracture	9	44.4	0.52	0.32
Autism sectrum	1	0.0	/	0.22

Based on the result from the bivariate analysis in Table 2 and Table 3, the variables proposed for the multi-variate logistic regression model with backward elimination included age (as a categorical variable), race, MCO, DAAs, whether patient got multiple DAA treatments (multiple treatment) and use of ribavirin. To fully rule out the possibility of high-frequency comorbidities playing a role in compliance, the most common top 10 comorbidities were also incorporated into model: CVD, SUD, liver fibrosis/cirrhosis, rheumatoid arthritis, depression, COPD/Bronhiectasis, asthma, anemia, CKD and Diabetes. The statistics for factors that remained after backward elimination were recalculated in the final regression model. As a result, five variables were ultimately shown to be independently associated with compliance. These include group with age equal to or greater than 60 in comparison with those in 50-59, liver fibrosis/cirrhosis, Aetna, Anthem, Humana and Passport with Wellcare as the reference MCO group, Anthem with Humana as the reference group, the use of ribavirin and being treated with more than 1 DAAs. Having rheumatoid arthritis and taking Sovaldi both approach but fell short of significance (p=0.05). Adjusting for the other covariates, members with an age greater than 60 were estimated to have 1.434 [95% CI: (1.045, 1.968)] times of the odds of achieving compliance than in those who were between age 50-59. Diagnosis of liver fibrosis or cirrhosis had 0.74 [95% CI: (0.57, 0.96)] times the odds of compliance of those who did not have this disease. Furthermore, lower odds of compliance were also found to be conditionally associated with the MCO affiliation. Specifically, the odds of compliance were estimated to be 0.58 [95% CI: (0.37, 0.89)], 0.35 [95% CI: (0.21, 0.58)], 0.64 [95% CI: (0.42, 0.99)] and 0.55 [95% CI: (0.40, 0.76)] respectively for patients managed by Aetna, Anthem, Humana and Passport, as compared with patients by Wellcare. Compared to those of Humana (0.55 [95% CI: (0.31, 0.96)]), beneficiaries served by Anthem were about half as compliant, indicating that disparity of

drug utilization and adherence management were present in the Kentucky Medicaid managed care organizations. Members who had had more than one DAAs in the two-year study period were estimated to have 0.50 [95% CI: (0.29, 0.86)] times of the odds of achieving compliance than in those who had one. Finally, the odds of being compliant is reduced significantly by 61.6% [95% CI: (0.26, 0.58)] with ribavirin as supportive therapy than those only on DAAs.

Table 4. Patient characteristics independently associated with hepatitis C therapy compliance

	Reference	p-value	Odds ratio	95% Confidence Interval
Age >= 60	50 <= Age <= 59	**0.0257**	1.434	1.045– 1.968
Liver Fibrosis/Cirrhosis	No	**0.0152**	0.741	0.570 – 0.963
MCO - Aetna	Wellcare	**0.0134**	0.575	0.371 – 0.892
MCO - Anthem	Wellcare	**<.0001**	0.351	0.211 – 0.584
MCO - Humana	Wellcare	**0.0429**	0.641	0.417 – 0.986
MCO - Passport	Wellcare	**0.0003**	0.554	0.403 – 0.761
MCO - Anthem	Humana	**0.0356**	0.547	0.311 – 0.960
Multiple DAAs	No	**0.0128**	0.502	0.291 – 0.864
Rheumatoid Arthritis	No	0.0706	0.789	0.610 – 1.020
Ribavirin	No	**<.0001**	0.384	0.256 – 0.576
Sovaldi	No	0.0818	1.485	0.951 – 2.317

DISCUSSION

This is the first retrospective observational study that analyzes compliance influencing factors in HCV infected, state Medicaid patients taking new generation hepatitis C drugs. There are several factors that seem to influence adherence in this population. Older age above 60 has a positive impact on adherence, while “liver fibrosis/cirrhosis” was found to impair compliance considerably. Disease management between MCOs also differs significantly. Gender, race, county of residency, number of comorbidities, comorbidities other than liver fibrosis or cirrhosis and whether patients received more than one DAA medication treatment were not shown to be relevant to compliance.

Because of the recent introduction of DAAs up to today and the unique nature of the study population, our finding on DAA compliance can hardly be compared with research

findings in general HCV infected patients taking ribavirin and/or interferons, in terms of both overall adherence rate and contributing factors of compliance. A prospective cohort study in 2010 in 1860 CHC patients initiating ribavirin and peginterferon revealed that only 38% of patients reported strict adherence to the regimen, defined as full-dose and persistent therapy as initially intended by physician (Marcellin, 2011). This stark comparison to 60.4% strict adherence rate with DAAs demonstrated the collaborative efforts from physicians, payers and patients to ensure treatment success. They found that HIV co-infection, no drug use during follow-up, genotype 3 and treatment naïve were independent predictors of adherence. A systemic review conducted in 2010 on factors influencing adherence in hepatitis-C infected patient concluded that factors, including psychiatric disorders, depression, higher ribavirin dose, negatively affected compliance and HIV co-coinfection and hemoglobin level seemed to play a positive role in promoting compliance (Mathes, Antoine, & Pieper, 2014).

In our patient population, many of these factors were either near identical at baseline or unidentifiable in prescription claims. For example, Kentucky Medicaid's FFS provider, Magellan, requires that patients with a history of psychosis, schizophrenia, bipolar disorder or schizoaffective disorder are ineligible for one of most commonly prescribed and evidence-supported regimen in hepatitis C genotype 1 infection (Sovaldi, interferon alfa and weight-based ribavirin combination treatment), unless they are on therapy and compliant with this therapy as reflected by pharmacy paid claim histories (Fried et al, 2013).

Many factors determine difference in compliance. These include internal factors, such as age, sex, race, hepatitis C genotype, comorbidities, all of which are impossible to change at the time of treatment. External factors, on the other hand, include all the environmental

circumstances that can be optimized throughout the treatment course. Treatment regimen, physicians and MCO enrollment are all examples of external factor.

Age seems to be an irrelevant determinant of compliance in our study population until patients reach the age of 60, when it starts to show a marked positive effect. This impact is not found in any previous studies done on hepatitis C patients using ribavirin and interferon. However, as counterintuitive as it may sound, increased likelihood of adherence with age has been demonstrated in multiple studies that investigated the determinants of adherence with antipsychotic medications (Gilmer et al, 2004) and rheumatoid arthritis (Viller et al, 1999). The same result was also seen in Medicaid population with other medical concerns, such as hypertension (Monane et al, 1996; Bailey, Lee, Somes, & Graham, 1996), diabetes using sulfonylurea regimen (Sclar et al, 1999) and hyperlipidemia (Avon et al, 1998). Why older adults are more compliant is unknown, but it may be due to a slower paced life, better communication with health care professionals and decreased financial pressure. Avon specifically proposed that the number of prescribed medications, rather than old age per say, is the risk factor for noncompliance. This supports the connection of multiple DAA treatment with decrease compliance in our study.

The study showed a link between both liver disease and rheumatoid arthritis and compliance. The lower compliance rate among patients with liver fibrosis or cirrhosis was well predicted in the clinical trials of DAAs. A systemic review of hepatitis C treatment published in 2014 on Nature outlined the poor response rate of DAAs in patients with HCV genotype 2: patients with cirrhosis or fibrosis responded less well to Sovaldi + pegylated interferon + weight-based ribavirin regimen (80% vs 92%) or Sovaldi + weight-based ribavirin alone therapy (54% vs 79%) (Kohli, Shaffer, Sherman, & Kottilil, 2014) than patients without it. The incomplete or

slow virologic response leads to a lack of motivation in physicians and patients, decreased adherence and early discontinuation of DAAs. In comparison, the link between rheumatoid arthritis and adherence is more straightforward. Rheumatoid arthritis is a chronic inflammatory disease affecting joints, causing stiffness, weakness, painful swelling and decreased range of motion (Arthritis Foundation, n.d.), thus directly hindering the medication taking behavior.

The high cost of these medications helps classify hepatitis C antivirals as specialty medications. Regardless of whether a certain DAA is on the Medicaid Preferred Drug List (PDL) or not, it is required that physicians file prior authorization forms and ensure that diagnostic and therapeutic criteria are met before a DAA is approved for initiation of the first cycle (Aetna Better Health of Kentucky, 2017; Anthem Blue Cross Blue Shield, 2017; Humana CareSource, 2017; Magellen Medicaid, 2017; Passport Health Plan, 2017; Wellcare of Kentucky, 2017). Once approved, the copay is comparable between DAAs and usually falls below $10 for a 28-day supply (Kentucky Cabinet for Health and Family Services (KCHFS), n.d.;). Instead, factors that tend to hinder treatment compliance in Medicaid population are typically adverse events or regimen complexity (in terms of dosing frequency and polypharmacy).

Ribavirin is sometimes used as supportive care to increase rates of sustained virologic response (SVR) or to shorten treatment duration without altering the rates of SVR (Pawlotsky, 2014). Pegylated interferon are also utilized in combination with DAAs to induce specific and nonspecific immune response against HCV and inhibit viral replication. They both have undesirable adverse effect, but ribavirin is more often associated with central nervous system, gastrointestinal, hematologic and dermatologic toxicities, such as headache, nausea, depression, hepatic toxicity, anemia, neutropenia, diarrhea and rash, thus leading to premature treatment discontinuation (Genetech, 2002).

Harvoni and Sovaldi have relatively high compliance rates among the eight DAAs used in this population. Both are dosed once daily, so the differences in compliance between the two usually lays in dosing complexity. Harvoni is commonly used as a single agent dosed daily in patients in chronic HCV infection without ribavirin, unless the patient is also a liver transplant recipient, while Sovaldi is often prescribed with ribavirin and interferon for genotype 1 infection (most of our population). However, after controlling for the use of ribavirin and interferon in the final model, Sovaldi was significantly more appealing to our patient population than other DAAs. The underlying mechanism for this huge variance is not clear. It can be due to the severe adverse events recently reported by the Institute for Safe Medication Practice. In the 12 months' FDA Adverse Event Reporting System (FAERS) data between Novermber 2015 – October 2016, Harvoni was the primary suspect for 116 liver failures, 91 cases were correlated with Sovaldi and 120 cases with Viekira pak (Quarter Watch, 2017). The exact association between adverse effects of DAAs and compliance should be further investigated in future studies. At the lowest compliance rate (31.4% and 33.3% respectively), Incivek and Viekira Pak each have a more frequent and complex dosing schedule. Incivek was discontinued in the US market for more than a year, but it was previously dosed at twice a day with or without ribavirin/peginterferon for chronic HCV infection other than genotype 1. Viekira Pak, on the other hand, is a copackaged product containing ombitasvir, paritaprevir and ritonavir as a fixed-dose combination tablet and dasabuvir as an individual tablet. Patients are supposed to take two combination tablets in the morning and one dasabuvir tablet twice daily.

Even though patients with Wellcare were shown to be more compliant than all other MCOs contracted with Kentucky Medicaid, it is not well understood why this is the case. Kentucky Medicaid issues a "Guide to choosing a Medicaid Health Plan" to help (potential)

members choose among Magellan, Aetna, Anthem, Huamna, Passport and Wellcare every year based on individual needs. The latest issue for 2017 indicated that Wellcare exceled in "Getting child care quickly", "21 and under dental visits", "Getting adult care quickly" and "Adult overall satisfaction with health plan". The connection between these performances and hepatitis C medication compliance management, however, is unknown. Wellcare, together with Coventry, Kentucky spirit, were the three health plans initially enrolling Medicaid beneficiaries when the implementation of Medicaid Managed Care was started in November 1, 2011. Additional managed care plans, Humana, Passport and Anthem, didn't begin to provide services to the entire Medicaid population until July 1, 2017 (Marton et al, 2016). With Wellcare being more experienced with the Kentucky Medicaid population, they are better at therapy monitoring, building appropriate clinical criteria and efficient communication with physicians.

The result of this study reflects the hepatitis C medication compliance in contiguously enrolled Kentucky Medicaid patients, but may not apply to overall Medical or general patients on DAAs. To remain consistent with national standard measurement for disease management (NCQA, 2008), 302 members were excluded from analysis due to excessive coverage gap. As a result, they either fall into an uninsured state of having incomes above Medicaid eligibility limits but below the lower limit for marketplace premium tax credits, or bumped to receive marketplace subsidies. Little data can be found on these people that fell into the gap in Kentucky, but it is clear that their quality of care can be severely compromised. In comparison to study population, this subgroup of Medicaid members is more likely to face challenges of higher co-pay, less close treatment monitoring and experience more treatment interruptions and coordination for transition of care. Chronic HCV patients of the same economic status outside Medicaid can be drastically distinctive as well. A study in 2010 that looked at the demographic

and health characteristics of the population who will be eligible for Medicaid under Affordable Care Act (ACA) found that both the nondisabled and the disabled adults who were currently enrolled in Medicaid were more likely to have poor general health, mental health and more chronic conditions on average relative to both uninsured and privately insured adults with incomes below 138% of the federal poverty level (FPL) (Holanhan, Kenney, & Palletier, 2010). They all imply that the resulted compliance in this study might be an optimistic estimation of DAA compliance in overall Medicaid patients and an underestimation of that in general population.

There are several limitations in this study that are worth noting. Our data were derived from Kentucky Medicaid outpatient pharmacy claims. They provided very limited information on the severity of HCV infection, comorbidities (HIV or Hepatitis B coinfections), prior treatment history and social history. Although having these data could greatly add to the predictable accuracy of our study, it takes extensive time and manpower to manually go over all the prior authorization claims for all the DAAs and collect those data in a uniform format. On the other hand, public information on MCO's prescription drug management, especially for specialty drugs, is nonexistent. Complete clinical criteria to get prior authorization approval are private information and not shared with the public. If the Kentucky Medicaid clinical criteria for all the MCOs and FFS could be accessed, we could determine the root cause for the difference in compliance.

In conclusion, access to hepatitis C antivirals does not come easily. Aside from the financial shackles that all health insurance provider face, patients must meet as many as more than 20 clinical criteria to be eligible for DAA. Once access is granted, patients are entitled to therapy for once in their lifetime unless resistance or intolerance develops during the treatment

course. Therefore, it is not surprising to see payers closely monitor lab test and treatment course, require prior authorization every step of the way and approve therapies by cycle. If patients could be screened for characteristics that have been known to predispose them to noncompliance and manage them alongside hepatitis C, we could make a huge impact on hepatitis C treatment outcome.

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