TREATMENT INITIATION AND DRUG COST BURDEN OF HEPATITIS C (HCV) THERAPIES AMONG HCV PATIENTS IN THE UNITED STATES WITH A PARTICULAR FOCUS ON THE HIV CO-INFECTED POPULATION

By

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A THESIS PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN PHARMACY

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To my beloved family and friends.
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I thank my adviser, Haesuk Park for her continuous guidance and support throughout this project. She has always been patient and considerate, yet she never got tired of challenging me and pushing this project forward. She is a remarkable adviser who never loses her positive attitude and humor and I am glad to be working under her supervision. I furthermore highly appreciate the advice, encouraging words, and excellent administrative support from my master’s degree committee member Richard Segal. In addition, I want to thank Carl Henriksen for his SAS coding support. The day will come when I find a coding problem that he cannot solve within 3 minutes.
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Abstract of Thesis Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Master of Science in Pharmacy

TREATMENT INITIATION AND DRUG COST BURDEN OF HEPATITIS C (HCV) THERAPIES AMONG HCV PATIENTS IN THE UNITED STATES WITH A PARTICULAR FOCUS ON THE HIV CO-INFECTED POPULATION

By

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Chair: Haesuk Park
Major: Pharmaceutical Sciences

To investigate the association of HCV treatment initiation rates and HIV co-infections among HCV patients before and after the market introduction of the new direct acting antivirals (DAAs). In addition, we aimed to estimate the financial burden of HCV treatments on patients and payers.

We used a large US commercial insurance database and performed multivariate logistic regression analyses in newly diagnosed HCV patients between 2009 and 2016. The Kruskal-Wallis test was used to compare patients’ out-of-pocket (OOP) costs and payers’ net-treatment costs per therapeutic group.

15,063 HCV patients in the pre-all-oral DAA period and 14,896 HCV patients in the all-oral DAA period were included in the analyses (382 [2.5%] and 429 [2.9%] HIV co-infections, respectively). HCV treatment initiation rates per 100 person-years saw significant absolute increases from pre-all-oral to the all-oral DAA period of 34% in HCV mono-infected and 88% among HCV/HIV co-infected patients (p>0.001). Multivariate logistic regression analyses indicated that during the pre-all-oral DAA period co-infected patients were significantly less likely to initiate treatments (OR, 0.62; 95% CI, 0.47-
0.81), but not significantly different with the new DAAs (OR, 1.05; 95% CI 0.85-1.30). Mean payers’ net-treatment costs (dual therapies, $20,820; all-oral DAAs, $99,661; p<0.001) and mean patients’ OOP costs (dual therapies, $593; all-oral DAAs $933; p<0.001) increased significantly from dual therapy to the interferon-free DAAs.

Numbers of HCV treatment initiations among HCV patients increased after all-oral therapies became available and was more pronounced among the HIV co-infected. However, patients’ OOP costs doubled, and payers’ expenditures saw an almost 5-fold increase.
An estimated 3.5 million individuals are infected with the Hepatitis C virus (HCV) and about 1.1 million people are positive carriers of the human immunodeficiency virus (HIV) in the United States (US).\textsuperscript{1,2} HIV and HCV co-infection is common due to the shared routes of transmission (i.e. percutaneous exposure to blood associated with injection drug use, poorly sterilized medical or invasive equipment, sexual transmission).\textsuperscript{3,4} Discussed HIV co-infection rates among HCV patients are highly dependent on underlying risk factors and range between 5 and 90\%, depending on the source population.\textsuperscript{5-9} Compared with HCV mono-infected subjects, those with concurrent HCV and HIV infections suffer from a more rapid progression towards cirrhosis and liver failure.\textsuperscript{10}

A meta-analysis by Chen et al. showed that after the introduction of highly active antiretroviral therapy (HAART), liver disease has become the major contributor to mortality among HIV-positive patients,\textsuperscript{11} suggesting the need for early initiation of HCV treatment among co-infected individuals. However, multiple studies have shown that treatment initiation in patients infected with HCV has been low since the introduction of the first HCV therapies in the early 1990s.\textsuperscript{12,13} This deficit has even been more pronounced among those co-infected with HIV.\textsuperscript{12} Among studies done in the US, only 7 - 12.5\% of HCV/HIV co-infected patients have received HCV treatment.\textsuperscript{12,14} Reported reasons were an increased pill burden, high side effect and drug-drug interaction (DDI) profiles, and a significantly poorer sustained virologic response (SVR) in HCV/HIV co-infected patients treated with the older first-line regimen peg-interferon and ribavirin (pegIFN/RBV), telaprevir, and boceprevir.\textsuperscript{15} Other patient related characteristics, i.e.
comorbidities, illicit drug use, compliance to follow up, or a controlled HIV infection have been identified to influence HCV treatment initiation in the HCV/HIV co-infected population.\textsuperscript{12,16}

The introduction of the second generation of direct acting antivirals (DAAs) simeprevir and sofosbuvir by the end of 2013 revolutionized the treatment of HCV infection. In the consecutive years, several new drugs and drug combinations gained FDA approval which has made interferon-containing treatments and telaprevir and boceprevir obsolete.\textsuperscript{15} The second generation DAAs are associated with SVRs of >95\% and a shortened treatment period from up to 48 weeks to either 8 or 12 weeks.\textsuperscript{17} Side effect incidence and severity of the new treatments improved significantly and DDIs with HIV medications can largely be circumvented by either selecting guideline recommended non-interacting HCV regimens or adjusting the HIV agents for the time during the HCV treatment.\textsuperscript{17} National and international hepatitis C guidelines now recommend that all treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease related to HCV, who are willing to be treated and who have no contraindications to treatment, must be considered for therapy.\textsuperscript{17,18} It is further pointed out that, based on existing knowledge, no absolute contraindications to the new DAAs exist.\textsuperscript{18}

Market approvals of the second generation DAAs have drawn intense attention from the media, policy makers, and researchers. The high price tags set by manufacturers sparked heated debates about how much societies are willing to and, more importantly, are able to pay for innovative medicines. In 2016, wholesale acquisition cost (WAC) of the new DAAs for recommended initial therapy of 12 weeks
ranged between $54,600 (Zepatier) and $147,000 (Daklinza+Sovaldi).\textsuperscript{19} In the US, private payers, Medicaid, and Medicare Services have been rationing the access to those therapies by setting up specific treatment restrictions and prior authorization guidelines.\textsuperscript{20}

Despite the vast prices, cost-effectiveness (CE) analyses of DAAs have continuously shown that these agents are, in general, cost-effective across all HCV genotypes compared to previous standard-of-care.\textsuperscript{21,22} However, due to the high efficacy and low safety concerns with the new all-oral DAAs compared to the older therapies, the number of patients eligible for treatment dramatically increased. This lead to concerns about massive and immediate upfront costs for payers, making the treatments virtually unaffordable for a large subset of patients.\textsuperscript{19,23} To date, little is known about how the FDA approvals of several new interferon-free all-oral therapies influenced patients’ OOP costs and payers’ net-treatment costs for HCV treatments.

The aims of our study were to compare HCV treatment initiation rates before and after the market introduction of second generation DAAs, to investigate if HIV co-infections influence treatment initiations, and furthermore to examine associations between patient characteristics and the initiation of HCV therapies. Our secondary aim was to estimate the financial burden of HCV treatments for patients and payers, comparing interferon containing dual and triple therapies, and the new interferon free all-oral DAA therapies.
CHAPTER 2
METHODS

Data Source

We conducted a retrospective claims data analysis using the Truven Health Analytics MarketScan® Commercial and Medicare Supplemental databases from January 2009 until December 2016. This nationwide administrative database includes commercial claims and encounters of employer-sponsored private and Medicare Supplemental health insurance plans of employees, their dependents, and retirees and covers 40 to 45 million lives each year. De-identified patient-level information on enrollment, demographics, and health care utilization such as physician outpatient office visits, hospital stays, and pharmacy claims with their respective dates of service are captured in the dataset.

Study Population

Our sample consisted of patients with a newly diagnosed chronic HCV infection between January 2010 and December 2016, while the 2009 data were used to ensure at least one year of claims prior to HCV diagnosis. We used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes [070.44, 070.54, 070.70, 070.71, V02.62] prior to October 2015, and the ICD Tenth Revision, Clinical Modification (ICD-10-CM) codes, [B18.2x, B19.2x, Z22.52] after their introduction in October 2015, to identify HCV patients. We included patients who (1) were older than 18 years of age at index, (2) had at least 1 inpatient or 2 outpatient HCV diagnoses within 1 year (index date = first HCV diagnosis), and (3) had one year of continuous insurance eligibility prior to and at least 6 months after the index date [Fig. 2-1]. Individuals who received HCV treatment during baseline, and those with a capitated
health plan or without prescription drug benefits were excluded as in the latter case claims data may not be complete for such patients.

The chronic HCV patients were further categorized based on a diagnosis of HIV recorded during the one-year baseline period prior to the index date. HIV co-infections among the HCV cohort were identified through ICD-9-CM codes [042, 079.53, V08] and ICD-10-CM codes [B20.xx, B21.xx, B22.xx, B23.xx, B24.xx, B97.35, Z21]. We excluded individuals who had their first HIV diagnosis after the index date.

To compare treatment initiation rates and its predictors prior and post introduction of the interferon-free all-oral DAAs, we divided patients into a “pre-all-oral DAA period” and an “all-oral DAA period” [Fig. 2-1]. The pre-all-oral DAA period included HCV patients who had their index and treatment initiation or end of follow-up between 01/01/2010 and 11/30/2013, approximately when simeprevir and sofosbuvir received FDA approval. Patients during the all-oral DAA period had to have their index and treatment initiation or end of follow-up between 12/01/2013 and 12/31/2016. Thus, subjects who did not meet these criteria were excluded. Prior to the introduction of the all-oral DAA agents, patients with co-morbid illnesses, a mild HCV disease status, or other reasons, deferred or were commonly not started on the old regimens, but instead watched, waited, and monitored their disease until the new DAAs were launched. Hence we decided on excluding patients whose time to treatment initiation could have been influenced by the so called “watchful waiting” strategy prior to November 2013.

Demographics (e.g. age, gender, region, type of health plan) and patients’ clinical characteristics were collected during baseline. We used ICD-9-CM and ICD-10-CM codes to identify comorbid conditions and we additionally captured cases of liver
transplants during baseline through Current Procedural Terminology (CPT) codes [for a full list of covariates see Appendix Table A-1].

HCV Treatment Initiation

HCV treatments included three classes: (1) Dual therapy - a combination therapy of an interferon (interferon alpha, interferon beta, peg-interferon alpha-2a or peg-interferon alpha-2b) and ribavirin, initiated within 45 days without any other HCV agents; (2) Triple therapy - a combination of boceprevir, telaprevir, sofosbuvir, or simeprevir plus peg-interferon and RBV, initiated within 45 days; 3) All-oral therapy included sofosbuvir + simeprevir +/- RBV, sofosbuvir + RBV, sofosbuvir/ledipasvir +/- RBV, sofosbuvir + daclatasvir +/- RBV, paritaprevir/ritonavir/ombitasvir +/- dasabuvir +/- RBV, elbasvir/grazoprevir +/- RBV, and sofosbuvir/velpatasvir +/- RBV, without the initiation of pegIFN. Treatment information was captured through National Drug Codes (NDCs) in prescription claims and with Healthcare Common Procedure Coding System (HCPCS) codes for injectable pegIFNs in inpatient and outpatient settings [for a full list of included drugs and their FDA approval dates see Appendix Table A-2]. We only included patients’ first HCV therapy regimen in the analysis, since treatment patterns and patient characteristics in non-responders or relapsers may be conditioned through the previous treatment and thus would bias our study results.25 Furthermore, previous research has shown that patients who already have been treated were significantly more likely to receive another course of HCV therapy compared to treatment naïve individuals.26-30

HCV Treatment Cost

The secondary outcomes were patients’ OOP costs and providers’ net-costs stratified by type of treatment. Here, we did not distinguish the study cohort based on HIV status, because co-infected patients receive similar HCV agents as mono-infected
patients according to the guidelines published in the DAA era. However, we further differentiated triple therapies between boceprevir or telaprevir and simeprevir or sofosbuvir, respectively, in combination with pegIFN and RBV because the drug price increased significantly with the introduction of sofosbuvir. The end of a given treatment regimen was defined as either a 60-day gap for pegIFN treatment or a gap of 14 days for the other agents. We excluded subjects from the cost analysis who had treatment durations of less than 8 weeks and longer than 52 across all groups in order to disregard outlier treatments in both directions. All costs were adjusted to 2016 dollars using the personal consumption expenditures inflation factor for health products from the US Bureau of Economic Analysis.

**Statistical Analysis**

We calculated crude incidence proportions of treatment initiations during the pre-all-oral DAA and the all-oral DAA period by dividing the number of treatment initiations during each period by the number of patients in that period.

Treatment initiation rates in both time periods were defined as the rate of initiation of an HCV treatment and calculated by dividing the number of patients who had at least one prescription, using NDCs and HCPCS codes in pharmacy or inpatient/outpatient claims, by the total person-years in each period.

Baseline characteristics and crude incidence proportions and rates were compared between HCV mono-infected and HCV/HIV co-infected patients using t tests Pearson’s chi square tests. We fitted multivariate logistic regression models during both study periods, respectively. Odds ratios (OR) and 95% confidence intervals (CI) for the association between HIV co-infection and initiating HCV treatment were estimated. We adjusted the regression models for patient characteristics that have been reported
previously to influence treatment decisions or HCV treatment outcomes including age, gender, alcohol – and substance use disorders, depression, schizophrenia, epilepsy, hepatitis a, hepatitis b, pancreatitis, anemia, diabetes, dyslipidemia, chronic pulmonary diseases, hypertension, heart failure, coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic kidney disease, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, other non-alcoholic liver conditions, other alcoholic liver conditions, liver transplant, sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, and pregnancy.\textsuperscript{12,16,27,33-37}

For our secondary outcomes we calculated descriptive statistics of costs stratified by patients’ most recent treatment regimens. The Kruskal-Wallis (KW) test and Dunn’s pairwise comparison for unequal sample sizes were applied to compare patients’ OOP costs and providers’ net-treatment costs per course of therapy between the four drug categories.\textsuperscript{38,39} For non-symmetrical distributions the KW test results in a higher power compared to the one-way ANOVA.\textsuperscript{38} We conducted all analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC). The statistical tests were performed at a significance level of $p<0.05$ for a two-sided test and we used a SAS macro developed by Elliott and Hynan for the KW tests.\textsuperscript{40} The study was conducted under a protocol approved by the institutional review board of the University of Florida in Gainesville, FL.
Figure 2-1. Study outline.
CHAPTER 3
RESULTS

Demographic and Clinical Characteristics

We identified 29,959 chronic HCV patients meeting the inclusion and exclusion criteria during January 2010 and December 2016, of which 811 (2.7%) individuals were co-infected with HIV. 15,063 patients were included in the pre-all-oral period and 14,896 individuals were eligible during the all-oral period, with 382 (2.5%) and 429 (2.9%) HCV/HIV co-infected patients, respectively [Fig. 3-1].

Table 3-1 summarizes the patient characteristics and comorbid conditions between HCV mono-infected and HCV/HIV co-infected patients during the pre-all-oral DAA and all-oral DAA period. In both study periods, HCV/HIV co-infected patients were more likely to be male (pre-all-oral: 83.2% vs. 61.3%, p<0.001; all-oral: 80.7% vs. 58.6%, p<0.001) compared to HCV mono-infected patients. HCV/HIV co-infected patients had similar comorbidities (e.g., alcohol use disorder, illicit drug use, diabetes) compared to HCV mono-infected patients, but they were more likely to have HBV co-infection (pre-all-oral: 7.9% vs. 3.1%, p<0.001; all-oral: 9.6% vs. 3.3% p<0.001) and less likely to have cirrhosis (pre-all-oral: 4.5% vs. 9.0%, p=0.021; all-oral: 4.2% vs. 6.7%, p=0.042).

Unadjusted Proportion and Rates of Treatment Initiations

A total of 8,908 (29.7%) patients in our cohort initiated HCV treatments within an average follow-up of 360 days. During the pre-all-oral DAA period, 18.6% (n=71) of HCV/HIV co-infected patients initiated HCV treatments, showing a significantly lower incidence proportion compared to the initiation rate of 26.9% (n=3,193) among the HCV mono-infected (p<0.001). [Fig. 3-2 (a) & (b)]. Among the mono-infected treatment
initiators, 47.7% (n=1,845) and 52.3% (n=2,023) initiated dual therapy and triple therapy, respectively. Among the HCV/HIV co-infected patients, however, only 32.4% (n=23) initiated triple therapy whereas 67.6% (n=48) started on pegIFN/RBV [Table 3-2]. During the all-oral DAA period, 32.9% (n=141) co-infected patients and 33.4% (n=4,828) mono-infected patients started treatments, respectively, showing no significant difference (p=0.827) [Fig. 3-2 (c) & (d)]. Among those treated, the majority of patients received interferon-free all-oral DAA therapies (93.6% in HCV/HIV co-infected and 96.2% in HCV mono-infected groups). [Table 3-2]. Crude treatment initiation rates per 100 person-years saw absolute increases from the pre-all-oral DAA to the all-oral DAA period, both in mono-infected patients by 34% and in co-infected individuals by 88% [Fig. 3-3].

During the pre-all-oral DAA period, HCV mono-infected patients on average started HCV therapy after 6.4 versus 5.7 months in HIV co-infected patients, showing no statistical significant difference (p=0.110). During the all-oral DAA period, however, HCV/HIV co-infected patients initiated HCV therapy significantly later compared to mono-infected patients (8.3 months vs. 6.0 months; p<0.001).

Odds of HCV Treatment Initiation

The univariate logistic regression model indicated that HCV/HIV co-infected patients were significantly less likely to initiate HCV treatments compared to mono-infected individuals during the pre-al-oral DAA period (unadjusted odds ratio [uOR], 0.64; 95% confidence interval [CI], 0.49-0.83). The estimates did not change significantly after adjusting for demographics and baseline covariates (adjusted OR [aOR], 0.62; 95% CI, 0.47-0.81). During the all-oral DAA period we observed no statistical significant difference in odds for HCV treatment initiations between mono- and
co-infected patients (uOR, 0.98; 95% CI, 0.80-1.20; aOR, 1.05; 95% CI, 0.85-1.30) [Table 3-3].

Table 3-3 shows patient characteristics included in our model and their influence on treatment initiation among HCV patients between 2014 and 2016. Patients in higher age groups (50-59 years [OR, 1.64; 95% CI, 1.49-1.81], ≥60 years [OR, 1.43; 95% CI, 1.29-1.60]), and those with a presence or history of other non-alcoholic liver conditions (OR, 1.32; 95% CI, 1.20-1.46) were more likely to initiate treatment. Factors associated with lowering the odds of HCV treatment initiations during the all-oral period included female gender [OR, 0.84; 95% CI, 0.78-0.91], alcohol use disorder [OR, 0.64; 95% CI, 0.55-0.75], illicit drug use disorder [OR, 0.66; 95% CI, 0.58-0.75], depression [OR, 0.79; 95% CI, 0.71-0.88], HBV co-infection [OR, 0.38; 95% CI, 0.29-0.48], anemia [OR, 0.72; 95% CI, 0.64-0.83], dyslipidemia [OR, 0.70; 95% CI, 0.64-0.76], congestive heart failure [OR, 0.55; 95% CI, 0.44-0.68], CKD [OR, 0.71; 95% CI, 0.59-0.85], decompensated cirrhosis [OR, 0.71; 95% CI, 0.56-0.89], alcohol related liver conditions [OR, 0.58; 95% CI, 0.38-0.87], and the presence or history of hepatocellular carcinoma [OR, 0.37; 95% CI, 0.23-0.60].

**HCV Treatment Costs**

Eligible treatment episodes of 7,318 HCV patients were included in the cost analysis. 1,469 (20%) patients were treated with dual therapy, 1,789 (24%) used triple therapy with boceprevir or telaprevir, 181 patients (2%) received triple therapy with simeprevir or sofosbuvir, and 3,879 (53%) patients were identified as all-oral DAA users. On average, treatment durations were 6.1, 6.3, 3.1, and 3.0 months (p<0.001), respectively.
A steep cost increase was observed among the net-treatment costs for payers. Whereas the cost for dual therapy was on average $20,820 (standard deviation [SD], $9,256) per concluded treatment, the mean costs for triple therapy with boceprevir or telaprevir summed up to $74,137 (SD, $21,596), $101,715 (SD, $15,597) for triple therapy with simeprevir or sofosbuvir, and $99,661 (SD, $46,379) for concluded all-oral treatments (p<0.001) [Fig. 3-4, Table 3-4].

We furthermore found a significant increase in patients' OOP costs. Patient paid on average $593 (SD, $1,406) for dual therapies, $798 (SD, $1,728) for triple therapy with boceprevir or telaprevir, $733 (SD, $1,781) for triple therapy with simeprevir or sofosbuvir, and $933 (SD, $6,145) for patients using all-oral DAAs [Fig. 3-4, Table 3-5]. However, we also observed the greatest variation of OOP among the latter group. Whereas 23% (N=905) of patients using the all-oral treatments had zero out-of-pocket costs, some (n=20) had to carry cost of more than $50,000 per course of therapy.
### Table 3-1. Patient characteristics, stratified by HIV indication & study period

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Pre-all-oral DAA Period</th>
<th>All-oral DAA Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCV+ (n=14,681)</td>
<td>HCV/HIV+ (n=382)</td>
</tr>
<tr>
<td>Days of follow-up, median (IQR)</td>
<td>349 (215, 595)</td>
<td>383 (252, 619)</td>
</tr>
<tr>
<td>Median age, years (IQR)</td>
<td>54 (48, 58)</td>
<td>48 (42, 55)</td>
</tr>
<tr>
<td>Men</td>
<td>7,319 (61.6%)</td>
<td>255 (83.6%)**</td>
</tr>
<tr>
<td>Women</td>
<td>4,554 (38.4%)</td>
<td>50 (16.4%)**</td>
</tr>
<tr>
<td>Alcohol disorder</td>
<td>818 (6.9%)</td>
<td>16 (5.2%)</td>
</tr>
<tr>
<td>Substance use disorder</td>
<td>902 (7.6%)</td>
<td>25 (26.0%)</td>
</tr>
<tr>
<td>Depression</td>
<td>1,903 (16.0%)</td>
<td>71 (23.3%)**</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>56 (0.5%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>138 (1.2%)</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>77 (0.6%)</td>
<td>5 (1.6%)*</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>353 (3.0%)</td>
<td>23 (7.5%)*</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>235 (2.0%)</td>
<td>6 (2.0%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1,783 (15.0%)</td>
<td>62 (20.3%)*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2,224 (18.7%)</td>
<td>46 (15.1%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>3,450 (29.1%)</td>
<td>89 (29.2%)</td>
</tr>
<tr>
<td>COPD</td>
<td>1,680 (14.1%)</td>
<td>47 (15.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5,149 (43.4%)</td>
<td>100 (32.8%)**</td>
</tr>
<tr>
<td>Heart failure</td>
<td>478 (4.0%)</td>
<td>7 (2.3%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1,058 (8.9%)</td>
<td>29 (9.5%)</td>
</tr>
<tr>
<td>PVD</td>
<td>679 (5.7%)</td>
<td>12 (3.9%)</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>561 (4.7%)</td>
<td>9 (3.0%)</td>
</tr>
<tr>
<td>CKD</td>
<td>560 (4.7%)</td>
<td>16 (5.2%)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1,031 (8.7%)</td>
<td>15 (4.9%)*</td>
</tr>
<tr>
<td>Decompensated Cirrhosis</td>
<td>666 (5.6%)</td>
<td>10 (3.3%)</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>153 (1.3%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Other non-alc. liver cond.</td>
<td>2,573 (21.7%)</td>
<td>61 (20.0%)</td>
</tr>
<tr>
<td>Other alc. liver cond.</td>
<td>168 (1.4%)</td>
<td>5 (1.6%)</td>
</tr>
<tr>
<td>Liver Transplant</td>
<td>106 (0.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>30 (0.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>313 (2.6%)</td>
<td>9 (3.0%)</td>
</tr>
<tr>
<td>SLE</td>
<td>59 (0.5%)</td>
<td>6 (2.0%)*</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>124 (1.0%)</td>
<td>2 (0.7%)</td>
</tr>
</tbody>
</table>

Abbreviations: Alc., alcoholic; CKD, Chronic Kidney Disease; Cond., condition; COPD, chronic obstructive pulmonary disease; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; IQR, Interquartile Range; PVD, Peripheral Vascular Disease; SLE, Systemic Lupus Erythematosus

*p<0.05, **p<0.001
Table 3-2. Absolute numbers of treatment initiations, stratified by HIV indication & study period

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pre-all-oral DAA period</th>
<th>All-oral DAA period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCV+ (n=14,681)</td>
<td>HCV+ (n=14,467)</td>
</tr>
<tr>
<td></td>
<td>HCV+/HIV+ (n=382)</td>
<td>HCV+/HIV+ (n=429)</td>
</tr>
<tr>
<td>Total initiated</td>
<td>3,868 (27.2%)</td>
<td>4,828 (33.3%)</td>
</tr>
<tr>
<td>PegIFN/RBV</td>
<td>1,845 (12.6%)</td>
<td>4,828 (33.3%)</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>2,023 (13.8%)</td>
<td>179 (1.2%)</td>
</tr>
<tr>
<td>All oral therapy</td>
<td>0 (0.0%)</td>
<td>4,643 (32.1%)</td>
</tr>
</tbody>
</table>

Abbreviations: DAA, direct acting antiviral; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; PegIFN, pegylated interferon; RBV, ribavirin
<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Pre-all-oral DAA period OR (95% CI)</th>
<th>All-oral DAA period OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main Variable of Interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV vs. no HIV</td>
<td>0.62 (0.47-0.81)</td>
<td>1.05 (0.85-1.30)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-49</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>50-59</td>
<td>1.17 (1.07-1.28)</td>
<td>1.64 (1.49-1.81)</td>
</tr>
<tr>
<td>60+</td>
<td>0.71 (0.63-0.80)</td>
<td>1.43 (1.29-1.60)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Women</td>
<td>0.91 (0.84-0.99)</td>
<td>0.84 (0.78-0.91)</td>
</tr>
<tr>
<td>Substances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol disorder</td>
<td>0.70 (0.58-0.85)</td>
<td>0.64 (0.55-0.75)</td>
</tr>
<tr>
<td>Substance use disorder</td>
<td>0.72 (0.61-0.85)</td>
<td>0.66 (0.58-0.75)</td>
</tr>
<tr>
<td>Psychiatric/Neurologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>0.80 (0.71-0.89)</td>
<td>0.79 (0.71-0.88)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>1.01 (0.54-1.90)</td>
<td>0.60 (0.33-1.04)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0.68 (0.45-1.05)</td>
<td>0.83 (0.60-1.14)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>1.52 (0.97-2.34)</td>
<td>0.80 (0.49-1.31)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>0.53 (0.40-0.69)</td>
<td>0.38 (0.29-0.48)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0.59 (0.41-0.84)</td>
<td>0.62 (0.47-0.83)</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.55 (0.48-0.64)</td>
<td>0.72 (0.64-0.83)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.00 (0.89-1.11)</td>
<td>0.95 (0.86-1.04)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.79 (0.72-0.87)</td>
<td>0.70 (0.64-0.76)</td>
</tr>
<tr>
<td>Obstructive lung diseases</td>
<td>0.75 (0.66-0.85)</td>
<td>0.77 (0.69-0.85)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.91 (0.84-0.99)</td>
<td>1.04 (0.96-1.13)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.41 (0.28-0.59)</td>
<td>0.55 (0.44-0.68)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0.70 (0.58-0.83)</td>
<td>0.95 (0.82-1.09)</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>0.77 (0.62-0.96)</td>
<td>0.95 (0.81-1.12)</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>0.70 (0.55-0.96)</td>
<td>0.89 (0.75-1.06)</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>0.41 (0.30-0.56)</td>
<td>0.71 (0.59-0.85)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>0.81 (0.68-0.98)</td>
<td>1.05 (0.88-1.26)</td>
</tr>
<tr>
<td>Decompensated Cirrhosis</td>
<td>0.49 (0.38-0.64)</td>
<td>0.71 (0.56-0.89)</td>
</tr>
<tr>
<td>Other non-alcoholic Liver Conditions</td>
<td>1.47 (1.33-1.61)</td>
<td>1.32 (1.20-1.46)</td>
</tr>
<tr>
<td>Other alcoholic Liver Conditions</td>
<td>0.81 (0.52-1.24)</td>
<td>0.58 (0.38-0.87)</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>0.17 (0.08-0.35)</td>
<td>0.37 (0.23-0.60)</td>
</tr>
<tr>
<td>Liver Transplant</td>
<td>0.25 (0.10-0.59)</td>
<td>0.97 (0.59-1.60)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>0.42 (0.15-1.22)</td>
<td>0.47 (0.20-1.08)</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>1.19 (0.94-1.52)</td>
<td>0.81 (0.64-1.04)</td>
</tr>
<tr>
<td>SLE</td>
<td>1.64 (0.96-2.79)</td>
<td>0.86 (0.47-1.57)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0.39 (0.24-0.62)</td>
<td>0.24 (0.15-0.38)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DAA, direct acting antiviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus; OR, odds ratio; SLE, systemic lupus erythematosus
### Table 3-4. Payers’ net-treatment cost per course of therapy

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Patients (N)</th>
<th>Mean</th>
<th>Median</th>
<th>IQR</th>
<th>99&lt;sup&gt;th&lt;/sup&gt; pctl.</th>
</tr>
</thead>
<tbody>
<tr>
<td>pegIFN/RBV</td>
<td>1,264</td>
<td>$20,934.14</td>
<td>$18,684.05</td>
<td>$8,815.70</td>
<td>$49,073.92</td>
</tr>
<tr>
<td>1. Gen. DAA</td>
<td>1,449</td>
<td>$71,503.23</td>
<td>$75,898.65</td>
<td>$23,345.32</td>
<td>$113,455.86</td>
</tr>
<tr>
<td>2. Gen DAA</td>
<td>4,033</td>
<td>$99,563.77</td>
<td>$93,586.53</td>
<td>$18,821.72</td>
<td>$229,658.43</td>
</tr>
</tbody>
</table>

Abbreviations: DAA, direct acting antiviral; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; PegIFN, pegylated interferon; RBV, ribavirin

### Table 3-5. Patients’ out-of-pocket cost per course of therapy

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Patients (N)</th>
<th>Mean</th>
<th>Median</th>
<th>IQR</th>
<th>99&lt;sup&gt;th&lt;/sup&gt; pctl.</th>
<th>Patients with zero cost, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pegIFN/RBV</td>
<td>1,264</td>
<td>$572.79</td>
<td>$291.32</td>
<td>$476.49</td>
<td>$4,756.58</td>
<td>130 (10.3%)</td>
</tr>
<tr>
<td>1. Gen. DAA</td>
<td>1,449</td>
<td>$772.18</td>
<td>$433.45</td>
<td>$585.10</td>
<td>$5,031.28</td>
<td>134 (9.2%)</td>
</tr>
<tr>
<td>2. Gen DAA</td>
<td>4,033</td>
<td>$921.64</td>
<td>$125.00</td>
<td>$269.28</td>
<td>$19,908.15</td>
<td>932 (23.0%)</td>
</tr>
</tbody>
</table>

Abbreviations: DAA, direct acting antiviral; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; PegIFN, pegylated interferon; RBV, ribavirin
Figure 3-1. Flow chart of the cohort creation.
Abbreviations: CCAE, Commercial Claims and Encounters; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HCV+, HCV mono-infected patients; HCV/HIV+, HCV/HIV co-infected patients; MDCR, Medicare Supplemental and Coordination.
Figure 3-2. Crude proportions of treatment initiations, by HIV infection and study period. Pre-all-oral DAA period, [(a) & (b)], p<0.001; all-oral DAA period [(c) & (d)], p=0.827. Abbreviations: HCV+, HCV mono-infected patients; HCV/HIV+, HCV/HIV co-infected patients.
Figure 3-3. Treatment initiation rates per 100 person-years, by HIV infection and study period.
Abbreviations: HCV+, HCV mono-infected patients; HCV/HIV+, HCV/HIV co-infected patients.
Figure 3-4. Payers’ mean net-treatment costs (p<0.001) and patients’ mean out-of-pocket costs (p<0.001) per course of therapy. Abbreviations: 1DAA, first generation direct acting antivirals; 2DAA, second generation direct acting antivirals; OOP cost, out-of-pocket cost.
This US population based, retrospective cohort study of privately insured individuals examined HCV treatment initiation rates and patient characteristics influencing the start of HCV treatments with a focus on HIV coinfection among HCV patients. The estimates we measured pre- and post-market introduction of the highly effective DAAs indicated that treatment initiation increased significantly across all patients infected with HCV. This trend seemed to be more significant among the HCV/HIV co-infected population (absolute increase by 34% in HCV mono-infected vs by 88% in HCV/HIV co-infected per 100 person-years; P<0.001). These findings were further confirmed by our multivariate logistic regression models which suggested that, between 2010-2013, the odds for initiating HCV therapies were significantly lower in HCV/HIV co-infected compared to HCV mono-infected patients (OR, 0.62; 95% CI, 0.47-0.81). However, disparities in treatment initiation in HCV/HIV co-infected patients disappeared after the introduction of the highly effective DAAs (OR 1.05; 95% CI 0.85-1.30).

Our findings corroborate other findings that treatment uptake improved with IFN-free DAA therapies in HCV/HIV co-infected patients. A study conducted within the Duke University Health System found that HCV treatment initiations significantly improved with the availability of IFN-free DAA therapies both in HCV mono- and HCV/HIV co-infected patients (35% in 2015 from <5% annually between 2011-2013). A recent study of US Veterans found that absolute probabilities of patients receiving treatment was slightly higher in HCV/HIV co-infected patients (20.6%) compared to HCV mono-
infected patients (16.5%) after 2013. A retrospective analysis of the Canadian Co-infection Cohort Study also showed a threefold increase of HCV treatment initiations among HCV/HIV co-infected patients after the introduction of the all-oral therapies. Another study conducted with US electronic health record data from the Observational Pharmacoepidemiology Research and Analysis (OPERA) cohort found that 35% of HCV/HIV co-infected and 28% of HCV mono-infected patients started any form of HCV treatment during 2011 and 2016, showing comparable results to our findings.

Previous research has demonstrated that in challenging populations, such as those with an HIV coinfection, safety and efficacy of the new agents are nearly identical to mono-infected patients. For HIV co-infected patients, who have access to the all-oral DAAs, eradication of HCV is considered to be medically achievable. Current guidelines recommend using the same treatment approaches for the co-infected, with the only difference being the necessity of recognizing and appropriately managing potential DDIs between HCV medications and HIV antiretroviral therapies. On the other hand, despite the high potential for HCV cure with the DAA therapy, a disturbing study finding was that two-third of HCV patients were not treated in the DAA era. This finding suggests that HCV patients are still encountering barriers to treatment even within a group with access to private, non-capitated health insurance including prescription drug benefits.

**Patient Characteristics Affecting HCV Treatment Initiation**

We found several patient-level characteristics associated with HCV treatment initiation. Patients aged ≥60 years were less likely to initiate HCV therapy prior to the availability of all-oral DAA therapies but were more likely to initiate treatments during the
all-oral DAA period. One reason may be the vastly improved toxicity profiles of the new DAAs which simplifies treatments especially in the older, frail population.

Furthermore, we found significantly lower odds of HCV treatment initiation in females compared to males during 2014 to 2016. More specifically, odds for treatment initiation were 16% lower in women compared to men. Historically, females have been less likely to initiate HCV treatment compared to males.\textsuperscript{26,27,45} Two reasons for the differences in treatment initiations may be considered. Firstly, ribavirin has been linked to teratogenic effects and the safety and efficacy of new DAAs in pregnant or breast-feeding women is unknown. Hence treatment is not recommended during pregnancy or in females who may become pregnant.\textsuperscript{17} Secondly, it has been shown that spontaneous clearance rates of chronic HCV are significantly lower in men compared to women, independent of age and modes of transmission.\textsuperscript{46} Male sex was furthermore identified as an independent risk factor for fibrosis progression in patients infected with hepatitis C.\textsuperscript{47-49} The gender difference in disease progression has been linked to the protective effects of estrogen on the liver in women.\textsuperscript{48,49} Hence, these reasons may partly influence treatment decisions despite the guidelines recommend treatment in all individuals infected with HCV, irrespective of the patient’s gender.\textsuperscript{17,18}

In our study, we found that substance use and alcohol use disorders are predictors for no treatment. Treatment exclusions were commonly justified by concerns of high re-infection risks among people who inject drugs and furthermore it was assumed that those patients will be unable to adhere to long and toxic treatments.\textsuperscript{50} Consequently, most payers (private and state/federal) imposed restrictions on patients with a present or recent alcohol or illicit drug use disorder.\textsuperscript{20} However, previous data
have demonstrated high treatment adherence, low treatment discontinuation and similar safety and effectiveness outcomes of HCV treatments in substance users compared to the general population.\textsuperscript{50-53} Furthermore, Alavi et al. showed that HCV treatment was associated with decreased ancillary injecting equipment sharing among people who inject drugs, supporting the beneficial outcomes in this population.\textsuperscript{53} These favorable effects of treating patients with current drug use extend beyond the direct impact on patients’ health since it will potentially also decrease the risk of transmission to others. Consequently, international guidelines now recommend HCV treatment for all individuals with an active or past substance or alcohol disorder.\textsuperscript{17,18}

Similar to previous studies,\textsuperscript{16,28,29,35,54} several underlying comorbidities such as depression, hepatitis B, pancreatitis, anemia, dyslipidemia, COPD, heart failure, CKD, and hepatocellular carcinoma continued to present substantial obstacles to HCV therapy even after the market introduction of the effective all-oral DAA agents. Based on the long term achievements in large prospective studies of over 95\% SVR following the treatment with second generation DAAs, national and international guidelines clearly recommended the treatment of all patients with chronic HCV infection irrespective of comorbidity status.\textsuperscript{17,18} As there are several effective therapeutic agents on the market, clinicians have the option of adjusting regimens based on patient specific characteristics.

Patients treated with interferon-based regimen commonly had lower SVRs and higher rates of adverse treatment effects, which complicated HCV therapy.\textsuperscript{55} However, with the new DAAs, efficacy and safety concerns diminished and guidelines incorporated treatment recommendations in those with compensated cirrhosis.\textsuperscript{17}
Similarly, our data shows that patients with compensated cirrhosis were less likely to initiate treatments during the pre-all-oral DAA period, but were equally likely started on HCV drugs during the all-oral period.

The numerous health benefits of achieving long-lasting SVR in HCV patients are well described.\textsuperscript{17} Besides the decrease in liver inflammation and the significant improvement of fibrosis status, a cure of HCV infection is associated with a more than 70% reduction in the risk of hepatocellular carcinoma and an estimated 90% reduction in the risk of liver-related mortality and liver transplantation.\textsuperscript{17} As advanced liver disease is the leading cause of death among hepatitis C patients co-infected with HIV, these individuals benefit significantly from treatment. Our data suggest that HCV patients diagnosed with any non-alcoholic liver conditions (i.e. toxic liver disease, liver necrosis, or liver abscess) initiate treatments more likely compared to those without any of these conditions. It is important to continue the trend of prioritizing HCV treatment among such individuals and to mitigate barriers among those with advanced liver disease.

**HCV Treatment Cost**

In addition to reporting the changes in treatment initiation rates, we also evaluated the economic burden of HCV treatment during the study period. We observed steep increases in HCV drug costs paid to providers from dual to all-oral treatments. Mean costs per regimen increased for payers by almost four-fold (dual therapy, $20,820 vs. all-oral therapy $99,661, p<0.001), showing the immense cost pressure the new HCV agents put upon health insurance companies. Patients’ copayment costs per course of therapy almost doubled from dual to all-oral therapies ($593 vs $933, p<0.001). Yet, great variations were observed among the latter group. Whereas almost one-fourth of patients treated with the new agents had zero out-of-pocket costs, some
patients had to pay more than $50,000 for their entire course of therapy. Thus, insurers seem to be willing to cover large parts of the drug costs for most patients who received the therapies, as these treatments potentially reduce downstream costs associated with progression of liver disease.²¹,²²,³³

Chhatwal et al. and He et al. conducted systematic reviews of cost-effectiveness studies on DAAs from a healthcare payer’s perspective and found the median threshold price below which the new agents would be deemed cost-effective ranged between $144,000 and $227,000 for hepatitis C genotypes 1 – 6.²¹,²² However, cost-effectiveness does not mean that drugs are necessarily affordable. Thus, current prices are threatening the sustainability of healthcare systems worldwide. Previous research conducted by the WHO found that treating the entire HCV population of Organization for Economic Co-operation and Development (OECD) member countries with the new all-oral DAAs would consume between 10.5% and 190.5% of each country’s total pharmaceutical budget (adjusted for purchasing power), even when a 23% price reduction on the pharmaceuticals was applied.²³ The high prices being charged for the new agents mean that only few patients can benefit, causing a chasm between the unprecedentedly high efficacy found in clinical trials and the effectiveness of drugs in the real world.

Between 2014 and 2017 nine major all-oral treatments and treatment combinations have been approved by the FDA as HCV therapies,¹⁷ with AbbVie’s Mavyret being the last DAA in August 2017. This first pan-genotypic all-oral DAA was launched at a price of $26,400 in the US for an 8-week treatment course, before discounts, which is a significant lower price and shorter treatment period compared to
other DAAs, such as Harvoni ($98,000 for a 12-week course) or Epclusa ($78,000 for a 12-week course). Unsurprisingly, Mavyret has seen a strong uptake by prescribers and quickly won 32% market share within a few months after the launch.\textsuperscript{56} Meanwhile in late 2017, both Merck and Janssen announced their decisions to discontinue programs of developing new HCV combination treatments (i.e., MK-3682B, MK-3682C, and JNJ-4178), thus draining the hepatitis C drug pipeline.\textsuperscript{57,58} The HCV drug market peaked in 2016/2017 and it may be necessary that other companies bring their prices closer to AbbVie’s Mavyret of $26,400 in order to prevent the loss of more market share. As these speculative price reductions would mark substantial price drops, they would, by far, not change the ongoing disproportionate allocation of available resources towards HCV treatments.

In a Lancet commentary, Kamal-Yanni compared the current pricing situation of HCV drugs with the situation when highly effective HIV drugs came on the market.\textsuperscript{59} The author discussed the use of mechanisms such as tiered pricing, and voluntary or compulsory licensing, yet concluded that, learning from the situation with HIV during the 1990s and early 2000s, sustained affordable medicines for HCV cannot be achieved without generic competition. However, manufacturers commonly file numerous additional patents to protect their original base patents for each molecule, allowing them to artificially prolong the monopoly on the drug and its ability to charge high prices for it.\textsuperscript{60} These secondary patents are often of questionable inventiveness, yet enable manufacturers to delay generic competition for several decades.\textsuperscript{60} In the case of Sovaldi (generic name: Sofosbuvir) for example, Gilead has filed three patents on the base compound sofosbuvir, and more than 24 additional patents that would secure Sovaldi’s
market exclusivity until into the late 2030s. Patient advocacy groups and organizations such as Doctors of the World have filed multiple lawsuits against these controversial patents. However, in order to reduce inappropriate market exclusivity extensions, legislative authorities need to adjust current regulations so that patent transparency increases, stricter patentability standards are initiated, and opportunities to challenge patent applications and patents are widened.

Besides improving patent laws, several other mechanisms have been suggested that would open the door for generic competition and slow down the escalating drug costs in the US. In a position paper published by the American College of Physicians (ACP), the authors call for (1) more transparency in the pricing, cost, and comparative value of drugs, (2) the use of quality-adjusted life-years (QALYs) when evaluating treatments, (3) allowing Medicare to negotiate drug prices, (4) reimporting drugs manufactured in the US, while assuring safety of the reimports, and (5) increasing value-based contracting.

With the introduction of interferon-free all-oral DAAs the limit to HCV cure has shifted from a lack of safe and effective treatment options to an economic barrier to existing treatments. Implementing the legislations proposed by the ACP may help to overcome those barriers so that more HCV patients can benefit from the effective therapies.

**Study Limitations**

There are several limitations to our study which must be considered when interpreting our findings. Specific clinical information (e.g., HIV viral suppression, HCV genotype, fibrosis stage) and sociodemographic characteristics (e.g., race, income) was not available, limiting our ability to control for underlying disease severity and other patient
characteristics. Hence, we cannot rule out residual confounding by unmeasured factors. In addition, we captured all comorbidities during the 12-month baseline period, thus it is possible that patients’ disease information was not fully captured. Nevertheless, there is no reason to believe that any of the above-mentioned limitations lead to misclassification of covariates in a differential manner. We furthermore found a comparatively low proportion of HCV/HIV coinfections among our sample of HCV patients. Since our dataset includes individuals and their dependents with employer-based insurance coverage, lower co-infection rates were expected. Thus, we emphasize that our results are only generalizable to the privately insured US population. Lastly, the net-costs for each pharmaceutical were measured on the basis of gross payment charges between the provider and the payer, excluding the deductible and copayments for the patient, and do not incorporate any drug discounts or proprietary rebate agreements. Therefore, the actual cost paid for HCV therapy may be significantly less than our estimations considering the high rebates and discounts negotiated between pharmaceutical companies and payers.

**Conclusions**

In conclusion, we found increasing trends of HCV treatment initiations after the market approval of the new DAAs, which were even more pronounced in HCV patients co-infected with HIV. In general, however, HCV treatment initiation rates remain comparably low. We found several comorbidities negatively influencing treatment initiations with all-oral DAAs in individuals infected with HCV (e.g., alcohol and substance use disorders), despite the guideline recommendations of starting HCV therapy in all patients. Although out-of-pocket costs for those receiving the new agents seem to be passably affordable, the cost burden for payers are immense, posing as the
major barrier to eradicating HCV. Further clinical and legislative effort is needed to promote access to HCV treatments in both HCV mono- and HCV/HIV coinfected patients and to balance corporate interests and public needs for effective medications.
## APPENDIX
### OPERATIONAL DEFINITIONS

Table A-1. Potential confounders and other covariates included in multivariate analyses

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Operational Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Year of age</td>
</tr>
<tr>
<td>Gender</td>
<td>Male, Female</td>
</tr>
<tr>
<td>Alcohol disorders</td>
<td>ICD-9-CM: 291.x, 303.x, 305.0, 535.3</td>
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<td></td>
<td>ICD-10-CM: F10.1, F10.2, F10.9, K29.2</td>
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<td></td>
<td>305.5, 305.6, 305.7, 305.8, 305.9, V65.42</td>
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<td>F16.x, F18.x, F19.x</td>
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<td>Depression</td>
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<tr>
<td></td>
<td>ICD-10-CM: F30.x, F31.x, F32.x, F33.x, F34.x,</td>
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<tr>
<td></td>
<td>F38.x, F39.x</td>
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<td>Schizophrenia</td>
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<td>ICD-10-CM: F20.x, F21.x, F22.x, F23.x, F24.x,</td>
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<td>F25.x</td>
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<td>Epilepsy</td>
<td>ICD-9-CM: 345.x</td>
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<td>ICD-10-CM: G40.x</td>
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<td>Hepatitis A</td>
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<td>ICD-10-CM: B15.x</td>
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<td>ICD-9-CM: 070.2, 0703</td>
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<td>ICD-10-CM: B16.x, B18.0, B18.1, B19.1</td>
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<td>Pancreatitis</td>
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<td>ICD-10-CM: K85.x, K86.x</td>
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<td>285.x, 286.x</td>
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<td>ICD-10-CM: E08.x, E09.x, E10.x, E11.x, E13.x</td>
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<td>ICD-10-CM: E78.x</td>
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<td>Hypertension</td>
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<td>ICD-10-CM: I10.x, I11.x, I15.x</td>
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<td>Congestive heart failure</td>
<td>ICD-9-CM: 398.91, 428.x</td>
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<td>ICD-10-CM: I09.81, I50.x, I51.x, I52.x</td>
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<td>Covariate</td>
<td>Operational Definition</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------</td>
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<td>Coronary artery disease (Ischemic Heart Disease)</td>
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<td>Peripheral Vascular Disease</td>
<td>ICD-9-CM: 440.x, 441.x, 443.x, 444.x, 447.x, 557.x</td>
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<td></td>
<td>ICD-10-CM: I70.x, I71.x, I72.x, I73.x, I74.x, I77.x, K55.x</td>
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<td>Cerebrovascular Disease</td>
<td>ICD-9-CM: 430.x, 431.x, 432.x, 433.x, 434.x, 435.x, 436.x, 437.x, 438.x</td>
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<tr>
<td></td>
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<tr>
<td>Chronic Kidney Disease</td>
<td>ICD-9-CM: 585.x</td>
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<td>ICD-10-CM: N18.x</td>
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<td>Cirrhosis</td>
<td>ICD-9-CM: 571.2, 571.5, 571.6</td>
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<td>ICD-10-CM: K70.3, K74.x</td>
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<td>Decompensated Cirrhosis</td>
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<td>ICD-10-CM: R18.x, I85.0, K65.0, K65.1, K65.2, K65.8, K65.9</td>
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<td>Hepatocellular Carcinoma</td>
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<td>ICD-10-CM: C22.x</td>
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<tr>
<td>Other non-alcoholic Liver Diseases</td>
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<td></td>
<td>ICD-10-CM: K71.x, K72.x, K73.x, K75.x, K76.x, K77.x</td>
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<td>Other alcoholic liver disease</td>
<td>ICD-9-CM: 571.0, 571.1, 571.3</td>
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<td>ICD-10-CM: K70.0, K70.1, K70.2, K70.4, K70.9</td>
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<td>Liver Transplant</td>
<td>ICD-9-CM: V42.7, 996.82, 50.5</td>
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<td>ICD-10-CM: Z94.4, Z48.23, T86.4</td>
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<td>CPT-4: 47133, 47135, 47136</td>
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<td>Sarcoidosis</td>
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<td>ICD-10-CM: D86.x</td>
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<td>Rheumatoid Arthritis</td>
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<td>ICD-10-CM: M05.x, M06.x</td>
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<td>Systemic Lupus Erythematosus [SLE]</td>
<td>ICD-9-CM: 710.0</td>
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<td>ICD-10-CM: M32.x</td>
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<tr>
<td>Pregnancy</td>
<td>ICD-9-CM: 650.x, 651.x, V22.x, V23.x, V616.x, V617.x, V7242.x</td>
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</table>
|                                                | ICD-10-CM: Z34.x, Z33.1                                                             

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Table A-2. List of hepatitis C treatments included in the analyses

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<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>FDA Approval Date</th>
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<td>Interferons:</td>
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<td>Interferon alfa-2a, Interferon alfa-2b,</td>
<td>Roferon</td>
<td>June 1986</td>
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<tr>
<td>Interferon alfacon-1, Peginterferon alfa-2a,</td>
<td>Intron A</td>
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<td>Peginterferon alfa-2b</td>
<td>Infergen</td>
<td>Oct 1997</td>
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<td>Ribavirin</td>
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<td></td>
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<td>CoPegus</td>
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<td>Moderiba</td>
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<tr>
<td>Ribapak</td>
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<td>Ribatab</td>
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<tr>
<td>Simeprevir</td>
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<td></td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
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<td></td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir/dasabuvir</td>
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<tr>
<td>Daclatasvir</td>
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<tr>
<td>Ombitasvir/Paritaprevir/Ritonavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbasvir/grazoprevir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir</td>
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</tbody>
</table>

Ledipasvir/sofosbuvir: Daklinza July 2015
Ombitasvir/paritaprevir/ritonavir/dasabuvir: Viekira Pak Dec 2014
Daclatasvir: Daklinza July 2015
Ombitasvir/Paritaprevir/Ritonavir: Technivie July 2015
Elbasvir/grazoprevir: Zepatier Jan 2016
Sofosbuvir/Velpatasvir: Epclusa June 2016
LIST OF REFERENCES


BIOGRAPHICAL SKETCH

Sascha van Boemmel-Wegmann was born and raised in Dormagen, Germany. In 2012 he received his Bachelor of Pharmacy degree from the Heinrich-Heine-University in Duesseldorf, Germany. After becoming a registered pharmacist in Germany, he worked for two years in community pharmacies in Dormagen and Cologne, Germany. In addition to working as a community pharmacist he joined the Department of Clinical Pharmacy at the University of Bonn between October 2012 and March 2013 as a research assistant under the supervision of Professor Ulrich Jaehde and helped implementing and evaluating a computer-based drug-drug-interaction management system in German community pharmacies. Sascha joined the PhD program at the Department of Pharmaceutical Outcomes and Policy at the University of Florida in 2014. During his graduate training, Sascha received several scholarships including travel grants from the office of research at the University of Florida (2016), a scholarship for the annual conference of the International Society of Pharmacoepidemiology [ISPE] (2016), a travel grant for the annual international meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) in Boston, MA (USA, 2017), and a scholarship for the ISPE Mid-year meeting in Toronto, Canada (2018). Sascha was furthermore an invited speaker at the 32\textsuperscript{nd} annual ISPE conference in Dublin, Ireland (2016), and the Gator Healthcare Forum in Gainesville, FL (USA, 2016). Between August 2016 and August 2017 Sascha served as the president of the Florida ISPOR student chapter. In addition, he was the elected College of Pharmacy Graduate Student President during the academic year of 2018/19. He has authored and co-authored several peer-reviewed publications and has presented his studies at national and international conferences. His research focuses on applied pharmacoepidemiologic
and pharmacoeconomic studies in the areas of infectious diseases and cancer, including drug use, healthcare resource utilization, and drug safety studies.