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Healthcare Costs and Resource Utilization in Treated Versus Untreated Chronically Infected Hepatitis C Patients

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Healthcare Costs and Resource Utilization in Treated Versus Untreated Chronically Infected Hepatitis C Patients

by

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Dedication

I dedicate this dissertation to my parents, who have made endless sacrifices as immigrants trying to provide more opportunities for their children.

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I want to thank my committee for their guidance and support during this process. Dr. Rascati, thank you for being a role model for me in so many ways. Dr. Wilson, thank you for believing in me when I first came to interview for the fellowship. Dr. Barner, thank you for your constant encouragement throughout the years. Dr. Richards, thank you for answering my many questions and always being available. Dr. Saab, thank you for all that you taught me about hepatitis C. I also want to thank Stephanie Crouch for going above and beyond to help all of us graduate students. Lastly, I thank my UT family – Lung-I Cheng, Haesuk Park, Michael Carlson, Cat Bui, and Milli Reddy. They are life-long friends who have helped to create such fond memories of Austin.

Healthcare Costs and Resource Utilization in Chronically Infected Hepatitis C Patients

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The University of Texas at Austin, 2013

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Successful treatment of chronic hepatitis C virus (HCV) leads to significant benefits in both hepatic and extrahepatic morbidity and mortality. However, treatment is costly and onerous. The purpose of this study was to evaluate the resource utilization and healthcare costs of chronic HCV patients who are treated versus those who are not treated.

Patients eligible for this study were Texas Medicaid patients ≥18 and ≤63 years who had evidence of chronic HCV during the identification period (1/1/07–9/30/11) and continuous enrollment throughout the analysis period. High dimensional propensity scoring techniques were used to match treated vs. untreated patients (1:2 ratio). Unadjusted and adjusted analyses compared the healthcare costs and utilization between patient cohorts at 6 and 18 months. For those treated, adherence was measured by proportion of days covered and persistence was evaluated as a gap in medication (of one fill) as determined by refill records.

There were a total of 24,032 patients identified with chronic HCV. After high dimensional propensity scoring, there were no significant differences in key clinical and demographic characteristics between treated (n=939) and untreated (n=1878) cohorts. Over 97% of patients had evidence of end stage liver disease at baseline. Based on adjusted analyses of total costs using a generalized linear regression model, the mean difference in costs between the treated vs. untreated patients was $13,960 (SE $458, p<0.001). At 18

months of follow-up, the adjusted mean all-cause costs were $20,834 higher for treated patients (n=456) compared to those untreated (n=849) ($p<0.001$); however, mean outpatient costs were $1,894 (SE $274) less in treated vs. untreated patients. For those treated, the average HCV medication PDC was 71%, and by the end of 24 weeks, only 42.3% of patients remained on HCV therapy.

This study did not show short-term cost offsets, but the sub-analysis following patients for 18 months showed trends in downstream cost offsets. Most patients had advanced liver disease, reducing the chances of successful treatment and averting liver disease sequelae. Earlier identification and treatment could bend the cost curve before these patients reached the more advanced stages seen in this costly cohort.

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Chapter 1: Hepatitis C Virus and the Burden of Chronic Hepatitis C Infection

Hepatitis C virus (HCV) infection has made media headlines recently due to the increasing awareness of the disease burden and the numerous new agents in the pipeline to address gaps with current treatments. If left untreated, HCV leads to liver cirrhosis, hepatocellular carcinoma (HCC), and death. Currently, HCV infection is the leading cause of both chronic liver disease and HCC. Furthermore, mortality associated with HCV is expected to increase dramatically over the next two decades as those with HCV are aging and developing more advanced liver disease.

1.1 EPIDEMIOLOGY OF HCV

1.1.1 Worldwide Epidemiology of HCV

The worldwide prevalence of HCV is estimated to be 2.35%, which translates to approximately 160 million infected persons. By region, there are 400,000 chronically infected subjects in Australia and Oceania, 14 million in the Americas, 16 million in the Middle East, 17.5 million in Europe, 28 million in Africa, and 83 million in Asia. [1] In Europe, prevalence greatly varies by country with low prevalence in Belgium (0.87%) to high rates in Central and Southern Italy (8.4-22.4%). [2] In the Middle East, Egypt has the highest prevalence of around 15%. [3] In Africa, prevalence data are incomplete, but indicate variation from 0-51%. [1] In Asia, intermediate rates of HCV have been reported, with higher rates in Thailand (3.2-5.6%) and some provinces in China, such as Hubei province (30.13%).

The future of global burden of HCV will increase dramatically within the next decade, mostly from HCV-related cirrhosis and deaths. These sequelae will be seen especially in Australia, Canada, France, the UK, and USA. In China, India, and the Middle East, there are increases in intravenous drug use (IVDU), which will also contribute to HCV burden in this decade. Due to their large populations, a 1% increase in IVDU in China and India would result in an additional 25 million HCV-infected persons. [1]

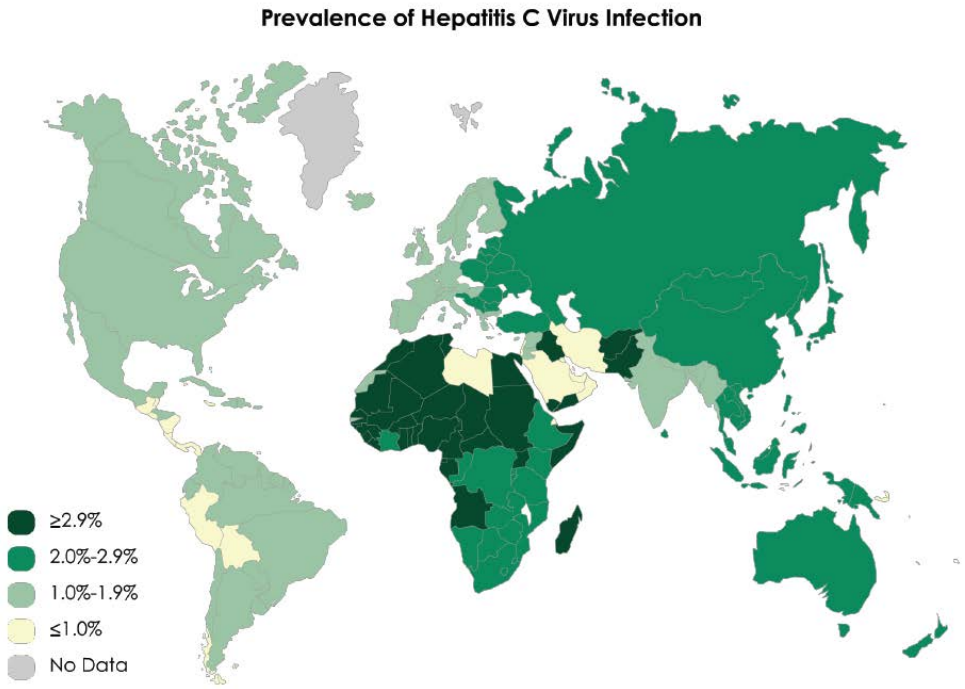


Figure 1.1.1: Worldwide Prevalence of Hepatitis C Virus Infection [4]

The incidence of HCV is difficult to measure, especially for less developed countries, due to the asymptomatic nature of acute infections. However, there are incidence data for Europe, Egypt and the US, which will be discussed more thoroughly in the next section. In Europe, the incidence has been from around 5 cases per 100,000 people per year to just over 8 cases per 100,000 people per year between 1995 and 2005. The greatest increases in the number of new HCV cases were for Austria, Czech Republic, and the United Kingdom.[5] (Figure 1.1.2) In Egypt, the country with the highest prevalence of HCV, there are around 610 new cases per 100,000 people, or around 500,000 new cases of acute HCV infection each year. [6] Although there is controversy over the fuel behind the epidemic, most think that the iatrogenic role of parental antichistosomal therapy to control endemic schistosomiasis (disease caused by a type of parasitic worm) decades ago

largely contributes. [7] Continuation of iatrogenic exposures is thought to contribute to ongoing HCV transmission. [8]

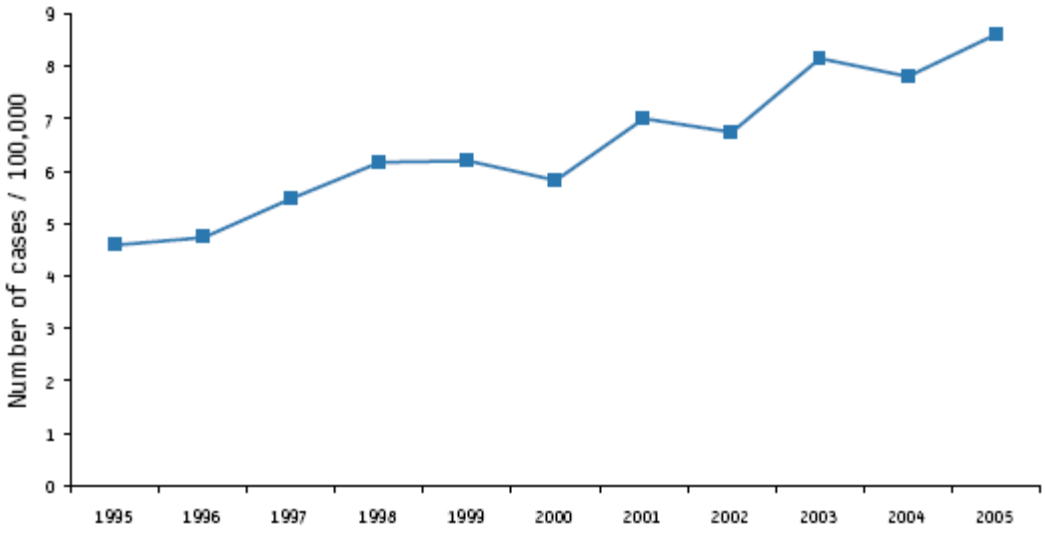


Figure 1.1.2: The incidence of reported hepatitis C cases in European Union and European Economic Area/European Free Trade Association countries in 1995-2005 [5]

1.1.2 US Epidemiology of HCV

Although the US has a lower percentage prevalence of HCV at around 1.6%, there are 4-6 million individuals with HCV in the country. [9] Baby boomers, or those born between 1946-1964 account for two-thirds of persons infected with chronic HCV. [10] (Figure 1.1.3)

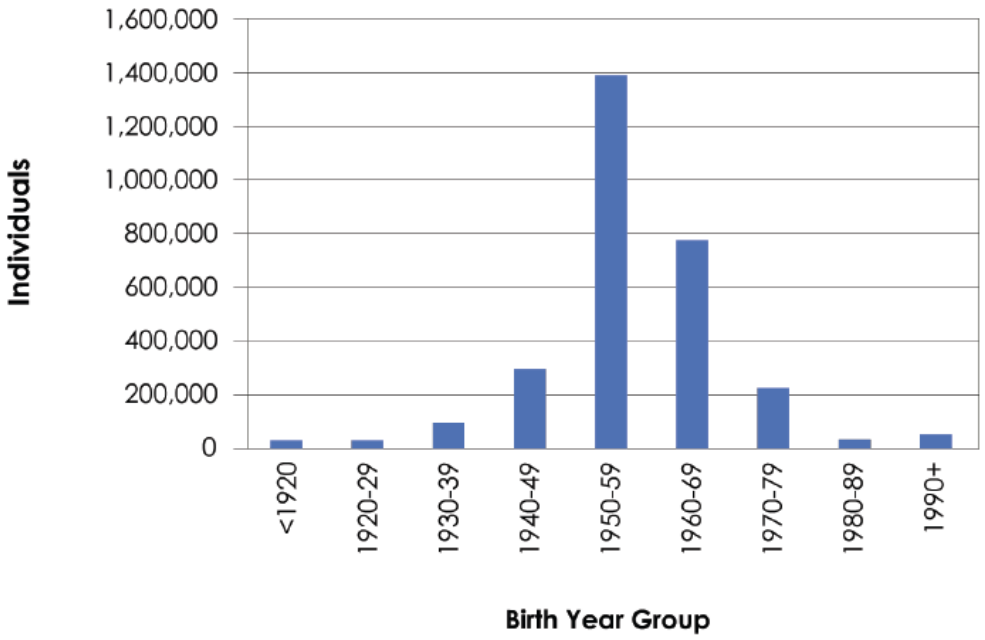


Figure 1.1.3: Prevalence of HCV by age in the US [10]

Besides the baby boomers, prevalence is also higher in males versus females and in non-Hispanic blacks versus non-Hispanic whites or Mexican-Americans. [11] In addition, the homeless population has a high prevalence of chronic HCV infection of 22% compared to 1.8% for the total US population. [12] Not surprisingly, a higher prevalence is also seen in alcoholics, incarcerated individuals, individuals with severe mental illness, and hemophiliacs. [13] Veterans, especially Vietnam veterans, also have a

disproportionately higher prevalence of 6%. [14] The greatest prevalence is seen in injection drug users as 60 to80% of those injecting drugs for at least 5 years are infected with HCV. [15]

Most of the prevalence estimates in the US are derived from the National Health and Nutrition Examination Survey (NHANES); however, this survey samples only the civilian, non-institutionalized population. Chak et al. found that based on the prevalence in published studies, the most conservative estimates state that there are at least 142,761 homeless persons, 372,754 incarcerated persons, and 6,805 persons on active military duty unaccounted for in the NHANES survey. [9] This would most certainly mean that the NHANES-derived US HCV prevalence rates are underestimated.

The incidence of HCV in the US peaked in 1992 at 2.4 cases per 100,000 population. In 2009, rates declined by 88% to 0.3 cases per 100,000. [16] The introduction of anti-HCV blood tests was the reason for the decline in the early 1990s. Since 1994, the risk of transfusion-associated HCV infection has been almost completely eliminated. [13] Also contributing to the decline was the lower rate of high-risk injection drug use since the 1970s and anti-HIV educational programs that promoted needle exchange. [17]

1.2 HCV PATHOPHYSIOLOGY

1.2.1 HCV Virology

Hepatitis C is a blood-borne ribonucleic acid (RNA) virus of the family Flaviviridae. The virion is composed of dimers of two of the structural proteins, E1 and E2, which radiate from the viral envelope. The viral nucleocapsid, which is inside the envelope, surrounds the viral genome and contains multiple copies of the HCV core protein. HCV virions are either bound to very low density lipoproteins (VLDL) or, low density lipoproteins (LDL), complexed with immunoglobulins, or circulate freely. The VLDL or LDL association may protect the virus from neutralization by antibodies and allows the virus to enter hepatocytes via LDL receptors. [18]

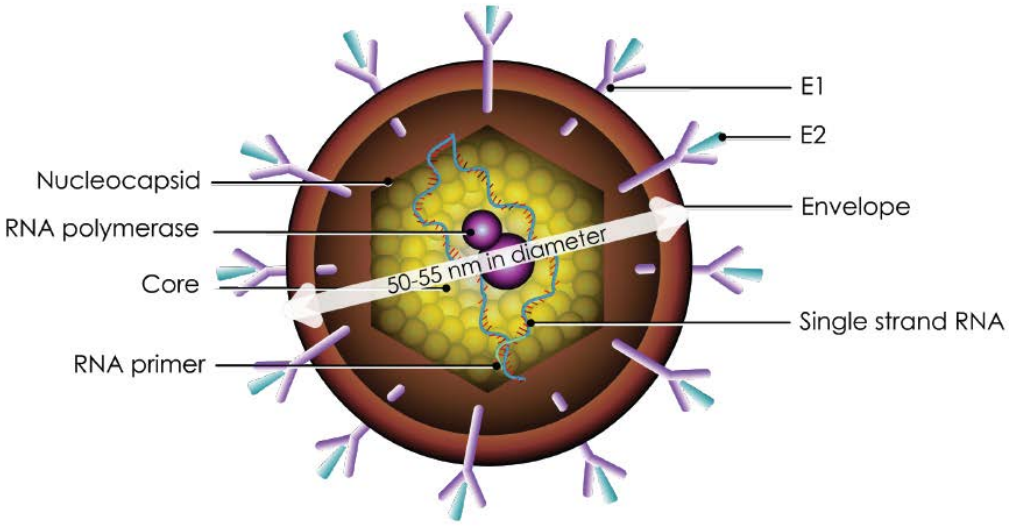


Figure 1.2.1: HCV virion [18]

The HCV genome consists of one 9.6 kb single-stranded RNA molecule with positive polarity and 2 untranslated, highly conserved regions, 5'-UTR and 3'-UTR, at both ends of the genome. The genome encodes a single polyprotein of 3011 amino acids that

are processed into 10 structural and regulatory proteins. The genomic RNA serves as messenger (mRNA) for translation of viral proteins. HCV replicates preferentially in hepatocytes. [18]

1.2.3 HCV Genotypes

There are 6 known genotypes for HCV and more than 50 major subtypes. The prevalence of each genotype varies as do the treatment response rates. Genotype 1 is the most common genotype accounting for 70 to 80% of HCV patients in the United States. Another 16 to 22% of HCV patients in the US have genotypes 2 or 3, which are the second most prevalent genotypes. Genotypes 2 and 3 patients respond better to existing therapy options than genotype 1 HCV patients. [13] The global distribution of genotypes can be found in Table 1.2.1. [19]

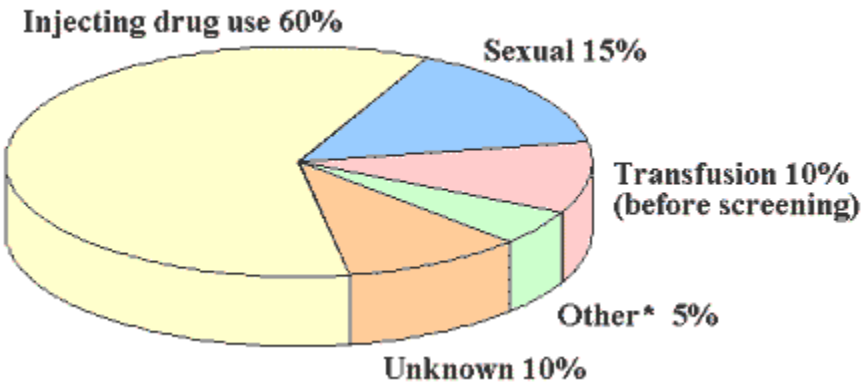
Table 1.2.1: Global distribution of genotypes and prevalence in the US [20]

Genotype	Distribution	US Prevalence
1a	Global	35-40% of HCV cases
1b	Global, especially prevalent in Southern and Eastern Europe, China and Japan	35-40% of HCV cases
2	Global	10% of HCV cases
3	Various regions throughout the world, but especially common in South Asia and Australia	6% of HCV cases
4	Middle East and Africa, especially Egypt (up to 90% of cases in Egypt)	<5% of HCV cases
5	Africa	<5% of HCV cases
6	Southern China and Southeast Asia	<5% of HCV cases

1.2.3 HCV Transmission

HCV is transmitted through blood and blood products. The virus is hardy and can survive outside of the body for up to 63 days (in a closed environment such as a syringe). Before 1992, HCV was spread by infected blood transfusions and organ transplants with approximately 8 to 10% of people who received transfusions in the 1970s and 1980s acquiring HCV by this route. [13]

The most significant mode of transmission for HCV is the sharing of contaminated needles. Other possible routes of HCV infection include receiving injuries in a healthcare setting, acquiring the infection during hemodialysis, vertical transmission from mother-to-child, sexual contact, sharing of contaminated blood through sharing of personal care items, body piercing, tattooing, and acupuncture. [15, 21] Figure 1.2.2 displays the sources of infection for persons with HCV.



*Hemodialysis, perinatal, occupational exposure

Figure 1.2.2: Sources of infection in persons with HCV [15]

1.2.4 HCV Morbidity and Mortality

An estimated 15 to 25% of those infected with HCV can spontaneously clear the virus without treatment; however, around 75% develop chronic infection. Most patients remain asymptomatic for 20 to 30 years, but eventually 60 to 70% of patients develop liver disease, and 4 to 20% develop cirrhosis. Manifestations of cirrhosis include encephalopathy, variceal bleeding, jaundice, and ascites. [22] The timing of progression to cirrhosis is not fully elucidated, but numerous studies indicate an association between age at infection and disease progression with older persons having more rapid disease progression. [23] Other factors known to accelerate the progression of liver disease include male gender, alcohol consumption, co-morbid liver disease and co-morbid HIV infection. Chronic HCV accounts for 50% of hepatocellular carcinoma cases in the US. There is a 4% increased risk of developing liver cancer each year after an HCV patient develops cirrhosis. [24]

Until recently, HCV was a relatively unrecognized public health issue in the US; however, many studies call attention to the increasing mortality from HCV. One model predicts that HCV-related mortality of those infected will increase from 2.1% in 2005 to 3.1% in 2021, while the standard mortality ratio is projected to decrease. These changes are due mostly to the aging of the HCV-infected baby boomer cohort and associated advanced liver disease from infections acquired decades ago. [25]

In another study, mortality rates were calculated by dividing the number of deaths from hepatitis B virus (HBV), HCV, or HIV infections listed as an underlying or contributing cause in death certificates, by the total US census population for each year, adjusted to the age distribution in 2000. The researchers found that deaths from HCV surpassed those from HIV in 2007 and are continuing to increase. From 1999 to 2007, they

found that HCV mortality increased by 0.18 per 100,000 person-years ($p=0.002$), HIV mortality decreased by 0.21 ($p=0.001$) and HBV mortality decreased by 0.02 ($p=0.25$). The study also found that factors associated with HCV-related deaths included chronic liver disease, HBV co-infection, alcohol-related conditions, minority status, and HIV co-infection. [26]

There are very few natural history studies of HCV infection. One community-based prospective study (The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (REVEAL)) in Taiwan showed significantly higher risk of dying from all causes, hepatic diseases, and extrahepatic diseases in anti-HCV seropositives with detectable HCV RNA levels compared with anti-HCV seropositives with undetectable HCV RNA and anti-HCV seronegatives ($p<0.001$). (Figure 1.2.3) A total of 19,636 participants seronegative for hepatitis B surface antigen (HBsAg) were included in this analysis, of whom, 18,541 (94.4%) were anti-HCV seronegative and 1095 (5.6%) were anti-HCV seropositive. There were a total of 2394 deaths over 317,742 person-years of follow-up with an average follow-up of 16.2 years. The overall mortality was 753.4 per 100,000 person-years. The adjusted hazard ratios (HRs) of the cause of death by serostatus are listed in Table 1.2.2. The HRs were adjusted for age, sex, cigarette smoking, alcohol drinking, betel nuts chewing (contains stimulant acrecoline), and central obesity. [27]

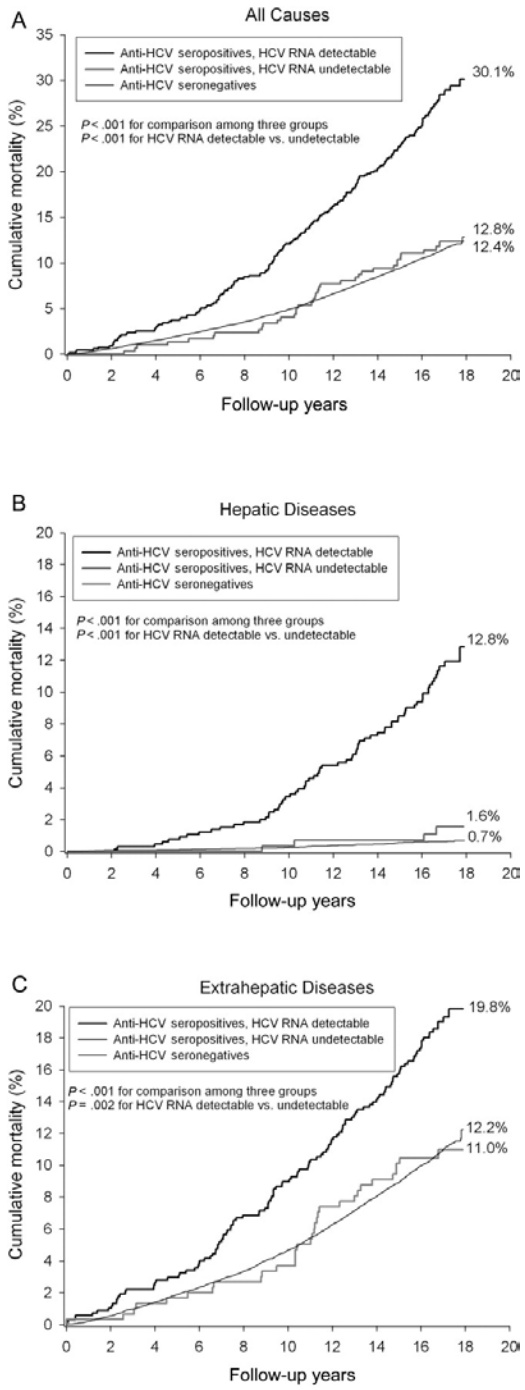


Figure 1.2.3: Cumulative mortality from all causes of death (A), hepatic diseases (B), and extrahepatic diseases (C) by serostatus of antibodies against hepatitis C virus (anti-HCV) and serum HCV RNA level at study entry [27]

Table 1.2.2: Mortality rates (per 100,000 person-years) and adjusted hazard ratios of specific causes of death by serostatus of antibodies against hepatitis C virus (Anti-HCV) at study entry [27]

	Anti-HCV (−), N = 18,541 (300,772 person-years)		**Anti-HCV (+), N = 1,095 (16,970 person-years)**		
Causes of Death (ICD-9 Codes)	**Death No.**	**Mortality Rate**	**Death No.**	**Mortality Rate**	**Multivariate-Adjusted Hazard Ratio (95% CI)**
All causes[a]	2132	708.8	262	1543.9	1.89 (1.66–2.15)
Hepatic diseases (155, 570–573)	112	37.2	83	489.1	12.48 (9.34–16.66)
- Liver cancer (155)	50	16.6	65	383	21.63 (14.83–31.54)
- Chronic liver diseases and cirrhosis (571–572)	58	19.3	18	106.1	5.38 (3.15–9.19)
Extrahepatic diseases	2020	671.6	179	1054.8	1.35 (1.15–1.57)
Cancers (140–239 except 155)	637	211.8	55	324.1	1.32 (1.00–1.74)
Nephritis, nephrotic syndromes and nephrosis (580–589)	69	22.9	12	70.7	2.77 (1.49–5.15)

[a] Numbers may not total due to multiple causes of death per person

Predictors of hepatocellular carcinoma (HCC) risk were also examined using the REVEAL cohort. Increased HCC risk was associated with an ALT ever >45 U/L, which suggests a role of ongoing inflammation in liver disease progression (HR: 4.52, 1.36-15.01). HCV RNA above undetectable levels was also a strong, long-term predictor of HCC risk in untreated patients (HR: 7.81, 2.34-26.11 for $\geq 10^5$ U/mL and HR: 4.71, 1.36-16.35 for low levels). There was an increasing cumulative risk of HCC for anti-HCV-

seropositive participants with undetectable, low, and high serum HCV RNA levels (1.1%, 6.4%, and 14.7%, respectively; $p<0.001$ for trend). Additionally, HCV-infected individuals with detectable viral load and genotype 1 (versus non-genotype 1) were found to be at an increased risk of HCC (HR: 2.28, 1.10-4.70). [28]

Another natural history study conducted with the Veterans population examined the association between HCV and HCC, intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), and pancreatic cancer. The study included 146,394 HCV-infected and 572,293 HCV-uninfected patients who received care at Veterans Affairs health care facilities between 1996 and 2004. Cases and controls were matched by age, sex, baseline visit date, and type of visit. The risk of intrahepatic cholangiocarcinoma (HR: 2.55, 1.31-4.95) and HCC (HR: 15.09, 13.44-16.94) was significantly higher in anti-HCV seropositives with detectable HCV RNA levels compared with non-HCV veterans. [29]

1.3 HCV MANAGEMENT AND TREATMENT

The full treatment guidelines for managing HCV were updated in 2009 by the American Association for the Study of Liver Diseases (AASLD), followed by another update in October 2011 after the new protease inhibitors were approved for treatment in chronic HCV genotype 1 patients. The guidelines provide recommendations for screening, laboratory testing, and treatment of both acute and chronic HCV infection. The grading system for recommendations can be found in Table 1.3.1. [30]

Table 1.3.1: AASLD grading recommendations [30]

Classification	**Description**
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment.
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure/ treatment is not useful/effective and in some cases may be harmful.
Level of Evidence	**Description**
Level A	Data derived from multiple randomized clinical trials or meta-analyses.
Level B	Data derived from a single randomized trial, or nonrandomized studies.
Level C	Only consensus opinion of experts, case studies, or standard-of-care.

1.3.1 Recommendations for Screening

Despite screening recommendations, 50-75% of those chronically infected with HCV are unaware of their infection. [31] According to the AASLD guidelines in 2009, the following persons should be screened for HCV infection (Class I, Level B) [30]:

- Persons who have injected illicit drugs in the recent and remote past, including those who injected only once and do not consider themselves to be drug users.
- Persons with conditions associated with a high prevalence of HCV infection including:
    - Persons with HIV infection
    - Persons with hemophilia who received clotting factor concentrates prior to 1987
    - Persons who have ever been on hemodialysis
    - Persons with unexplained abnormal aminotransferase levels
    - Prior recipients of transfusions or organ transplants prior to July 1992 including:
        - Persons who were notified that they had received blood from a donor who later tested positive for HCV infection
        - Persons who received a transfusion of blood or blood products
        - Persons who received an organ transplant
- Children born to HCV-infected mothers
- Health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood
- Current sexual partners of HCV-infected persons

Recently, the CDC developed evidence-based recommendations for birth cohort screening. The following questions were asked: 1) What is the effect of a testing strategy based on birth year versus the standard of care (i.e., risk-based testing) for identification of HCV infection?; 2) Should HCV testing (versus no testing) be conducted among adults at average risk for infection who were born between 1945 and 1965?; 3) Among persons tested for and identified with HCV infection, is treatment-related sustained virological response (SVR) (versus treatment failure) associated with reduced liver-related morbidity and all-cause mortality?; 4) Should HCV testing followed by brief alcohol intervention

(versus no intervention) be carried out to reduce or stop drinking among HCV-infected persons? Two independent reviewers searched MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials, Sociological Abstracts, and the Database of Abstracts of Reviews of Effects to identify English-language studies related to the questions from 1995 to May 2011. The Grading of Recommendations Assessment, Development, and Evaluation framework was used to develop these recommendations. The final quality of evidence for the outcomes was categorized into 1 of 4 levels: very low, low, moderate, and high. The strength of the recommendation was assessed by 9 workgroup members from the Division of Viral Hepatitis, who evaluated the quality of evidence, benefits and harms, values and preferences (of persons being targeted for testing), and resource implications before arriving at a consensus on the recommendations. Recommendations were categorized into strongly for or against the recommendation, or conditionally for or against the recommendation.

The workgroup found 30 observational studies that noted positive outcomes, such as decreased mortality and reduction in the incidence of HCC with achievement of SVR. In addition, an NHANES analysis found that anti-HCV prevalence in the 1945 to 1965 birth cohort was 3.25% versus 0.8% among adults aged 20 years or older who were born outside of the birth cohort. The workgroup also noted that alcohol reduction intervention was effective at reducing alcohol consumed per week. Based on these findings, the following recommendations were made:

1. The CDC recommends that adults born during 1945 to 1965 should receive 1-time testing for HCV without prior ascertainment of HCV risk. (Grade: strong recommendation; moderate-quality evidence).

2. The CDC recommends that all persons identified with HCV infection should receive a brief alcohol screening and intervention as clinically indicated,

> followed by referral to appropriate care and treatment services for HCV infection and related conditions (Grade: strong recommendation; moderate-quality evidence).[32]

Similar to the CDC recommendations on birth cohort screening, the US Preventive Services Task Force (USPSTF) recommends the following:

1. Recommends screening for HCV infection in adults at high risk *(Grade B)*
2. Recommends that clinicians consider offering screening for HCV infection in adults born between 1945 and 1965 *(Grade B)*

Grade A and B indicates that USPSTF recommends the service and due to the Affordable Care Act, payers are now required to cover Grade A and B recommendations with no patient contributions. The guidelines were updated by a review from the Agency for Healthcare Research and Quality (AHRQ) of new studies published since 2004. The evidence on the benefits of treatment on HCV morbidity and mortality contributed to the Grade B recommendation. [33, 34]

1.3.2 Recommendations for Laboratory Testing

There are two main laboratory tests used to screen for HCV, which include (1) serologic assays that detect specific antibody to hepatitis C virus (anti-HCV) and (2) molecular assays that detect viral nucleic acid.

The enzyme immunoassays available include Abbott HCV EIA 2.0 (Abbott Laboratories, Abbott Park, IL) and ORTHO_HCV Version 3.0 ELISA (Ortho-Clinical Diagnostics, Raritan, NJ), as well as one enhanced chemiluminescence immunoassay (CIA) VITROS_ Anti-HCV assay, (Ortho- Clinical Diagnostics, Raritan, NJ). The specificity of current EIAs for anti-HCV is greater than 99%. Since the availability of real-time polymerase chain reaction (PCR)-based assays and transcription-mediated amplification (TMA) assays, with sensitivities of 10 to 50 IU/mL, qualitative assays are not used as often. Quantitative assays should be used to monitor therapy and all currently available assays have excellent specificity of 98 to 99%.

Genotype determination is important to determine duration of therapy. The available assays include Trugene 5_NC HCV Genotyping Kit (Siemens Healthcare Diagnostics Division, Tarrytown, NY), INNO-LiPa HCV II, (Innogenetics, Ghent, Belgium), and Versant HCV Genotyping Assay 2.0 (Siemens Healthcare Diagnostics Division, Tarrytown, NY).

The AASLD guidelines make the following recommendations on laboratory testing [30]:

1. Patients suspected of having acute or chronic HCV infection should first be tested for anti-HCV (Class I, Level B)

2. HCV RNA testing should be performed in:
    a) Patients with a positive anti-HCV test (Class I, Level B)

b) Patients for whom antiviral treatment is being considered, using a sensitive quantitative assay (Class I, Level A)
c) Patients with unexplained liver disease whose anti-HCV test is negative and who are immunocompromised or suspected of having acute HCV infection (Class I, Level B).

3. HCV genotyping should be performed in all HCV-infected persons prior to interferon-based treatment in order to plan for the dose and duration of therapy and to estimate the likelihood of response (Class I, Level A).

1.3.3 Recommendations on Tests for Fibrosis

Fibrosis tests are often used to inform physicians of the progression of disease and decision to treat with anti-HCV therapies. The AASLD guidelines state three reasons for performing liver biopsy: 1) it provides helpful information on the current status of the liver injury; 2) it identifies features useful in the decision to embark on therapy; and 3) it may reveal advanced fibrosis or cirrhosis that necessitates surveillance for hepatocellular carcinoma (HCC) and/or screening for varices. There are three scoring systems: French Metavir, the Batts-Ludwig, the International Association for the Study of the Liver (IASL) and the Ishak Scoring systems. (Table 1.3.2) Metavir scoring is used most often.

Table 1.3.2: Comparison of scoring system for histological stage [30]

Stage	**IASL**	**Batts-Ludwig**	**Metavir**	**Ishak**
0	No fibrosis	No Fibrosis	No fibrosis	No fibrosis
1	Mild fibrosis	Fibrous portal expansion	Periportal fibrotic expansion	Fibrous expansion of some portal areas with or without short fibrous septa
2	Moderate fibrosis	Rare bridges or septae	Periportal septae 1 (septum)	Fibrous expansion of most portal areas with or without short fibrous septa
3	Severe fibrosis	Numerous bridges or septae	Porto-central septae	Fibrous expansion of most portal areas with occasional portal to portal bridging
4	Cirrhosis	Cirrhosis	Cirrhosis	Fibrous expansion of most portal areas with marked bridging (portal to portal and portal to central)
5	N/A	N/A	N/A	Marked bridging (portal to portal and portal to central) with occasional nodules (incomplete cirrhosis)
6	N/A	N/A	N/A	Cirrhosis

Liver biopsy can determine fibrosis stage in a granular fashion; however, the procedure can cause pain, bleeding and perforation of other organs. In addition, the procedure is subject to sampling error, requiring special expertise for histopathology interpretation. It is also expensive and patients may not want this invasive procedure. Other means to determine fibrosis stage are limited to only detecting minimal fibrosis or cirrhosis, two extreme ends. [35-37]

Experts initially did not recommend biopsy in the presence of persistently normal aminotransferase values as they thought it was indicative of minimal fibrosis. [38] However, evidence has shown that around a quarter of these patients still have significant fibrosis and, thus, their treatment should not differ from those with elevated aminotransferase values. [39]

AASLD makes the following recommendations for tests for fibrosis [30]:

> 1. A liver biopsy should be considered in patients with chronic hepatitis C infection if the patient and health care provider wish information regarding fibrosis stage for prognostic purposes or to make a decision regarding treatment (Class IIa, Level B)
>
> 2. Currently available noninvasive tests may be useful in defining the presence or absence of advanced fibrosis in persons with chronic hepatitis C infection, but should not replace the liver biopsy in routine clinical practice (Class IIb, Level C).

1.3.4 Treatment Goals and Outcomes

The primary treatment goal is to prevent complications and death from HCV infection. Since HCV disease progression is slow, surrogate virological parameters rather than clinical endpoints are used to measure response to therapy. (Table 1.3.3)

Table 1.3.3: Definition of virologic responses during therapy [30]

Virological Response	Definition	Clinical Utility
Rapid virological response (RVR)	HCV RNA negative at treatment week 4 by a sensitive PCR-based quantitative assay	May allow shortening of course for genotypes 2&3 and possibly genotype 1 with low viral load
Early virological response (EVR)	≥ 2 log reduction in HCV RNA level compared to baseline HCV RNA level (partial EVR) or HCV RNA negative at treatment week 12 (complete EVR)	Predicts lack of SVR
End-of-treatment response (ETR)	HCV RNA negative by a sensitive test at the end of 24 or 48 weeks of treatment	
Sustained virological response (SVR)	HCV RNA negative 24 weeks after cessation of treatment	Best predictor of a long-term response to treatment
Breakthrough	Reappearance of HCV RNA in serum while still on therapy	
Relapse	Reappearance of HCV RNA in serum after therapy is discontinued	
Nonresponder	Failure to clear HCV RNA from serum after 24 weeks of therapy	
Null responder	Failure to decrease HCV RNA by < 2 logs after 24 week of therapy	
Partial responder	Two log decrease in HCV RNA but still HCV RNA positive at week 24	

The primary outcome in clinical trials is sustained virological response (SVR), which is also considered a “cure” due its correlation with improved HCV mortality and morbidity. [40] Rapid virological response (RVR) predicts a high likelihood of achieving an SVR, and several studies have examined shortening the duration of therapy with achievement of RVR. Ferenci et al. found that the highest SVR rates were achieved in patients with RVR at week 4; however, the corresponding negative predictive value (NPV) (74%) was too low to make RVR a decision criterion. [41] On the other hand, failure to achieve early virological response (EVR) is the most accurate predictor of failing to achieve SVR. In a study by Davis G et al., almost all patients (>99%) who failed to achieve EVR also failed to clear the virus. [42]

1.3.5 HCV Treatment

HCV treatment has evolved significantly over the years and will continue to do so. In 2014, the AASLD issued new guidelines based on the new direct acting anti-viral (DAA) agents. Since this retrospective analysis was based on the previously recommended regimens, this section focuses on the treatments recommended by the AASLD guidelines until 2013. Section 1.3.6 details the newer agents and new recommendations.

The first agent, interferon alpha-2b, was approved by the FDA for the treatment of hepatitis C in 1991. Treatment required three million units of interferon injected three times a week for 24 to 48 weeks and the SVR rates were approximately 9% for genotype 1 and 30% for genotypes 2 and 3. In 1998, interferon was approved in combination with ribavirin (800-1200mg/day) for 48 weeks for genotype 1 and 24 weeks for genotypes 2 and 3. With this combination, overall SVR rates for genotype 1 were 27 to 29% and 60 to 62% for genotypes 2 and 3. In 2001, pegylated interferon alpha-2b (Peg-Intron, Schering Plough Corp., Kenilworth, NJ) was approved in combination with ribavirin, again improving both SVR rates (41% for genotype 1, and 82% for genotypes 2 through 6) and ease of administration with once a week dosing (1.5 μg/kg/week). Another pegylated interferon was approved in 2002 - peginterferon alfa-2a (Pegasys, Hoffmann-La Roche, Nutley, NJ), which has similar effectiveness and once weekly dosing (180 ug/week) with ribavirin. A major breakthrough in treatment came in 2011 with the approval of protease inhibitors, telaprevir (Incevik, Vertex Pharmaceuticals, Cambridge, Massachusetts) and boceprevir (Vitrelis, Merck & Co., Whitehouse Station, New Jersey), which are indicated for the treatment of chronic HCV infection in genotype 1 patients in combination with pegylated interferon and ribavirin.

The AASLD recommends selecting patients for therapy with the following criteria (Table 1.3.4) [30]:

Table 1.3.4: AASLD treatment selection criteria [30]

Characteristics of Persons for Whom Therapy Is Widely Accepted	Characteristics of Persons for Whom Therapy Is Currently Contraindicated	Characteristics of Persons for Whom Therapy Should Be Individualized
• Age 18 years or older, and	• Major uncontrolled depressive illness	• Failed prior treatment (non-responder and relapsers) either interferon with or without ribavirin or peginterferon monotherapy
• HCV RNA positive in serum, and	• Solid organ transplant (renal, heart, or lung)	• Current users of illicit drugs or alcohol but willing to participate in a substance abuse program (such as a methadone program) or alcohol support program. Candidates should be abstinent for a minimum period of 6 months
• Liver biopsy showing chronic hepatitis with significant fibrosis (bridging fibrosis or higher), and	• Autoimmune hepatitis or other autoimmune condition known to be exacerbated by peginterferon and ribavirin	• Liver biopsy evidence of either no or mild fibrosis
• Compensated liver disease (total serum bilirubin <1.5 g/dL; INR 1.5; serum albumin >3.4, platelet count 75,000 mm and no evidence of hepatic decompensation (hepatic encephalopathy or ascites), and	• Untreated thyroid disease	• Acute hepatitis C
• Acceptable hematological and biochemical indices (Hemoglobin 13 g/dL for men and 12 g/dL for women; neutrophil count 1500/$mm^3$and serum creatinine <1.5 mg/dL, and	• Pregnant or unwilling to comply with adequate contraception	• Coinfection with HIV
• Willing to be treated and to adhere to treatment requirements, and	• Severe concurrent medical disease such as severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, chronic obstructive pulmonary disease	• Under 18 years of age
• No contraindications	• Age less than 2 years	• Chronic renal disease (either requiring or not requiring hemodialysis)
	• Known hypersensitivity to drugs used to treat HCV	• Decompensated cirrhosis
		• Liver transplant recipients

1.3.5.1 Treatment for Genotypes 2 and 3

The treatment for genotypes 2 and 3 involve a dual therapy regimen with pegylated interferon (PegIFN) and ribavirin (RBV). There are two available pegylated interferons in the US, peginterferon alfa-2b (Peg-Intron, Schering Plough Corp., Kenilworth, NJ), and peginterferon alfa-2a (Pegasys, Hoffmann-La Roche, Nutley, NJ). Peginterferon alfa-2b is dosed at 1.5 μg/kg/week in combination with ribavirin 800 mg daily. Peginterferon alfa-2a is administered at a fixed dose of 180 μg/week given subcutaneously together with ribavirin 800 mg daily. In clinical trials, SVR rates were 70 to 90% for treatment-naïve genotype 2 and 3 patients. [43] [44, 45] Funded by the AHRQ's Effective Health Care Program, a recent meta-analysis was conducted to evaluate HCV therapies. Included trials evaluated similar populations, interventions, comparisons, and outcomes and pooled relative risks (RRs) were estimated using the DerSimonian–Laird method in a random-effects model. The authors found in their evaluation of 7 trials that dual therapy with PegIFN alfa-2b was associated with slightly lower likelihood of achieving SVR than dual therapy with PegIFN alfa -2a (pooled RR=0.87 (95% CI=0.80-0.95), I^2 =27%). The authors also found that 24 weeks of dual therapy with 2a and 2b was more effective than 12 to 16 weeks for achieving SVR (RR=1.2 (95% CI=1.0-1.3), I^2=80%) unless the patients had evidence of RVR (RR=0.99 (95% CI=0.96-1.1), I^2=66%). [46]

AASLD treatment guidelines recommend the following for treatment of genotype 2 and 3 infections[30]:

1. Treatment with peginterferon plus ribavirin should be administered for 24 weeks, using a ribavirin dose of 800 mg (Class I, Level A).

2. Patients whose treatment continues through 24 weeks and whose measurement of HCV RNA with a highly sensitive assay is negative should be retested for HCV RNA 24 weeks later to evaluate for an SVR (Class I, Level A).

3. Patients with HCV-related cirrhosis who achieve an SVR, regardless of the genotype, should continue to be monitored at 6 to 12 month intervals for the development of HCC (Class IIa, Level C).

1.3.5.2 Treatment for Genotype 1

The standard of care for genotype 1 patients prior to the May 2011 introduction of the new protease inhibitors (PIs) was PegIFN plus RBV. The introduction of new PIs, telaprevir (Incevik, Vertex Pharmaceuticals, Cambridge, Massachusetts) and boceprevir (Vitrelis, Merck & Co., Whitehouse Station, New Jersey), indicated for genotype 1 HCV patients in combination with interferon and ribavirin was a significant advancement in treatment for these patients. These agents inhibit the HCV nonstructural protein 3/4A serine protease. Boceprevir treatment involves a 4-week PegIFN + RBV lead-in with 24, 32, or 44 weeks of triple therapy with boceprevir+PegIFN + RBV depending on treatment experience and response. Telaprevir treatment involves 12 weeks of telaprevir, then 12 or 24 weeks of PegIFN + RBV, for a total treatment of 24 to 48 weeks depending on treatment experience and response. Treatment-experienced patients require longer duration of therapy. These patients are defined as null responders, partial responders or relapsers: null responders are those whose HCV RNA levels did not decline by at least 2 log IU/mL at treatment week 12, partial responders are persons whose HCV RNA level dropped by at least 2 log IU/ML at treatment week 12, but HCV RNA was detectable at week 24; and relapsers are those whose HCV RNA levels become undetectable during treatment and then reappear after treatment end.

In the Phase III pivotal trials, boceprevir had overall SVR rates of 63% and 66% for response-guided treatment and fixed treatment duration of 48 weeks, respectively,

compared to 38% in the PegIFN + RBV arm in treatment-naïve subjects. [47] In the treatment-experienced trial, boceprevir had SVR rates of 69 to 75% in relapsers and 40 to 52% in partial responders versus 29% and 7%, respectively, in the PegIFN + RBV arm. [48] In the telaprevir treatment-naïve trials, the SVR rates were 69% and 75% for 8 and 12 weeks of telaprevir treatment, respectively, compared to 44% for PegIFN-RBV therapy. [49] Patients in the telaprevir treatment groups who achieved an "extended RVR" (eRVR), which for this drug was defined as undetectable (<10-15 IU/mL) HCV RNA levels at weeks 4 and 12, stopped therapy at week 24, whereas those in whom an eRVR did not occur received a total of 48 weeks of PegIFN and RBV. For treatment-experienced patients, the SVR rates in the telaprevir trial were 64% and 66% in the telaprevir-containing arms without and with a 4-week lead-in with PegIFN + RBV, respectively, compared to 17% in the PegIFN + RBV arm. Specifically, SVR was 83% and 88% in relapsers, 59% and 54% in partial responders, and 29% and 33% in null responders compared to 24% in relapsers, 15% in partial responders and 5% in null responders in the control arm. [50] The meta-analysis by Chou et al. found that triple therapy with both boceprevir and telaprevir was associated with significantly higher likelihood of achieving SVR than dual therapy for 48 weeks. For triple therapy with boceprevir for 48 weeks versus dual therapy for 48 weeks, the absolute increase in SVR rate was 31 (95% CI=23-39) percentage points (RR=1.8 (95% CI=1.6-2.1), I^2=0%). For triple therapy with telaprevir for 24 weeks versus dual therapy for 38 weeks, the absolute increase in SVR rate was 22 (95% CI=13-31) percentage points (RR=1.5 (95% CI=1.3-1.8), I^2=0%). [46]

The AASLD recommends the following for treatment-naïve and treatment-experienced genotype 1 patients [51]:

For treatment-naïve patients: [51]

1. The recommended dose of boceprevir is 800 mg administered with food three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 24-44 weeks preceded by 4 weeks of lead-in treatment with peginterferon alfa and ribavirin alone (Class 1, Level A).

2. Patients without cirrhosis treated with boceprevir, peginterferon, and ribavirin, preceded by 4 weeks of lead-in peginterferon and ribavirin, whose HCV RNA level at weeks 8 and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (4 weeks lead-in with peginterferon and ribavirin followed by 24 weeks of triple therapy) (Class 2a, Level B).

3. Treatment with all three drugs (boceprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24 (Class 2a, Level B).

4. The recommended dose of telaprevir is 750 mg administered with food (not low-fat) three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 12 weeks followed by an additional 12-36 weeks of peginterferon alfa and ribavirin (Class 1, Level A).

5. Patients without cirrhosis treated with telaprevir, peginterferon, and ribavirin, whose HCV RNA level at weeks 4 and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks (Class 2a, Level A).

6. Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peginterferon and ribavirin should receive therapy for a duration of 48 weeks (Class 2b, Level B).

7. Treatment with all three drugs (telaprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >1,000 IU/mL at treatment weeks 4 or 12 and/or detectable at treatment week 24 (Class 2a, Level B).

For treatment-experienced patients: [51]

1. Re-treatment with boceprevir or telaprevir, together with peginterferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peginterferon alfa and/or ribavirin (Class 1, Level A).

2. Re-treatment with telaprevir, together with peginterferon alfa and weight-based ribavirin, may be considered for prior null responders to a course of standard

interferon alfa or peginterferon alfa and/or weight-based ribavirin (Class 2b, Level B.)

3. Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers (Class 2a, Level B for boceprevir; Class 2b, Level C for telaprevir), may be considered for partial responders (Class 2b, Level B for boceprevir; Class 3, Level C for telaprevir), but cannot be recommended for null responders (Class 3, Level C).

4. Patients re-treated with boceprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA > 100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance (Class 1, Level B).

5. Patients re-treated with telaprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA > 1,000 IU at weeks 4 or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance (Class 1, Level B).

1.3.5.3 Adverse Events with PegIFN, RBV, and PIs

Treatment with PegIFN and RBV is associated with many adverse events. Ten to 14% of patients discontinued therapy in the pivotal trials due to an adverse event, and the most common adverse events were influenza-like side effects such as fatigue, headache, fever and rigors (>50% of patients), and psychiatric side effects such as depression, irritability and insomnia (22-31% of patients). These adverse events are attributable to PegIFN therapy. [44, 52]

The most common side effect of ribavirin is hemolytic anemia. Dose modification for anemia (hemoglobin level <10 g/dL) was required in 9% to 15% of patients in the pivotal trials. [44, 52] Ribavirin is also teratogenic and requires the use of strict contraceptive methods during treatment and 6 months thereafter.[53, 54]

When comparing the two PegIFNs in a meta-analysis, PegIFN alfa-2b was associated with higher risk of headache (RR=1.1 (95% CI=1.1-1.2), I^2=0%), but lower risks

for serious AEs (RR=0.74 (95% CI=0.57-0.95), I^2=0%), neutropenia (RR=0.61 (95% CI=0.46-0.83), I^2=0%) and rash (RR=0.79 (95% CI=0.71-0.88), I^2=0%) compared to Peg-IFN alfa-2a.

PIs add to the adverse events of dual therapy with PegIFN + RBV. The most common adverse events with telaprevir-based therapies are rash, anemia, pruritis, nausea and anorectal symptoms, while the most common with boceprevir-based regimens are anemia and dysgeusia. Rash led to discontinuation in 6% of patients in the telaprevir Phase III trials, with serious skin reactions in <1%, including Stevens-Johnson syndrome or DRESS (Drug reaction, or rash, with eosinophilia and systemic symptoms). [53] Anemia occurred in 45 to 50% of patients on boceprevir compared to 29% on PegIFN + RBV and 36% of patients on telaprevir versus 14% in patients on dual therapy. [53, 54] AASLD recommends management of anemia by reducing the ribavirin dose. [51]

The Chou et al. meta-analysis showed that boceprevir for 48 weeks was associated with a higher risk of neutropenia (RR=1.8 (95% CI=1.5– 2.3, I^2=0%), dysgeusia (RR=2.5, 95% CI=2.0–3.2, I^2=0%), anemia (RR=2.0, 95% CI=1.4–2.8, I^2=0%) and thrombocytopenia (RR=3.2, 95% CI=1.2–8.2, I^2=0%) versus dual therapy for 48 weeks. TVR associated with increased risk of anemia (RR=1.3, 95% CI=1.1-1.5, I^2=0%) and rash (RR=31.4, 95% CI=1.1-1.7, I^2=0%) compared to dual therapy for 48 weeks. [46]

1.3.6 Future HCV Treatment

Although PIs represent a major breakthrough in HCV treatment, many barriers to treatment still exist. In particular, PIs are associated with many adverse events, they are only indicated for genotype 1 treatment, have a low barrier to resistance, and have limited efficacy in difficult-to-treat populations like patients with advanced liver fibrosis. To overcome the risk of treatment failure in such patients, more than one potent DAA agent

or quadruple drug regimens may be required. Additionally, up to 30% of patients are relatively or absolutely contraindicated to any interferon-based therapy. [55] In fact, a study at the Veterans Administration, which has more than 190,000 chronically infected HCV patients, found that 64.4% of the VA population has contraindications to interferon therapy due to the high rates of psychiatric disease and other comorbidities. Only 11.6% of patients received therapy with PegIFN + RBV, and a mere 3.5% achieved SVR, underscoring the importance of finding better HCV therapies. [14]

Fittingly, more than 50 novel agents and 100 different combinations of HCV treatments are currently under investigation. Besides PIs, the other main DAA drugs classes are NS5A inhibitors and N5B polymerase inhibitors. NS5A inhibitors work by inhibiting the HCV life cycle at multiple stages of replication, assembly and release. Their pan-genotypic nature lends them to be highly promising combination therapy partners for interferon-free regimens. N5B inhibitors are divided into two types: (1) nucleoside analog inhibitors, which mimic the natural substrates of the polymerase and consequently cause direct chain termination; and (2) non-nucleoside inhibitors that bind to a different allosteric enzyme site, which results in a conformational protein change before the elongation complex is formed. These inhibitors are also optimal partners for interferon-free regimens given their broad genotypic coverage and high barrier to resistance. Other new compounds in development include NS4B inhibitors, which are entry or assembly inhibitors, host-targeting agents like cyclophilin A inhibitors, and immune-modulatory agents like toll-like receptor agonists.

Sofosbuvir, a NS5A inhibitor, and simeprevir, a second generation PI, were recently approved in December 2013. These agents, either combined together, or in combination with PegIFN + RBV are now the recommended regimens for patients with

genotype 1 infection per the updated AASLD guidelines. The other regimens, including PegIFN + RBV with or without telaprevir or boceprevir, are no longer recommended. For genotype 2 and 3 patients, sofosbuvir in combination with RBV is recommended and PegIFN + RBV is no longer recommended. [56]

Given these promising agents, the prospect of interferon-free combination for HCV is a close reality. [55, 57] As more patients will be eligible for treatment, it is important to understand the clinical and economic implications of treating a disease that can remain asymptomatic for many years.

1.3.7 Outcomes of Achieving SVR

Numerous studies have shown the benefits of achieving SVR on HCV morbidity and mortality. In a meta-analysis of 8 European follow-up studies, Veldt et al. evaluated long term follow-up of European patients with a sustained virological response to interferon monotherapy. Clinical outcomes for these patients were favorable with a low 1% (95% CI=0.0-2.3) rate of decompensation after five years and no one developing hepatocellular carcinoma (HCC). Survival of patients achieving an SVR with IFN monotherapy was comparable to age- and sex-matched general population (standard mortality ratio being 1.4 (0.3-2.5)). [58]

One study at a single center in France followed patients treated with PegIFN + RBV in clinical trials from 1987 to 2007. The median follow-up was 3.5 years and patients were contacted for follow-up evaluations. The risk of HCC was significantly higher in the non-SVR group compared with patients who achieved an SVR (rate per 100,000 person-years was 5.85 (95% CI=4.23-7.47) versus 1.24 (95% CI=0.28-2.20), respectively, ($p<0.001$). Likewise, the incidence rate of liver-related complications per 100 person-years was also significantly higher in patients who did not achieve SVR (4.16, 95% CI=2.73–5.59) compared to SVR patients (0.62, 95% CI=0-1.28, $p<0.001$). In addition, the incidence rates of liver-related death was 3.76 (95% CI=2.47-5.05) in non-SVR patients versus 0.61 (95% CI=0-1.29) in SVR patients ($p<0.001$). This study demonstrates that positive prognostic impact of SVR on HCC, liver-related complications and survival. [59]

Another retrospective analysis of veterans who received PegIFN + RBV at any VA medical facility between 2001 and 2008 assessed the impact of SVR on all-cause mortality. Eligible patients included those with HCV genotypes 1, 2, or 3 and did not have either HIV or HCC at baseline. The cohort was almost all men (96%) with an average age $\geq$50 years

and substantial comorbidities. The SVR rate for genotype 1 was 35%, 72% for genotype 2 and 62% for genotype 3. Patients with all genotypes who achieved an SVR had a significantly lower cumulative mortality rate compared with patients who did not achieve an SVR ($p<0.0001$). The hazard ratio for death after treatment with PegIFN + RBV for SVR versus non-SVR was 0.70 (95% CI=0.59-0.83, $p<0.001$) for genotype 1, 0.64 (0.46-0.88, $p=0.006$) for genotype 2 and 0.51 (0.35-0.73, $p=0.002$) for genotype 3. Clinicians may be hesitant to treat patients due to the expense and uncertainty in patients with comorbidities and may wait to treat until evidence of cirrhosis. However, these findings underscore the importance of treating HCV even in the presence of relatively high rates of comorbidities. Moreover, SVR was associated with a substantial mortality benefit even in patients without cirrhosis. [60]

A large, international, multicenter, long-term follow-up study of 5 large hepatology units of tertiary care centers in Europe and Canada examined the association between SVR and all-cause mortality in chronic HCV patients with histological proof of advanced fibrosis or cirrhosis (Ishak score 4-6) who started on interferon-based therapy between 1990 and 2003. The primary outcome measure was all-cause mortality. Secondary clinical outcome measures were liver failure, HCC, and liver-related mortality or liver transplantation. This study was a re-evaluation of a previous study by Veldt et al. using the same centers, which showed a reduction in liver failure events at 5 years in patients with SVR (5-year occurrence, 0% versus 13.3%, 95% CI=8.4-18.2%]; unadjusted hazard ratio, 0.03, 95% CI=0.00-0.91). [61] In this study, 192 patients (36%) achieved SVR and 338 patients (64%) did not. The median follow-up duration was 8.4 years (interquartile range [IQR]: 6.4-11.4) with 86% of patients with having complete follow-up. Of note, follow-up duration was shorter for patients with SVR (median=6.6 years, IQR=5.0-8.3)

versus patients without SVR (median=8.1 years, IQR=5.7-11.1), due to advancements in interferon therapy. However, the authors noted that they think it is unlikely that the follow-up difference had a substantial effect on the results since clinical events followed linear patterns over time. The 10-year cumulative occurrence rates for all-cause mortality were 8.9% (95% CI=3.3-14.5%) for patients with SVR and 26.0% (95% CI=20.2-28.4%) for patients without SVR. In the Cox proportional hazards model, SVR was associated with a statistically significant reduction in the hazard of overall death (adjusted HR = 0.26, 95% CI=0.14-0.49, $p<0.001$). Multivariate analysis indicated that older age, HCV genotype 3 infection, higher Ishak fibrosis score, presence of diabetes, and history of severe alcohol use were also significantly associated with all-cause mortality. The 10-year occurrence rates for liver-related mortality or liver transplantation was 1.9% (95% CI=0.0-4.1%) in patients with SVR versus 27.4% (95% CI=22.0-32.8%) in patients without SVR. For hepatocellular carcinoma, rates were 5.1% (95% CI=1.3-8.9%) for patients with SVR and 21.8% (95% CI=16.6-27.0%) for those without SVR; and for liver failure, 2.1% (95% CI=0.0-4.5%) with SVR and 29.9% (95% CI=24.3-35.5%) without SVR. Again, more severe liver fibrosis, older age, and a history of severe alcohol use were risk factors for both HCC and liver failure, while male gender, presence of diabetes, and genotype 3 were significantly associated with HCC occurrence only. Overall, this study found an almost 4-fold lower risk of all-cause mortality in patients who achieved SVR compared to those who did not. Compared to other studies, this one investigated all-cause mortality as a single outcome and examined only patients with advanced fibrosis or cirrhosis. In addition, this study found a 2-fold increased risk of all-cause mortality and HCC in patients with HCV genotype 3 infection, which is associated with more rapid fibrosis progression. (Figure 1.3.1) [62]

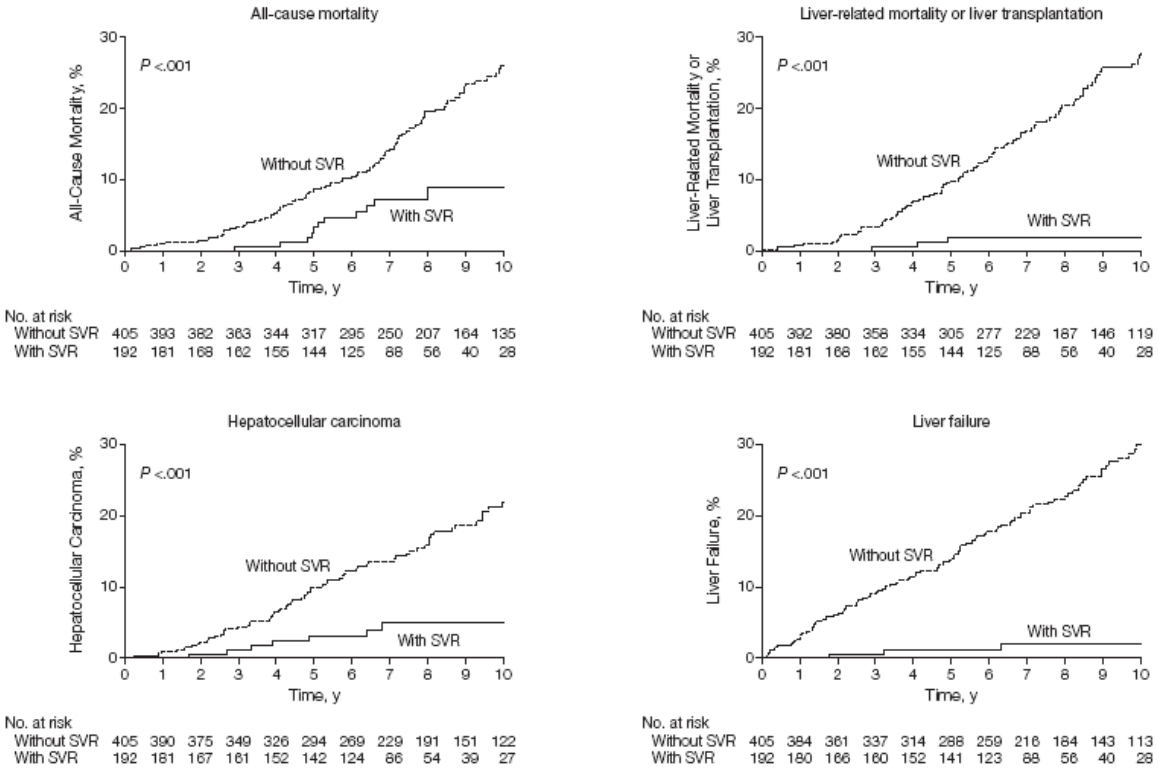


Figure 1.3.1: Survival outcomes for all-cause mortality, liver-related mortality or liver transplantation, hepatocellular carcinoma, and liver failure in patients with chronic hepatitis C and advanced hepatic fibrosis with and without sustained virological response (SVR) [62]

In addition to improved clinical outcomes, achievement of SVR has also been associated with improvement in fibrosis stage. A prospective study of 38 patients with pretreatment cirrhosis and an SVR with IFN-based therapy evaluated the impact of SVR on the full spectrum of histopathologic features of HCV-related cirrhosis. These patients were assessed over 4 years post SVR and received either PegIFN + RBV (74%) or IFN + RBV (26%). The study endpoints were fibrosis/cirrhosis regression rates on paired liver biopsies, necro-inflammation, progenitor cell proliferation, lobular metabolic zonation, and

sinusoidal capillarization. Twenty-three of 38 patients (61%) showed an improvement of at least one point in METAVIR fibrosis stage. Two improved to mild fibrosis (F1). SVR was associated with decrease area of fibrosis in 34 patients (89%), as measured by digitizing Sirius Red staining of biopsy specimens. The specimens also showed a disappearance of progenitor cells, the metabolic zonation restoration, but also the persistence of portal inflammation and of sinusoidal capillarization. [63]

In addition to the hepatic-related benefits, attainment of SVR also has a positive impact on extrahepatic manifestations of HCV. One such benefit is a reduction in the incidence of diabetes. HCV infection is associated with the development of insulin resistance and the association occurs regardless of liver disease severity. As such, the prevalence of diabetes mellitus is increasing in the HCV-infected population compared to the general population. The impact of SVR on the impact of SVR on the development of new-onset insulin resistance among non-diabetic, white HCV-infected patients treated with PegIFN + RBV (n=399) was assessed. In this cohort, the SVR rate was 63% and the majority of new-onset insulin resistance cases were in non-SVR versus SVR patients (17% versus 7%, p=0.007). In a logistic regression analysis, both treatment failure (OR=2.81, 95% CI=1.39-5.67, p=0.004) and 10% body mass increase (OR=6.42, 95% CI=1.69-24.3, p=0.006) were significantly associated with the development of insulin resistance. This study indicates that treating HCV could reduce the potentially serious long-term complication of diabetes mellitus. [64]

Another potential extrahepatic benefit of SVR is a reduction in myocardial injury. There are preliminary reports that suggest that HCV infection may be associated with several myocardial diseases, including dilated cardiomyopathy (DCM). A single-center study in Japan enrolled 217 chronic HCV patients with no overt ischemic or valvular

disease. These patients were given interferon-based therapy for 6 months with a 6-month follow-up. The SVR rate in this cohort was 46%, with a relapse rate of 28.5%. Myocardial condition was examined by routine cardiac function and thallium-201 myocardial perfusion imaging, which permits non-invasive detection of coronary artery disease and myocardial conditions. A total of 87% of patients had evidence of myocardial injury. In the 92 patients with SVR, myocardial perfusion normalized by the completion of treatment and was sustained over the 6-month follow-up. In contrast, the 57 patients who relapsed lost the benefit of improved myocardial severity score at the end of treatment. Patients not responding to IFN-based therapy had no improvement in their myocardial severity score. [65]

These studies, which clearly show a significantly association between SVR and improved clinical outcomes and mortality, were the basis of recommending birth cohort screening. [34] Outcomes for all-cause mortality, liver-related mortality or liver transplantation, hepatocellular carcinoma, and liver failure are improved in those patients who achieve SVR, regardless of cirrhosis status. In addition, there are extrahepatic benefits of achieving SVR, such as lower incidence of diabetes and myocardial injury.

1.4 ECONOMIC BURDEN OF HCV IN THE US

1.4.1 Advanced Liver Disease Forecast

Although the incidence of new infections has declined dramatically over the past two decades, the prevalent population with HCV is aging and developing more advanced liver disease. Davis G et al. developed a multicohort natural history model using statistical modeling techniques and the latest epidemiologic, demographic, and natural history data to model the evolution of chronic HCV infection. The model divided acutely infected individuals into 6 cohorts to apply specific transition states for chronicity, fibrosis, progression and complications. Transition states and probabilities were estimated from the literature and HCV incidence rates between 1960 and 2006 were estimated from a previous model that calculated past incidence of acute HCV infection using the actual prevalence measured in the NHANES survey. According to the model, the peak prevalence of chronic HCV infection occurred in 2001 at 3.6 million and thereafter would reach half its peak level by 2030. (Figure 1.4.1) The proportion of cases with advanced fibrosis was predicted to rise during the next two decades with 25% of the HCV population having cirrhosis in 2010 and 45% in 2030. The total number of cases with cirrhosis was estimated to peak at 1.0 million in 2020 and then decline. Cirrhosis and liver-related complications were most common in those over 60 years of age. This study indicates that as the HCV population ages, the sequelae of HCV infection will begin to appear. [66]

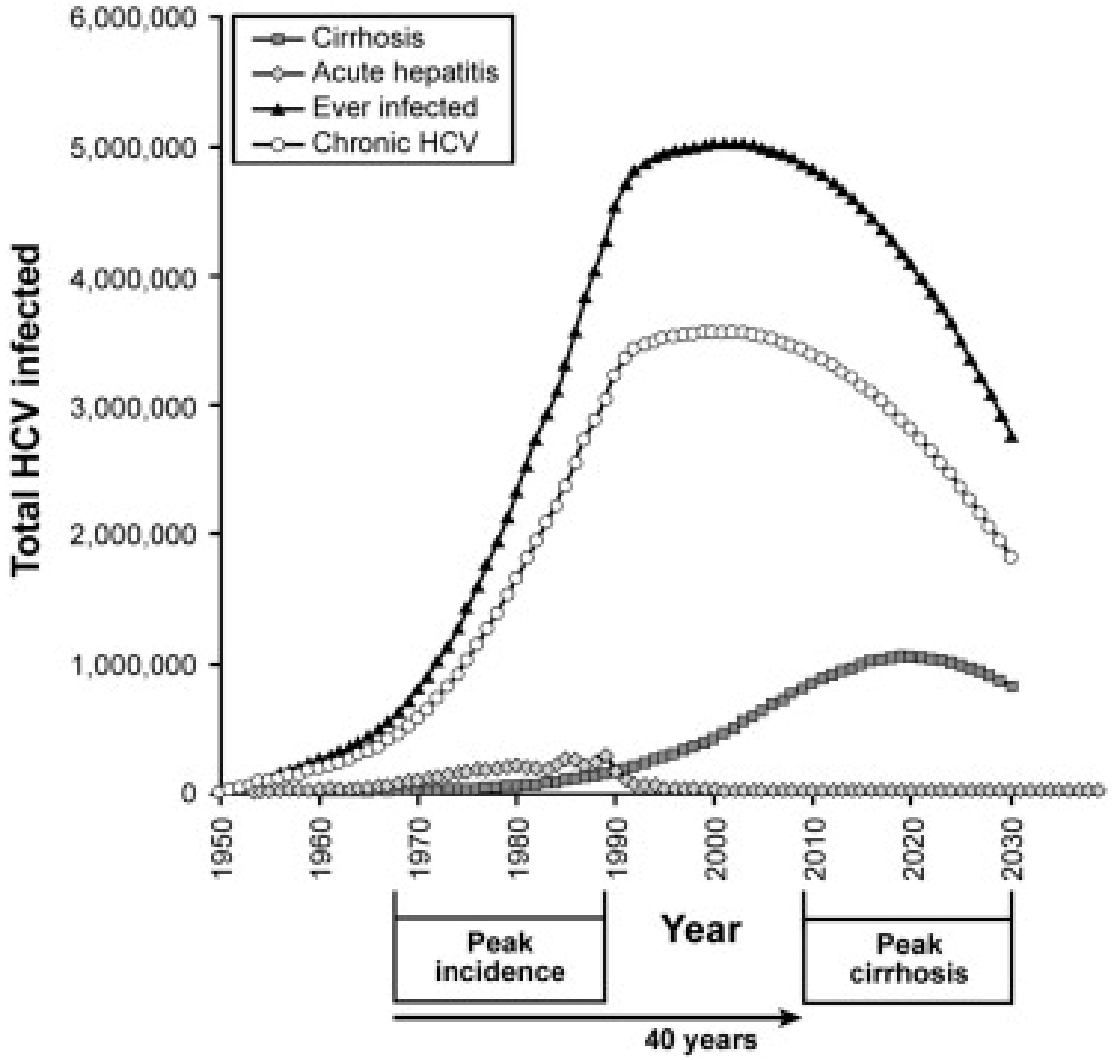


Figure 1.4.1: Estimates by year of prevalent cases ever infected (top line), with chronic hepatitis C (open circles), and cirrhosis (solid squares). Acute infections (solid gray line) peaked between 1970 and 1990. [66]

Milliman also published a recent report with similar estimates based on a model assuming transition states from the literature and mortality from the US Census Bureau. They found that the number of patients with decompensated liver disease will more than

quadruple from 30,000 to 150,000 over the next 10 years. The number with hepatocellular carcinoma was forecasted to triple from 5,000 to 15,000. [10]

A recent paper examined the observed and projected age-specific trends in the burden of HCV complicated by hepatocellular carcinoma on liver transplant in the US. Projections were obtained on the annual trends of all adult patients who were registered on the liver transplant waiting list in the US from 1995 to 2010 from the Organ Procurement and Transplantation Network (OPTN).

From 1995 to 2010, 126,862 new registrants for liver transplantation were found in the database and 52,540 (41%) were for HCV-associated liver disease. Those born between 1941 and 1960 accounted for 81% of the new liver transplant registrants with HCV. In this cohort, the number of registrants with HCV and HCC increased approximately 4 fold between 2000 and 2010. Projections based on rates observed up to 2010 predicted that by 2015, up to 40% of new registrants with HCV who are over 60 years old are expected to have HCC. This study confirms the birth cohort effect shown in other studies as the increasing incidence of HCC is a significant contributor to an increase in the demand for liver transplantation among those HCV patients born between 1941 and 1960. [67] As expected, the economic burden of HCV will increase dramatically as the disease progresses.

1.4.2 Economic Consequences of HCV Infection

An understanding of the cost of hepatitis C sequelae is important for assessing the future economic burden of HCV. A systematic literature search was conducted to identify studies evaluating the US cost of HCV infection sequelae using PubMed and the HCV database at the Center for Disease Analysis, which contains over 2700 indexed and nonindexed sources from 1985 to 2010. Of the 400 articles initially identified, a total of 50 were included with US cost data.

The economic burden in the articles was estimated by top down and bottom up approaches. In the top down approach, national estimates from the National Hospital Discharge Survey (NHDS), National Ambulatory Medical Care Survey (NAMCS), and National Hospital Ambulatory Medical Care Survey (NHAMCS) datasets were used to estimate the costs of inpatient hospital stays, physician office visits, emergency room visits and hospital outpatient visits, respectively. Indirect costs were calculated using the average length of stay and total days of care obtained from these databases. Direct and indirect costs from the top down approach are listed in Table 1.4.1. [68]

Table 1.4.1: Summary of top-down studies reporting total annual costs (in millions of US dollars in the reported year) [68]

Sequelae	**Direct Cost ($M)**	**Indirect Cost ($M)**	**Total Cost ($M)**	**Year**
Chronic liver disease and cirrhosis–all causes	$1,421	$222	$1,643	1998
Chronic Hepatitis C	$1,065	$1,784	$2,849	2004
	$694	$51	$745	1998
	$1,660	$3,370	$5,050	1997
HCC–all causes	$261	$1,319	$1,580	2004
	$978	$10	$988	1998
	$241			1988
	$509			2000
HCC–Hepatitis C	$140	$290	$430	1997

$M = Millions of US dollars in the reported year

The bottom up approach involved estimating costs from a disease progression analysis using Markov models. Most of these estimates came from Bennett et al., which evaluated the cost effectiveness of a single course of PegIFN in patients with histologically mild chronic hepatitis C. [69] The estimates from the cost of liver transplantation was referenced from a recent meta-analysis summarizing the studies on the costs of liver transplantation. (Table 1.4.2) [70]

Table 1.4.2: Summary of studies reporting incremental cost by sequelae (2010 US dollars per patient per year) [68]

Sequelae	Base cost /Patient/Yr	Min cost /Patient/Yr	Max cost /Patient/Yr
Mild chronic HCV infection	$145		
Moderate chronic HCV infection	$155		
Compensated cirrhosis	$1,110	$585	
Hepatocellular carcinoma	$44,200	$23,755	
Liver transplantation	$201,110	$178,760	$223,460
Subsequent Year	$37,535	$30,550	$46,750

There was considerable variability in the projected cost with annual direct costs ranging from $694 to $1,660 million for chronic hepatitis C. The large difference in forecast was due to the differing methodologies, such as top-down or bottom-up approaches, and estimates on the number of cases over time. [68]

Davis K et al. used the Integrated Health Care Information Services (IHCIS) Managed Care Benchmark Database, which is a commercially-available source of administrative medical and pharmacy claims data from 30 managed care organizations (MCOs) across the US to analyze direct costs in chronically-infected HCV patients. Patients with an ICD-9 diagnosis of HCV and no hepatitis B diagnosis with 6 months baseline and 12 months post-diagnosis of continuous plan enrollment were included. Those with HCV were matched with controls without HCV (1:1) on age, sex and plan enrollment. All cost outcomes were assessed using multivariate generalized linear models with a log link function and adjustment for the following covariates: age, sex, geographic location (Northeast versus other regions), type of insurance (HMO versus other), and Charlson Comorbidity Index (CCI) score. When laboratory data were available, analyses

were stratified by viral genotype, SVR attainment, and underlying disease severity, which was estimated using the aspartate aminotransferase-to-platelet ratio index (APRI) score.

A total of 20,662 patients met the inclusion criteria and were matched closely to their controls on the pre-specified parameters. In comparison to the matched controls, more HCV-infected patients had hospitalizations (24% of HCV cases versus 7% of controls, $p<0.001$), emergency room visits (32% versus 15%, $p<0.001$), and laboratory tests (79% versus 35%, $p<0.001$). Adjusted all-cause costs per HCV patient was almost quadruple those per control patient ($20,961, SD $12,182) versus $5,451, SD $10,863), respectively, $p<0.001$). The higher inpatient costs largely drove this difference as costs were $5,892, SD $6,302 per HCV patient compared to $1,159, SD $3,794 per control ($p<0.001$), as well as high prescription costs ($6,191, SD $2,021 versus $1,315, SD $3,813), respectively, $p<0.001$). By genotype, costs were higher for genotype 2 and 3 patients (n=83) compared to genotype 1 patients (n=248) ($9,877, SD $1,100 versus $12,433, SD $3,302, respectively); however, the difference was driven almost entirely by higher drug costs and associated office visits. A total of 62% of genotype 2 and 3 patients received HCV treatment compared to only 35% of genotype 1 patients. In those with higher APRI scores (>1.5) (n=116), total adjusted costs were around two times higher than costs in those with low APRI scores (≤0.5) (n=2,384) ($12,481, SD $7,514 versus $6,839, SD $1,660, n=2,384, respectively, $p<0.001$). During the minimum 6-month period after the end of treatment, patients who achieved SVR (n=336) incurred less costs than those who did not (n=239) ($717, SD $432 versus $1,436, SD $1,933, $p<0.001$). These stratified results are limited by the small sample sizes and the populations were not matched on many other important clinical characteristics, such as baseline comorbidities. Nevertheless, this study

was an important contribution to underscore the high direct medical costs in patients with HCV. [71]

McAdam-Marx et al. [72] conducted a retrospective analysis from a managed care perspective of all-cause and incremental per-patient-per-year cost associated with chronic HCV in the US; results were published shortly after Davis K et al. This analysis evaluated four cohorts of patients: patients with chronic HCV infection as evidenced by two ICD-9 codes at least one month apart, with no evidence of advanced liver disease and their matched controls, as well as patients who had diagnosis codes indicating both chronic HCV and advanced liver disease and their matched controls. Patients with a diagnosis of chronic HCV without advanced liver disease were further stratified into groups of those with and without compensated cirrhosis. All patients were required to have at least 6 months of pre-diagnosis data and 6 months post-diagnosis data for those with only HCV and at least 1 day post-diagnosis for those with both HCV and advanced liver disease. For comparison group patients, the index date was the date of the first claim for any medical care occurring on or after the median number of pre-index days for the corresponding HCV cohort. Up to 10 controls were matched to each HCV patients with the following matching criteria: age bands, gender, geographical location (state), pre-index comorbidities, modified CCI score, and annualized pre-index costs. The study period spanned from July 1, 2001 through March 31, 2010. Incremental per-patient-per-year (PPPY) all-cause health care costs were calculated by cohort, whereby the total allowed charges for patients in the cohort was added, and then divided by the total number of days of enrollment in the cohort, and then multiplied by 365 days. Direct all-cause PPPY health care costs were evaluated overall and by stage of liver disease. Bootstrapping was used to generate descriptive statistics and t-

tests compared costs between cases and controls. The results are illustrated in Figures 1.4.2-1.4.4. [72]

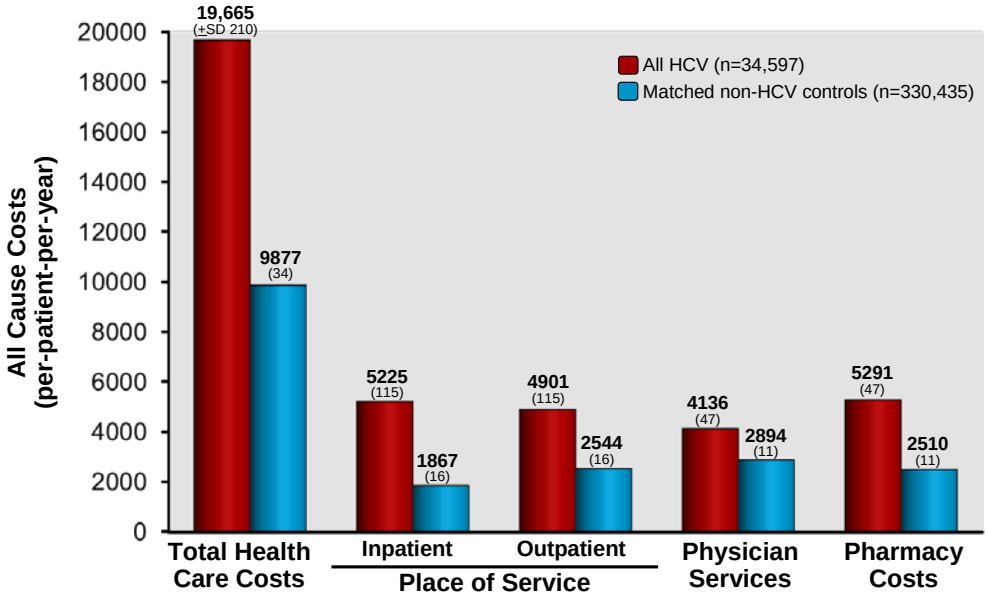


Figure 1.4.2: All cause health care costs for all HCV patients and matched controls (USD 2009 Per Member Per Year) [72]

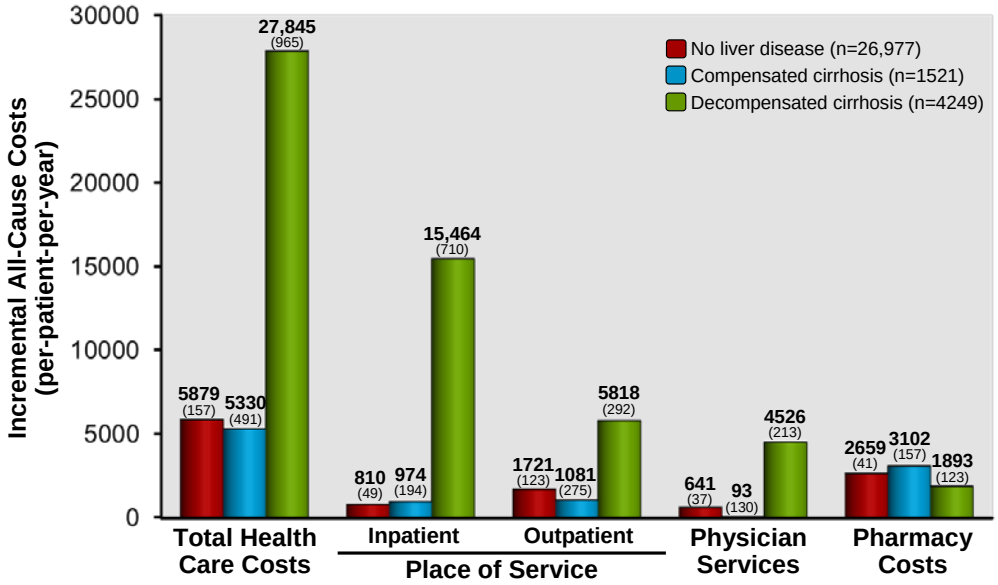


Figure 1.4.3: HCV incremental all-cause health care costs by liver disease severity (USD 2009 Per Member Per Year) [72]

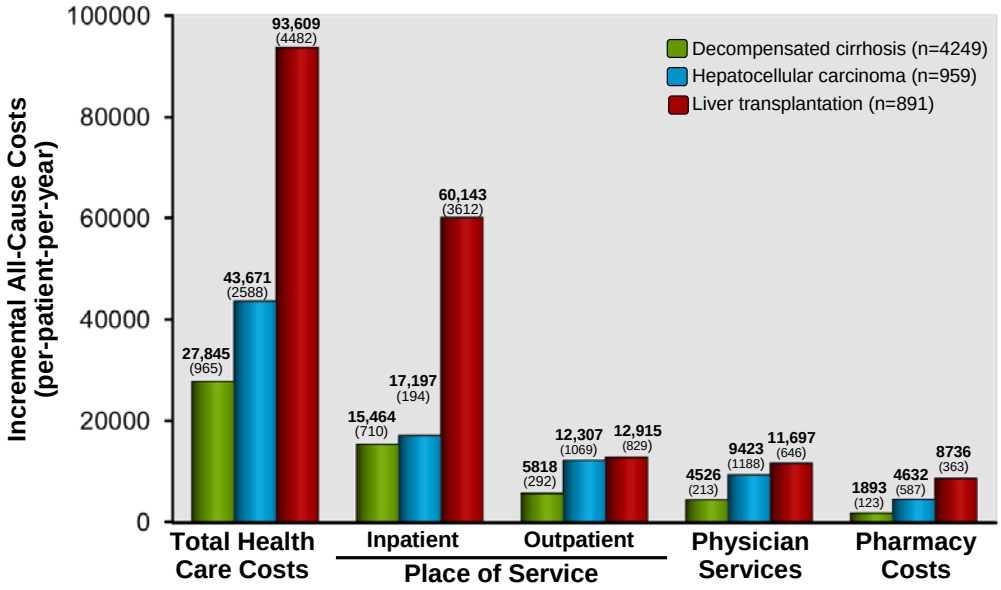


Figure 1.4.4: HCV incremental all-cause health care costs by liver disease severity (USD 2009 Per Member Per Year) [72]

Costs were almost twice as high in HCV-infected patients in comparison to their matched controls. In addition, those with advanced liver disease also had substantially higher costs than those HCV patients without advanced disease. Like the Davis K et al. publication, the McAdam-Marx et al. study was based on a sample of patients with commercial health insurance and was conducted from a private payer perspective. Total costs were similar in both studies, but the incremental cost difference between HCV-infected patients and controls was higher in Davis K et al. study ($15,510) than in the McAdam-Marx et al. study ($9,788). The discrepancy could potentially be explained by differences in their methodologies: the Davis K et al. study did not match on specific comorbidities or pre-index date costs, and these patient characteristics were not included

in their regression analyses. The McAdam-Marx et al. study also stratified results by liver disease severity unlike previous publications. [72]

Another recently published study, by Gordon et al. evaluated costs of care for patients with HCV by liver disease severity using a large US private insurance database. [73] The liver disease categories included non-cirrhotic liver disease (NCD), compensated cirrhosis (CC), and end-stage liver disease (ESLD) as defined by the International Classification of Diseases (ICD-9) codes. Patients were identified as having chronic HCV infection between January 1, 2003 and August 31, 2010 using the following criteria (Table 1.4.3):

Table 1.4.3: Chronic HCV diagnosis criteria used by Gordon et al. [73]

ICD-9-CM Code	Description	Inclusion criteria (1 of the following)
	1.Chronic HCV diagnosis codes	A single claim with one of these diagnosis codes OR
070.44	Chronic hepatitis C with hepatic coma	
070.54	Chronic hepatitis C without mention of hepatic coma	
	2.Unspecified HCV diagnosis codes	2 claims with one of these diagnosis codes on separate dates of service OR
V02.62	Hepatitis C carrier	
070.70	Unspecified viral hepatitis C without hepatic coma	
070.71	Unspecified viral hepatitis C with hepatic coma	
	3.Acute and unspecified HCV diagnosis codes	2 claims with one of these diagnosis codes spaced at least 6 months apart
070.41	Acute hepatitis C with hepatic coma	
070.51	Acute hepatitis C without mention of hepatic coma	
070.62	Hepatitis C carrier	
070.70	Unspecified viral hepatitis C without hepatic coma	
070.71	Unspecified viral hepatitis C with hepatic coma	

Medical and pharmacy claims data, enrollment information, linked laboratory and mortality information from commercial health plan enrollees were analyzed from January 1, 2002 to August 31, 2011. Patients were required to have 1 year of baseline information prior to the index date, which was defined as the date of the first HCV diagnostic code for those with NCD and the date of the first claim for their assigned severity level for patients

with CC or ESLD, and at least 30 days of follow-up after the index date. Claims analyses were based on amounts paid by the health plans rather than billed costs. Three hepatologists decided on the three disease severity strata by consensus and patients were assigned to the highest severity category for which they had a qualifying code. Sub-analyses evaluated costs of orthotopic liver transplantation (OLT) and hepatocellular carcinoma for those with ESLD. Costs and utilization outcomes were analyzed using 1-part and 2-part generalized linear models (depending on number of 0 outcomes) with gamma distribution and log link.

A total of 53,296 patients with chronic HCV infection were included in the study (78% with NCD, 7% with CC and 15% with ESLD). The mean age was 49.6 years and mean duration of follow-up was 634 days. Statistically significant differences were detected between patients with NCD and CC and between those with NCD and ESLD with older mean age, larger proportion of male patients, and higher Charlson comorbidity score in those with more advanced disease (CC and ESLD). All-cause and HCV-related costs are listed in Table 1.4.4 by liver disease severity cohorts. [73]

Table 1.4.4: All cause and HCV-related per patient per month costs by liver disease severity ($US 2010) [73]

	Total N=53,796	NCD N=41,858	CC N=3,718	ESLD N=8,220	CC versus NCD *P*-value	ESLD versus NCD *P*-value
All cause costs						
Total health care costs (SD)	1,987.44 (6,459.84)	1,419.77 (4,689.36)	1,870.46 (4,448.25)	4,931.01 (11,911.22)	<0.001	<0.001
Inpt	749.34 (5,020.60)	391.66 (3,005.17)	417.85 (3,509.02)	2,720.63 (10,432.26)	0.659	<0.001
Outpt	647.97 (1,861.22)	509.75 (1,516.17)	698.61 (1,371.89)	1,328.93 (3,090.80)	<0.001	<0.001
ER	24.26 (114.76)	19.05 (83.20)	20.38 (91.72)	52.52 (214.93)	0.394	<0.001
Other	151.39 (2,506.35)	123.53 (2,476.15)	116.61 (1,255.81)	309.02 (3,024.58)	0.772	<0.001
Pharmacy costs	414.48 (865.39)	375.78 (845.33)	617.01 (1,011.63)	519.93 (873.19)	<0.001	<0.001
HCV-related costs						
Total health care costs	1,115.37 (5,083.45)	650.31 (2,713.82)	1,067.47 (2,941.49)	3,505.20 (10,995.61)	<0.001	<0.001
Inpt	665.06 (4,772.80)	312.85 (2,587.05)	334.09 (2,674.37)	2,608.33 (10,359.53)	0.642	<0.001
Outpt	210.70 (809.87)	129.92 (443.59)	303.95 (587.35)	579.85 (1,720.85)	<0.001	<0.001
ER	3.98 (48.95)	1.57 (24.31)	2.28 (29.54)	17.02 (109.91)	0.154	<0.001
Other	37.75 (964.34)	22.35 (235.08)	22.99 (126.68)	122.86 (2,406.12)	0.787	<0.001
Pharmacy costs	197.88 (630.31)	183.63 (611.72)	404.16 (847.41)	177.15 (590.91)	<0.001	<0.001

SD = Standard Deviation; NCD = Non-Cirrhotic Disease; CC = Compensated Cirrhotic; ESLD = End Stage Liver Disease

Mean all-cause per member per month (PPPM) costs were 32% and 247% higher for patients with CC and ESLD, respectively, compared to those with NCD ($1,870, SD $4,448 and $4,931, SD $11,911 versus $1,420, SD $4,689, $p<0.001$). Overall, 56% of costs were HCV-related and the proportion increased with severity; 46% HCV-related for those with NCD, 57% for CC patients, and 71% for ESLD patients. The largest cost components were inpatient costs for those with ESLD (56%) and ambulatory costs for those with CC (37%) and NCD (36%). Costs for ESLD patients with OLT were approximately 3 times greater than costs in patients without OLT ($12,087, SD $21,041 versus $4,394, SD $10,734, respectively, $p<0.001$). For ESLD patients with HCC, costs were two times higher than those ESLD patients without HCC ($9,378, SD $14,632 versus $4,254, SD $11,291, respectively, $p<0.001$).

The estimates by Gordon et al. of the annual cost of caring for a patient with CHC ($24,176) is similar to estimates reported in other recent studies ($19,665-$20,961). Both the McAdam-Marx et al. and Gordon et al. used the OptumInsight commercial claims database. The higher costs in the Gordon et al. study are likely due to the differing analysis periods and codes used to define the populations. Like the McAdam-Marx et al. analysis, the Gordon et al. study concurs that the direct costs associated with CHC infection are high, and increase in association with the progression of liver disease. [73]

1.4.3 Cost Effectiveness of HCV Treatment

In addition to the economic burden of chronic HCV infection, the economic benefits of treatment are important to understand as those with infection are progressing to more advanced stages of liver disease and as new therapies are quickly emerging. There are many cost-effectiveness analyses published on cost per quality adjusted life years for PegIFN + RBV and triple therapy with PegIFN + RBV + PIs. All of these cost-effectiveness analyses are based on a Markov decision analytic model, in which patients cycle through various health states from mild fibrosis (Metavir score F0) to compensated cirrhosis, and finally decompensated cirrhosis to hepatocellular carcinoma and liver transplantation. The simulation is carried out until all patients died of liver-related or other causes. A common Markov model illustration can be found in Figure 1.4.5. [74] For a long-term chronic health condition like hepatitis C, the Markov model is an appropriate method to use.

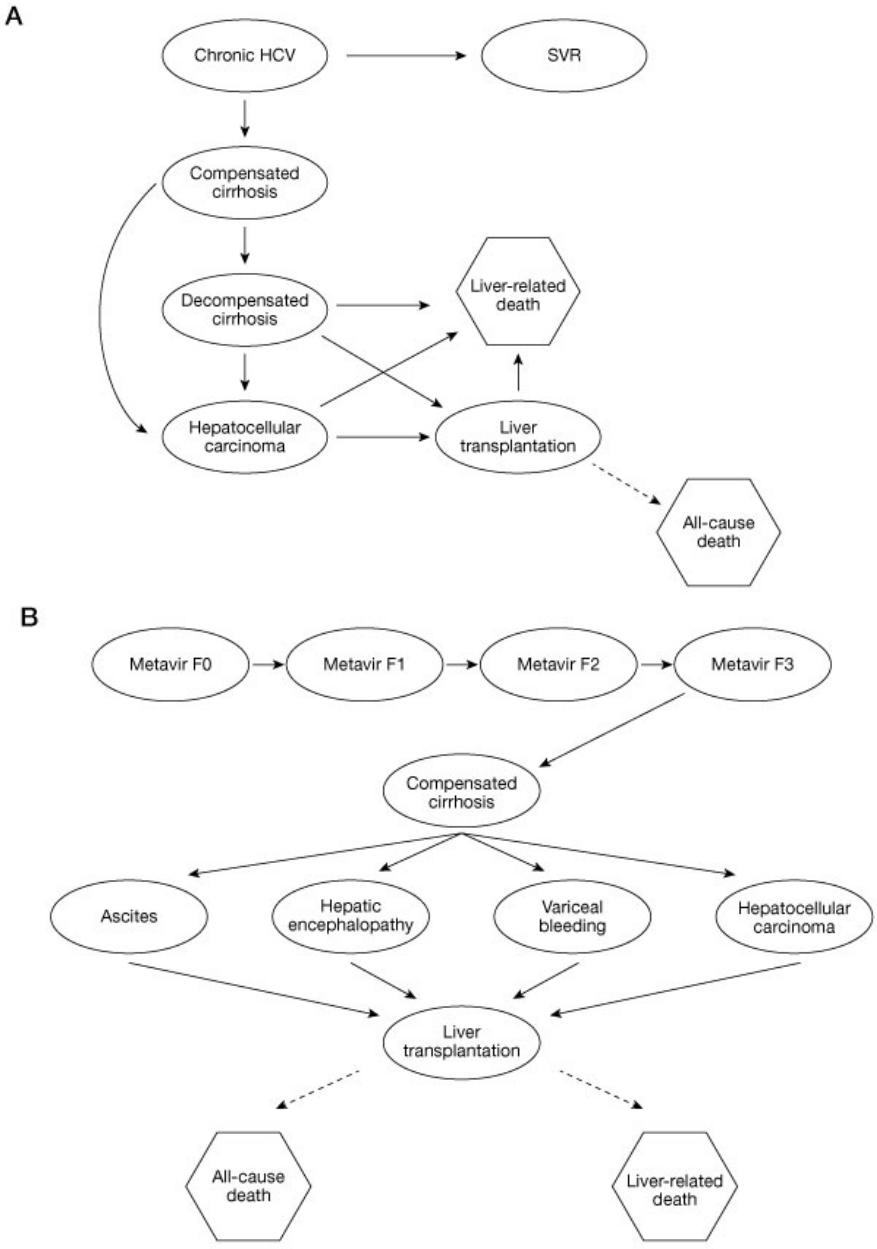


Figure 1.4.5: Markov models of HCV infection with (A) a single pre-cirrhosis state and (B) with multiple pre-cirrhosis HCV states as well as multiple decompensated states. The dashed lines represent the fact that death can occur from any state and liver-related death from a decompensated state. SVR = sustained virological response. [74]

Although all of the models follow a similar decision tree pathway, the transition probabilities, utility values, effectiveness and cost estimates vary and should be assessed critically. In addition, the natural history of hepatitis C infection is not completely elucidated as it is non-linear and heterogeneous; consequently, some degree of structural uncertainty in all decision models exists. Many of the natural history assumptions are based on modeling work done by Bennett et al. and Wong et al. in the late 1990s. [69, 75] These models based their natural history estimates on pooled data from three retrospective studies following patients by serial liver biopsies who subsequently tested positive for HCV antibody [76-78], as well as on data from the only retrospective study of the natural history of patients with compensated cirrhosis and chronic hepatitis C by Fattovich et al. [79] The assumptions of the model were validated by comparing to Seeff et al. [80, 81], a long-term follow-up study of 568 patients with acute post-transfusion hepatitis C patients, which is regarded as a conservative view of disease progression. The Markov models by Bennett et al. and Wong et al. predicted that 2.3% of patients would die of liver disease after 18 years compared to 3.3% in the Seeff et al. study. In comparison to the Fattovich et al. retrospective natural history study, which predicted a 5-year survival rate of 50% in those with compensated cirrhosis, the Bennett et al. and Wong et al. models predicted a 5-year survival rate of 55%. [69, 75, 79] From these studies, most models commonly assume that the annual probability of progressing from mild-to-moderate fibrosis is 0.041, and from moderate fibrosis to cirrhosis is 0.073. [82]

As mentioned previously, the standard of care for genotypes 2 and 3 patients is still PegIFN + RBV. There are several published US analyses comparing this regimen to no treatment and the previous therapy of IFN + RBV. Salomon et al. compared no treatment to (1) monotherapy with IFN alfa-2b, (2) monotherapy with PegIFN alfa-2b, (3)

combination therapy with IFN + RBV, and (4) combination therapy with PegIFN + RBV from a US third party payer perspective. They used data on disease progression from a previous analysis, which estimated plausible ranges for risks of progression based on a systematic literature review. This study estimated a probability of developing cirrhosis during a 30-year period between 13 and 46% for men and 1 and 29% for women. [83] The population included in the model was a cohort of asymptomatic 40-year-old patients with mild chronic HCV infection and no histological evidence of fibrosis and elevated ALTs. Treatment costs based on mean wholesale drug costs and management costs of treating complications and adverse events were included. The incremental cost effectiveness ratios (ICERs) were $15,000 per quality adjusted life year (QALY) for non-genotype 1 male patients and $24,000 for non-genotype 1 female patients compared to no treatment. Women benefited on improved quality of life, but not as much as males on survival. Wong et al. published another US-based analysis in 44 year old adult patients with mild-to-moderate, treatment-naïve chronic hepatitis C patients. This analysis compared IFN-alfa 2b with PegIFN alfa-2b in combination with 800 mg of RBV or weight-based RBV. The model also evaluated the utility of a 12- and 24-week viral response tests as a means of reducing antiviral treatment morbidity and costs. For genotype 2 and 3 patients, the ICER was $680 per QALY with PegIFN + weight-based RBV and 24-week viral tests, and $5,000 per QALY in the intent-to-treat analysis (without viral test) compared to no treatment. [84] These studies both indicate that the PegIFN + RBV treatment for genotype 2 and 3 patients is cost-effective, falling below the commonly accepted $50,000 per QALY threshold.

For genotype 1, the new standard of care is PI-based triple therapy. Since PIs were just approved in May 2011, very few cost effectiveness analyses are published. Liu et al.

recently published a cost effectiveness study of triple therapy in genotype 1 patients from a US societal perspective. Cohorts were defined by age, sex, race (white and black), IL-28B genotype (CC and non-CC types), and initial fibrosis stage (Metavir score of F0-F4). Patients were divided into groups of those with mild fibrosis (F0-F2) and those with advanced fibrosis (F2-F4). The three strategies considered in the model included: patients treated without IL-28B genotyping with either (1) dual therapy (PegIFN + RBV) or (2) triple therapy (PI + PegIFN + RBV), and (3) IL-28B-guided triple therapy strategy with non-CC types to triple therapy and CC to dual therapy. IL-28B is a genotype test that predicts response to interferon therapy. Those with CC genotype are known to respond better to therapy.

Like the dual therapy models, this was a Markov model with health states starting from F0 and progressing to liver transplant. Treatment effectiveness was based on data from IL-28B analyses of cohorts in Phase 3 clinical trials. Utility estimates were taken from previous dual therapy studies, but additional utility decrements for 1 year of therapy were -0.11 and -0.165 for dual versus triple therapy due to the increased adverse events with triple therapy. Direct medical costs were estimated with fibrosis stage-specific considerations. In addition, costs were halved once the patients achieved SVR. Another key assumption was similar treatment adherence rates for dual and triple therapy (70% of patients taking PegIFN + RBV more than 80% of the time). The results are shown in Figure 1.4.6.

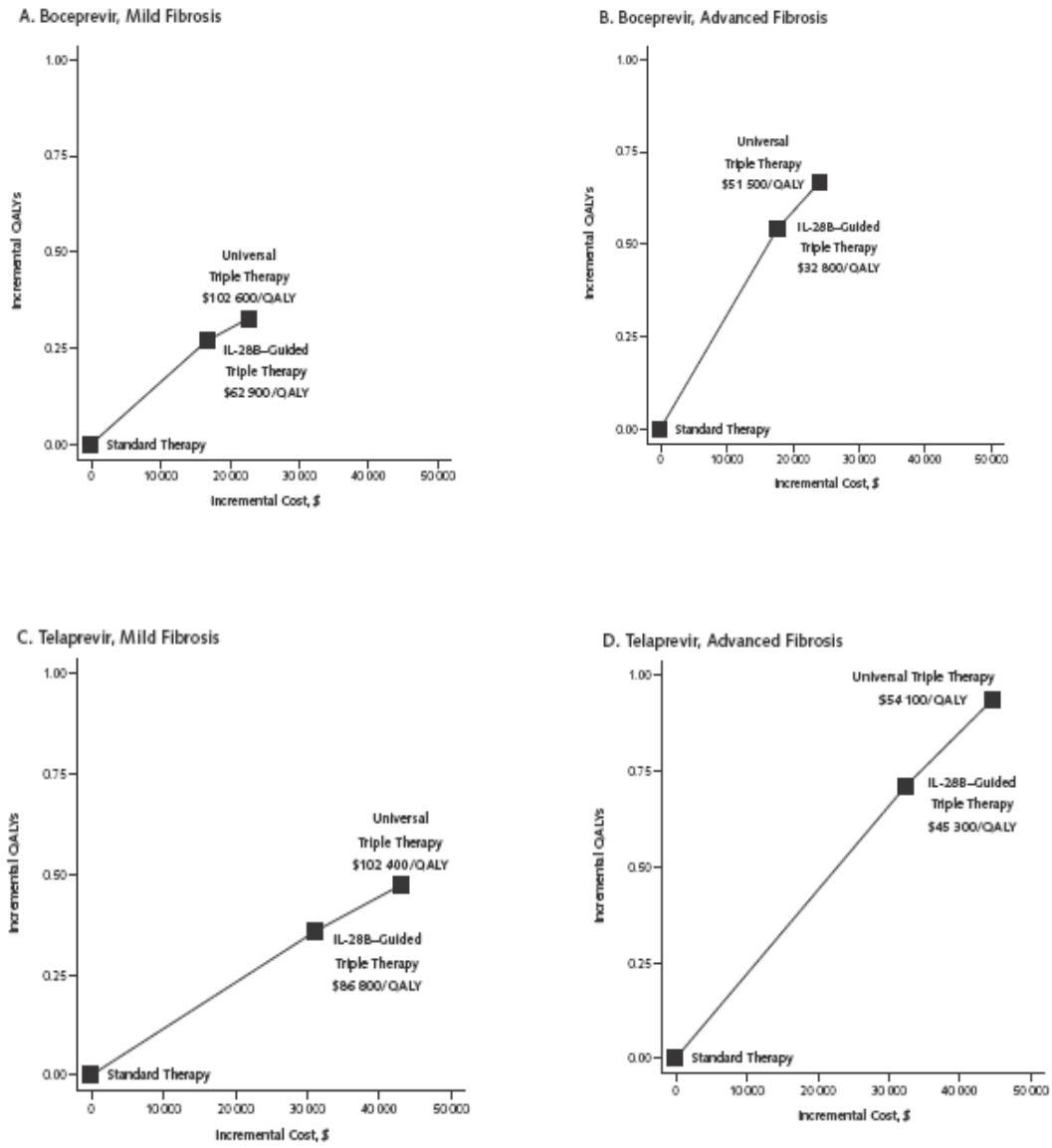


Figure 1.4.6: Cost-effectiveness results: incremental costs incurred and quality adjust life years (QALYs) for each intervention [85]

Overall, universal triple therapy yield greater health benefits than both standard therapy and IL-28B-guided triple therapy at $50,000 per QALY compared with IL-28-

guided triple therapy for patients with advanced fibrosis. However, results were sensitive to adherence rates and treatment costs. Sensitivity analyses showed that when adherence to standard therapy remained at 70% but was as low as 50% for triple therapy, then universal triple therapy was more costly and achieved no additional benefit compared with IL-28B guided triple therapy. For patients with mild fibrosis, universal triple therapy was not cost-effective. IL-28B-guided triple therapy costs $62,900 per QALY compared with standard therapy for patients with mild fibrosis. [85]

These cost-effectiveness studies with reasonable ICERs imply that treatment saves downstream costs of progressing disease. However, these models look at a lifetime horizon and the immediate impact on costs are unknown. Few studies compare costs between treated and untreated HCV patients. Gordon et al. found that mean all-cause per person per month (PPPM) health-care costs were 29% higher for non-treated patients compared to those completing treatment using data from a large commercial claims database. Patients were included in the "treated" cohort if they had evidence of anti-HCV treatment during the two year period prior to the index case date and were assigned to the following 3 liver disease severity cohorts per Gordon et al.: non-cirrhotic liver disease (NCD), compensated cirrhosis (CC), and end-stage liver disease (ESLD). [73, 86] Only 18% (4,116) out of 33,450 patients received anti-HCV treatment in the 2-year baseline period. Regardless of liver disease severity, the treated cohort had lower costs than the untreated cohort during the follow-up period. (Figure 1.4.7) [86, 87]

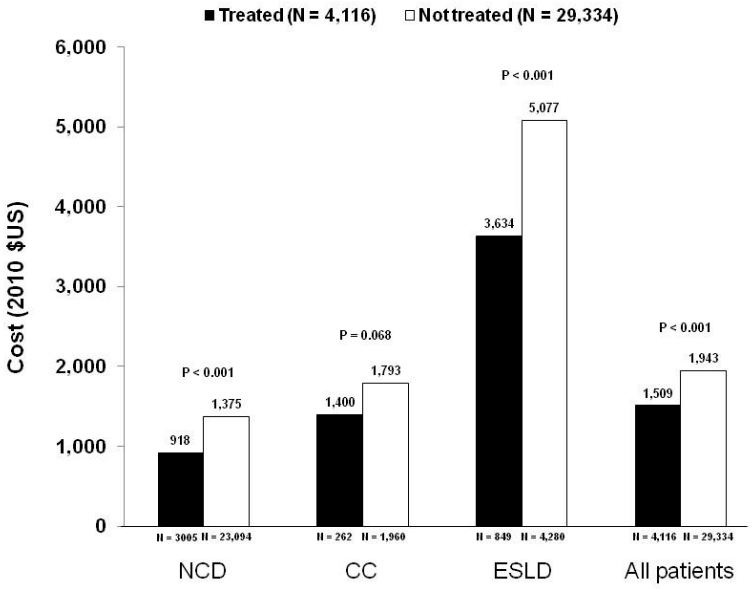


Figure 1.4.7: Mean, all-cause follow-up costs in patients who did and did not complete anti-HCV treatment ($US 2010) [87]

In a recent study of the Kaiser northern California HCV population, Manos et al. found total adjusted costs were significantly higher in the non-SVR group than in the SVR group, with rate ratios (RRs) and 95% CIs ranging from 1.26 (95% CI=1.13-1.40) to 1.64 (95% CI=1.38-1.96), driven mostly by hospital and outpatient pharmacy costs. Post-treatment al-cause costs per person per year were $6,301 for those with SVR vs. $10,149 for those without SVR. The adjusted yearly difference in total mean costs was $2,648 (95% CI=737-4,560). One advantage of this study over Gordon et al. is the availability of SVR information. However, this study may have limited generalizability as it includes one

integrated system from one geographic area. Despite these limitations, both studies show a benefit to treatment or achieving SVR. [88]

1.5 HCV IN TEXAS

Texas has been at the forefront of raising awareness of HCV by implementing a statewide initiative starting in 1998 to conduct seroprevalence studies to estimate the current and future impact of hepatitis C on the state, offer HCV counseling and testing services, provide HCV training to counselors, offer HCV education to health care professionals, and lastly to conduct public awareness, education, and outreach activities. [89]

The prevalence of HCV in Texas was estimated to be 1.79% or 387,395 Texans infected in 2000, which is higher than the prevalence in the overall country (1.6%). These estimates originated from a Markov model that used National Health and Nutrition Examination Survey III data on the national prevalence of HCV and weighted the survey data by Texas census data and characteristics. By race, the prevalence rate was estimated to be 1.38% among whites, 2.82% among non-Hispanic blacks, 2.00% among Hispanics, and 1.79% among others. About one-fourth (22.9%) of those infected were between the ages of 45 and 64. County prevalence varied from 1.25% to 2.63% with higher percentages along the US-Mexico border. However, due to smaller populations in more rural areas, most cases were located near major Texas cities. The model predicted that an increasing proportion of patients would develop cirrhosis over the next two decades, rising from 28.1% in 2000 to 40.6% in 2025. In addition, the model conservatively estimated that the proportion of patients with cirrhosis who decompensate will continue to rise, reaching >12% by 2025. Similar to the rest of the country, an increase in the number of cases with complications of liver failure, HCC, and death due to liver disease is expected. [90]

In terms of incidence, Texas has reported less than 100 cases of acute hepatitis C each year since 2005, and 37 cases were reported with an incidence rate of 0.1 per 100,000 population in 2007. [89]

Texas implemented "The Hepatitis C Initiative" in 1998 after the health department noticed an increase in the reported cases of HCV infection in Travis County. At that time, the department of health formed a hepatitis C state workgroup, which included representatives from Hep C Connection of Colorado, the Texas Medical Association (TMA), the blood bank industry, the Texas Department of Criminal Justice (TDCJ), and various employees of the Texas Bureau of Communicable Disease and HIV and STD Prevention. A white paper was drafted with the following recommendations: [91]

1. Seroprevalence studies in high risk populations and better surveillance systems for the general population are needed to estimate the current and future impact of hepatitis C in Texas.
2. Prevention counseling by trained staff and diagnostic testing should be available to persons at high risk for hepatitis C.
3. The department should build on - not supplant - its HIV/STD system of counseling, diagnosis and treatment referral to include hepatitis C.
4. Increased hepatitis C prevention efforts to reduce transmission risks are needed. These include risk reduction (needle exchange) programs and affordable drug and alcohol treatment programs and facilities.
5. Persons who have hepatitis C infection require a medical system which can provide definitive diagnosis and appropriate treatment.

The white paper concluded the executive summary with the following statement, "What must be realized is that ultimately the cost to society of not providing screening, counseling, and treatment will be much higher." [91] This paper was used to draft House Bill 1652, which passed in May 1999 and appropriated $3 million for this initiative for the next biennium. The workgroup continues to meet twice a year and acts as an advisory

workgroup to the Texas Department of Health to implement projects and programs aimed to reduce the burden of HCV. [89]

1.6 SUMMARY

There are approximately 160 million individuals worldwide infected with hepatitis C, a blood-borne RNA virus, with around 4 to 6 million of those patients residing in the United States. [1, 9]

Chronic infection with HCV leads to significant morbidity, including compensated and decompensated liver disease and hepatocellular carcinoma. The number of deaths from HCV surpassed those from HIV in recent years due to the prevalent baby-boomer population with advancing liver disease. [10, 66, 67]

Until 2013, the first-line treatment for HCV genotype 2 and 3 infection was dual therapy with PegIFN and RBV. The standard of care for genotype 1 infection was triple therapy with a protease inhibitor in combination with PegIFN and RBV. [30, 51] Although achievement of SVR clears the virus and averts downstream sequelae, these therapies are associated with many adverse events and SVR rates are still not optimal, especially in certain subpopulations, such as treatment-experienced and African-American patients. [55, 57]

Given the aging HCV patient population and the upcoming wave of costly new direct-acting antivirals, the economic implications of HCV infection and treatment have been of much interest. The two main economic burden studies have shown that the per member per year costs from a US payer's perspective increased exponentially with liver disease severity (Table 1.6.1). [72, 73]

Table 1.6.1: Annual cost of Hepatitis C sequelae from a US payer's perspective

Source	Year	Mild-Moderate Chronic Hepatitis C	Compensated Cirrhosis	Decompensated Cirrhosis	Hepatocellular Carcinoma	Liver Transplant
McAdam Marx[69]	2009		$14,915	$16,911	$58,529	$113,282
Gordon et al.[70]	2010	$17,277	$22,752		$112,537	$145,045

For the majority of treatment regimens, the ICERs were under the $50,000 threshold due to the benefits of achieving SVR on morbidity and mortality. [58-65] The ICERs for PegIFN + RBV treatment for genotype 2 and 3 patients ranged from $680 to $24,000 compared to no treatment, depending on response guided therapy protocol and RBV dose. [82, 83] The ICERs for triple therapy with the new PIs ranged from $32,800 to $102,600 compared to dual therapy depending on response-guided therapy, stage of fibrosis and assumptions on number of patients being treated. [85] Although these modeling projections indicate that treatment may be cost-effective, very few published studies directly evaluate the downstream costs in treated compared to untreated chronically infected HCV patients, and none of them studied the more vulnerable Medicaid population. These shorter-term, direct costs are important to elucidate as US payers seek to understand the benefits of therapy in an environment where patients move in and out of health plans.

Texas was the first state to recognize the growing burden of HCV and implemented "The Hepatitis C Initiative" in 1998. [89] There are several factors that will prompt the state's HCV workgroup to be in decision-making mode for the next few years: (1) the new CDC recommendations to screen the 1945 to 1965 birth cohort for HCV, which will

consequently identify more patients [32]; (2) the growing evidence that achieving SVR has both hepatic and extrahepatic benefits [58-65]; and (3) the new DAAs to be approved within a year, which will increase the number of patients and providers seeking treatment. [55, 57] Given the above factors and the state's interest in HCV, this study aims to evaluate the resource utilization and healthcare costs in treated versus untreated chronic hepatitis C patients within the Texas Medicaid system.

Chapter 2: Methodology

This chapter outlines the methodology used to retrospectively evaluate healthcare costs and resource utilization for Texas Medicaid HCV patients treated with HCV drug therapy compared to those who do not receive treatment using. Outcomes are stratified by liver disease severity, as well as triple and dual therapy regimens. This section contains a detailed description of the objectives, hypotheses, as well as study design and statistical analyses.

2.1 STUDY PURPOSE AND OBJECTIVES

2.1.1 Study Purpose

The majority of HCV patients do not receive treatment due to the asymptomatic nature of the disease and the adverse events and contraindications associated with the currently available therapies. However, those patients who are successfully treated with an achievement of SVR see significant benefits in both hepatic and extrahepatic morbidity and mortality. The purpose of this study was to evaluate the resource utilization and healthcare costs of those chronically infected HCV patients who are treated with drug therapies versus those who are not treated. Other objectives were to compare adherence, resource utilization and healthcare costs for those treated with the triple therapy HCV regimen (protease inhibitor in combination with PegIFN + RBV) versus dual therapy (PegIFN + RBV). Results were stratified by liver disease severity.

The cohorts of chronically infected HCV patients analyzed in this study are described as:

Cohort 1: Patients with chronic HCV who do not have a record of prescription drug claims for HCV therapies (untreated cohort)

Cohort 2: Patients with chronic HCV who are treated with triple or dual therapy (treated cohort)

2a: Patients with chronic HCV who are treated with a triple therapy regimen (protease inhibitor in combination with PegIFN + RBV, triple therapy cohort)

2b: Patients with chronic HCV who are treated with a dual therapy regimen (PegIFN + RBV, dual therapy cohort)

Below is a detailed description of the study objectives and hypotheses.

2.1.2 Objectives and Hypotheses

Objective 1: To compare patient characteristics for chronically infected HCV patients who are treated with HCV drug therapies versus those who are not receiving treatment before and after matching patient cohorts by high dimensional propensity scoring

$H_{0\ (1a)}$: Mean age will not differ significantly between treated and untreated cohorts before or after matching.

$H_{0\ (1b)}$: The proportion of patients in each gender category will not differ significantly between treated and untreated cohorts before or after matching.

$H_{0\ (1c)}$: The proportion of patients in each race category will not differ significantly between treated and untreated cohorts before or after matching.

$H_{0\ (1d)}$: The mean comorbidity score will not differ significantly between treated and untreated cohorts before or after matching.

$H_{0\ (1e)}$: The proportion of patients with at least one clinically relevant comorbidity will not differ significantly between treated and untreated cohorts before or after matching.

$H_{0\ (1f)}$: The proportion of patients with at least one hospitalization will not differ significantly between treated and untreated cohorts before or after matching.

$H_{0\ (1g)}$: The mean number of baseline unique non-HCV-related prescription drugs will not differ significantly between treated and untreated cohorts before or after matching.

$H_{0\ (1h)}$: The mean number of baseline outpatient visits will not differ significantly between treated and untreated cohorts before or after matching.

$H_{0\ (1i)}$: Baseline healthcare costs will not differ significantly between treated and untreated cohorts before or after matching.

$H_{0\ (1j)}$: The proportion of patients with NCD, CC, ESLD, and LT will not differ significantly between treated and untreated cohorts before or after matching.

Objective 2: To compare healthcare costs and resource utilization for HCV patients who are treated with drug therapies versus those who are not receiving treatment during the 6 month follow-up period

$H_{0\ (2a)}$: Total all-cause healthcare costs for HCV patients will not differ significantly between treated versus untreated cohorts.

$H_{0\ (2b)}$: Hospitalization costs and number of hospitalizations will not differ significantly between treated versus untreated cohorts.

$H_{0\ (2c)}$: Emergency room visit costs and number of visits will not differ significantly between treated versus untreated cohorts.

$H_{0\ (2d)}$: Outpatient costs and number of outpatient visits will not differ significantly between treated versus untreated cohorts.

$H_{0\ (2e)}$: Prescription drug costs and number of prescription drugs will not differ significantly between treated versus untreated cohorts.

Objective 3: To compare healthcare costs and resource utilization for HCV patients who are treated by liver disease severity during the 6 month follow-up period

$H_{0\ (3a)}$: In treated cohort, total all-cause healthcare costs will not differ significantly for those with more severe liver disease compared to those without cirrhosis.

$H_{0\ (3b)}$: In treated cohort, hospitalization costs and number of hospitalizations will not differ significantly for those with more severe liver disease compared to those without cirrhosis.

$H_{0\ (3c)}$: In treated cohort, emergency room costs and number of visits will not differ significantly for those with more severe liver disease compared to those without cirrhosis.

$H_{0\ (3d)}$: In treated cohort, outpatient costs and number of visits will not differ significantly for those with more severe liver disease compared to those without cirrhosis.

$H_{0\ (3e)}$: In treated cohort, prescription drug costs and number of prescriptions will not differ significantly for those with more severe liver disease compared to those without cirrhosis.

Objective 4: To compare healthcare costs and resource utilization for HCV patients who are untreated by liver disease severity during the 6 month follow-up period

$H_{0\ (4a)}$: In untreated cohort, total all-cause healthcare costs will not be significantly higher for those with more severe liver disease compared to those without cirrhosis.

$H_{0\ (4b)}$: In untreated cohort, hospitalization costs and number of visits will not be significantly higher for those with more severe liver disease compared to those without cirrhosis.

$H_{0\ (4c)}$: In untreated cohort, emergency room visit costs and number of visits will not significantly differ for those with more severe liver disease compared to those without cirrhosis.

$H_{0\ (4d)}$: In untreated cohort, outpatient costs and number of visits will not significantly differ for those with more severe liver disease compared to those without cirrhosis.

$H_{0\ (4e)}$: In untreated cohort, prescription drug costs and number of prescriptions will not be significantly higher for those with more severe liver disease compared to those without cirrhosis.

Objective 5: To compare HCV-related healthcare costs and resource utilization for HCV patients who are treated with drug therapies versus those who are not receiving treatment during the 6 month follow-up period

$H_{0\ (5a)}$: Total HCV-related healthcare costs for HCV patients will not differ significantly between treated versus untreated cohorts.

$H_{0\ (5b)}$: HCV-related hospitalization costs and number of hospitalizations will not differ significantly between treated versus untreated cohorts.

$H_{0\ (5c)}$: HCV-related emergency room visit costs and number of visits will not differ significantly between treated versus untreated cohorts.

$H_{0\ (5d)}$: HCV-related outpatient costs and number of outpatient visits will not be significantly different between treated and untreated cohorts.

Objective 6: To compare adherence and discontinuation rates for chronically infected HCV patients on triple therapy versus dual therapy during the 6 month follow-up period

$H_{0\ (6a)}$: Mean medication adherence for HCV drug regimens will not differ significantly for patients on triple therapy compared to patients on dual therapy.

$H_{0\ (6b)}$: The proportion of patients who are adherent (PDC ≥ 80%) to HCV drug therapy will not differ significantly for patients on triple therapy compared to patients on dual therapy.

$H_{0\ (6c)}$: The proportion of patients who discontinue HCV therapy prematurely will not differ significantly for patients on triple therapy compared to patients on dual therapy.

Objective 7: To compare healthcare costs and resource utilization for chronically infected HCV patients on triple therapy versus dual therapy during the 6 month follow-up period

$H_{0\ (7a)}$: Total all-cause healthcare costs for treated HCV patients will not differ significantly for patients on triple therapy versus dual therapy.

$H_{0\ (7b)}$: Hospitalization costs and number of hospitalizations will not differ significantly for treated patients on triple therapy versus dual therapy.

$H_{0\ (7c)}$: Emergency room visit costs and number of visits will not differ significantly for treated patients on triple therapy compared to dual therapy.

$H_{0\ (7d)}$: Outpatient costs and number of outpatient visits will not be significantly different between treated patients on triple versus dual therapy cohorts.

$H_{0\ (7e)}$: Prescription drug costs and number of prescription drugs will be significantly higher for those on triple therapy versus dual therapy.

Objective 8: To compare HCV-related healthcare costs and resource utilization for chronically infected HCV patients on triple therapy versus dual therapy during the 6 month follow-up period

$H_{0\ (8a)}$: Total HCV-related healthcare costs for treated HCV patients will not differ significantly for patients on triple therapy versus dual therapy.

$H_{0\ (8b)}$: HCV-related hospitalization costs and number of hospitalizations will not differ significantly for treated patients on triple therapy versus dual therapy.

$H_{0\ (8c)}$: HCV-related emergency room visit costs and number of visits will not differ significantly for patients on triple therapy compared to dual therapy.

$H_{0\ (8d)}$: HCV-related outpatient costs and number of outpatient visits will not be significantly different between treated patients on triple therapy versus dual therapy.

$H_{0\ (8e)}$: HCV-related prescription drug costs and number of prescription drugs will not differ significantly for patients on triple therapy versus dual therapy.

Objective 9: To compare healthcare costs and resource utilization for HCV patients who are treated with drug therapies versus those who are not receiving treatment during the 1.5 year follow-up period

$H_{0\ (9a)}$: Total all-cause healthcare costs for HCV patients will not differ significantly for treated versus untreated patients.

$H_{0\ (9b)}$: Hospitalization costs and number of hospitalizations will not differ significantly for treated versus untreated patients.

$H_{0\ (9c)}$: Emergency room visit costs and number of visits will not differ significantly for treated versus untreated cohorts.

$H_{0\ (9d)}$: Outpatient costs and number of outpatient visits will not be significantly different between treated and untreated cohorts.

$H_{0\ (9e)}$: Prescription drug costs and number of prescription drugs will not be significantly different between treated and untreated cohorts.

2.2 DATA SOURCE AND STUDY DESIGN

This was a retrospective, longitudinal analysis of treated and untreated chronically infected HCV patients using Texas Medicaid claims data.

2.2.1 Data Source

The data source for this study was the Texas Medicaid claims database. Data files included eligibility and demographic information for each person, along with inpatient, outpatient, and prescription drug claims. Demographic characteristics captured include gender, race, date of birth, and county of residence. Plan enrollment information was also available with specific plan codes and eligibility dates. The claims files were divided by fee-for-service (FFS) and managed care organization (MCO) claims. The claims data included five diagnosis codes for each visit, date of visit, procedure codes, provider information and paid amounts. The prescription drugs data included dispense date, National Drug Code (NDC), quantity, days supply, and amount paid. Due to a previous system overhaul, this analysis utilized claims from January 1, 2007 through December 31, 2012.

2.2.2 Study Population

The two main included cohorts of patients are those with chronic HCV infection who have been treated with HCV dual or triple therapy as evidenced by prescription drug claims (treated) and those who do not have evidence of treatment (untreated). The two cohorts were matched via high dimensional propensity scoring with a 2:1 (untreated:treated) ratio. The cohort of treated patients was further categorized into subgroups of patients being treated with triple therapy versus dual therapy.

2.2.2.1 Inclusion Criteria

Patients eligible for this study were Texas Medicaid patients ≥18 years and ≤63 years old with both pharmacy and medical benefits who had evidence of chronic HCV infection during the identification period (January 1, 2007 – June 30, 2011) (Table 2.2.1). All included patients had evidence of continuous enrollment for 6 months before the index date and at least 6 months after the index date.

The treated cohort had evidence of chronic HCV and at least one claim for interferon and ribavirin or telaprevir/boceprevir plus interferon and ribavirin. The untreated cohort had evidence of chronic HCV but no prescription drug claim for currently available therapies.

Within the treated cohort, the triple therapy cohort was identified by at least one claim for telaprevir or boceprevir. The dual therapy cohort was identified by at least one claim for PegIFN.

2.2.2.2 Exclusion Criteria

Those patients with acute HCV infection were excluded. The Gordon et al. algorithm was applied to ensure only those chronically infected will be included.[73] (Table 2.2.1) The patient selection scheme can be found in Figure 2.2.1.

Table 2.2.1: ICD-9 code algorithm to identify chronically infected HCV patients [73]

ICD-9-CM Code	**Description**	**Inclusion criteria** (1 of the following)
	1.Chronic HCV diagnosis codes	A single claim with one of these diagnosis codes OR
070.44	Chronic hepatitis C with hepatic coma	
070.54	Chronic hepatitis C without mention of hepatic coma	
	2.Unspecified HCV diagnosis codes	2 claims with one of these diagnosis codes on separate dates of service OR
V02.62	Hepatitis C carrier	
070.70	Unspecified viral hepatitis C without hepatic coma	
070.71	Unspecified viral hepatitis C with hepatic coma	
	3.Acute and unspecified HCV diagnosis codes	2 claims with one of these diagnosis codes spaced at least 6 months apart
070.41	Acute hepatitis C with hepatic coma	
070.51	Acute hepatitis C without mention of hepatic coma	
070.62	Hepatitis C carrier	
070.70	Unspecified viral hepatitis C without hepatic coma	
070.71	Unspecified viral hepatitis C with hepatic coma	

2.2.2.3 Sample Size

Since the prevalence of HCV is low at 1 to 2%, all those with chronic HCV within the Texas Medicaid system who fulfill the inclusion criteria were included in this analysis. The power analyses are shown in Section 2.4.

2.2.2.4 Stratifications

Results were stratified by liver disease severity within the treated and untreated patient cohorts. Liver disease severity was identified by ICD-9 codes per Gordon et al. [73] (Table 2.2.2)

Table 2.2.1: Disease severity cohort as determined by ICD-9 and procedure codes [73]

Disease severity cohort	Conditions or procedures	ICD-9 or CPT
Non-cirrhotic disease (NCD)	No listed conditions or procedures	
Compensated cirrhosis (CC)	Cirrhosis	571.5
End-stage liver disease (ESLD)	Liver transplant	V42.7
	Hepatocellular carcinoma	155.0
	Liver failure, including hepatorenal syndrome	572.4
	Hepatic encephalopathy	572.2
	Portal hypertension	572.3
	Esophageal varices	456.0
	Other gastrointestinal hemorrhage	578
	Ascites	789.5
	Other sequelae of chronic liver disease	572.8
	Abdominal paracentesis procedures	54.91
	Shunts and catheter procedures	50.29
	Treatment of varices	42.91 42.33 44.91 43.41
	Portal decompression procedures	51.43

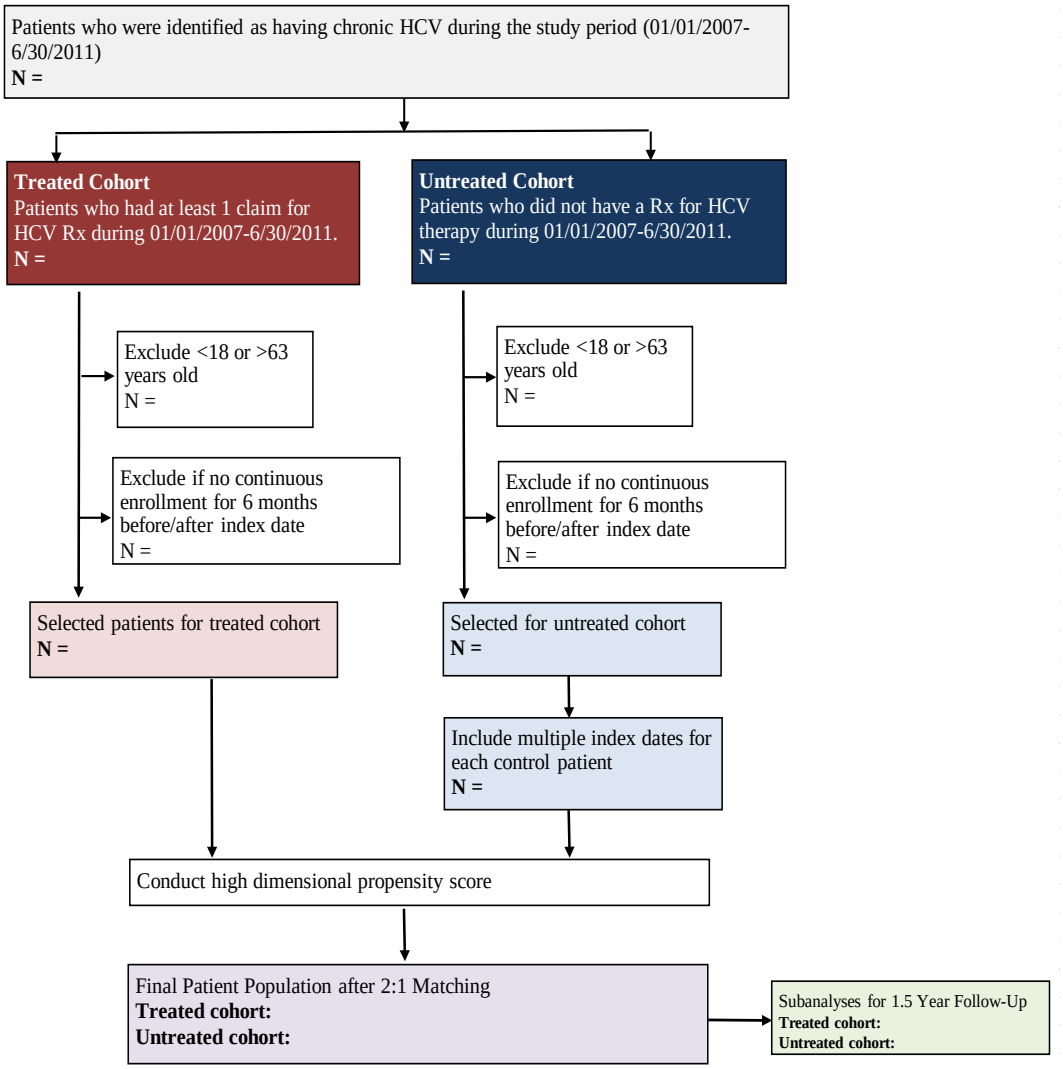


Figure 2.2.1: Patient selection scheme

2.2.3 Study Period

The identification period for this study was from January 1, 2007 through September 30, 2011. The index date for the treated cohort was the date of the first prescription for either interferon and ribavirin or telaprevir plus interferon and ribavirin or

boceprevir plus interferon and ribavirin. Telaprevir and boceprevir were approved in May 2011 so only 6 months of follow-up were available for patients on triple therapy. For the untreated cohort, the index date was the date of the HCV-related ICD9 code closest to the matched treated patient's index date. Patients were observed for 6 months prior to the index date and 6 months after the index date. Sub-analyses were performed for those patients who had follow-up of 1.5 years to see if longer term follow-up impacted the difference healthcare costs and resource utilization between treated and untreated patients. Figure 2.2.2 displays the study periods for the various assessments.

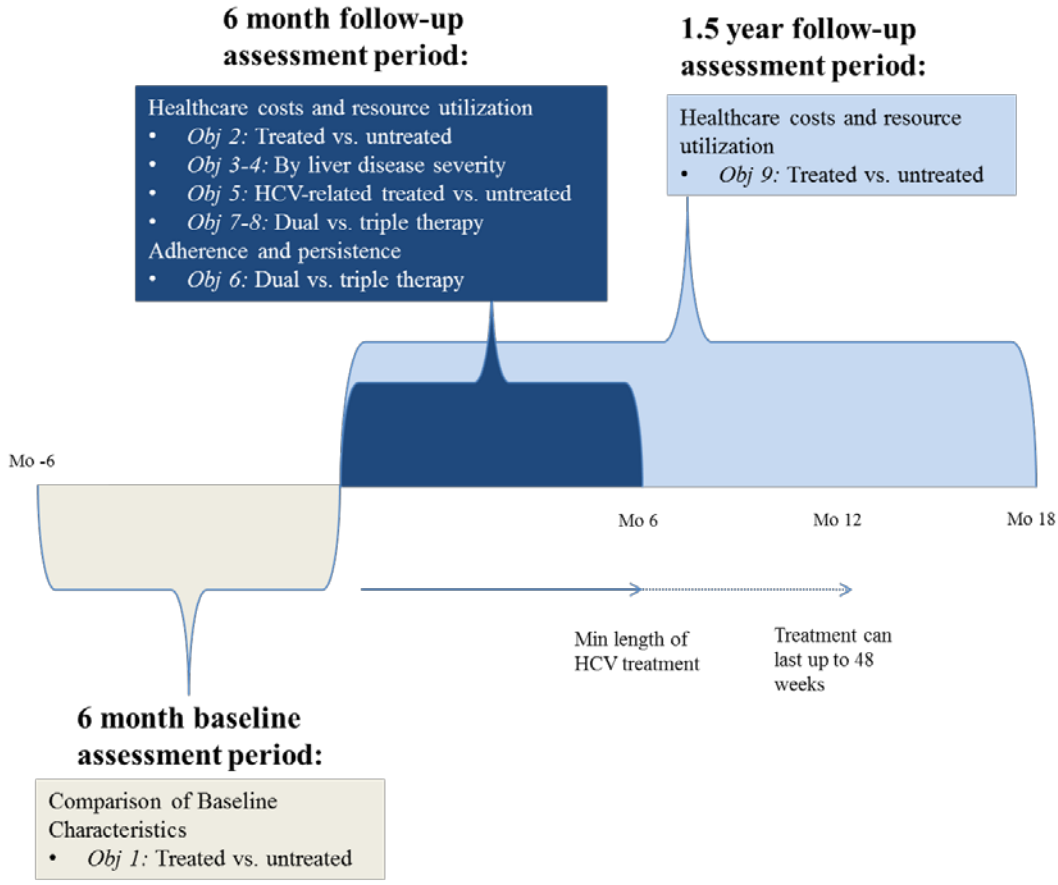


Figure 2.2.2: Study periods of assessments

2.3 STATISTICAL ANALYSIS PLAN

An a priori significance level of $\alpha = 0.05$ was applied to all statistical analyses. All data manipulation and statistical analyses was performed using SAS software (version 9.2; SAS Institute Inc, Cary, North Carolina) and Stata (version 11.1; Stata Corp, College Station, Texas).

2.3.1 Matching Cohorts of Patients Using High Dimensional Propensity Scoring

High dimensional propensity scoring techniques were used to match treated vs. untreated patients (1:2 ratio) per previously published work by Schneeweiss et al. [92]

High-dimensional propensity scoring is a relatively new method to match patient populations using longitudinal healthcare claims. These claims contain numerous proxies, such as diagnoses and procedure codes, for the health status of a patient as illustrated in Figure 2.3.1.

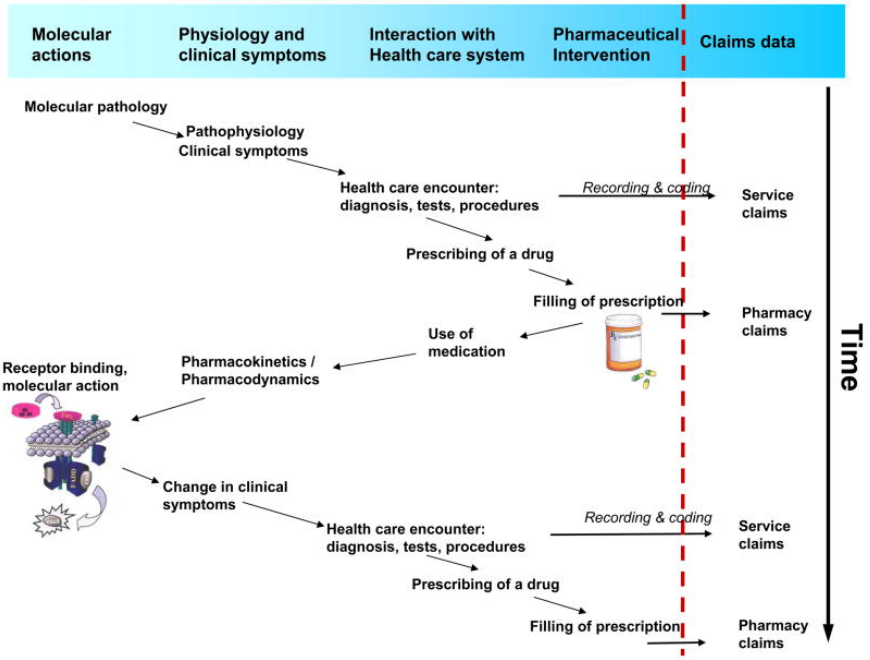


Figure 2.3.1: Proxies in healthcare utilization databases [92]

The high dimensional propensity scoring method involved several steps, including (1) identifying data dimensions, e.g. diagnoses, procedures, and medications, (2) empirically identifying candidate covariates, (3) assessing recurrence of codes, (4) prioritizing covariates, (5) selecting covariates for adjustment, and (6) estimating the exposure propensity score.

1. Identifying data dimensions

The appropriate data parameters were identified, and those that were surrogates for the exposure were removed. Specifically, all diagnosis codes, procedural codes, and National Drug Codes (NDC) in the patients' inpatient, outpatient, and prescription drug claims during the 6 month baseline period were included as data dimensions. Those that were related to hepatitis C and liver disease, such as liver transplant, were removed. The inclusion of surrogates that are related to the study exposure but not the outcome can bias the results.

2. Identifying candidate empirical covariates

The top *n* covariates were identified as candidate empirical covariates by the high dimensional scoring macro code. The granularity of the ICD-9 code was set at 5 digits.

3. Assessing recurrence

The frequency of each code was assessed by dividing the code into three binary variables: (1) ≥ 1 time, (2) ≥ median number of times, and (3) ≥ 75th percentile number of times. For a *p* data dimension (eg. diagnosis, procedure code, medication), there could be up to *p***n**3 covariates.

4. Prioritizing covariates

Covariates were prioritized across data dimensions by their potential to control for confounding that was not conditional on exposure and other covariates. The confounded

or apparent relative risk (ARR) is a function of the imbalance in prevalence of a binary confounding factor among exposed (P_{C1}) and unexposed (P_{C0}) subjects and association between a confounder and the study outcome (RR_{CD}).

$$ARR = RR \times \frac{P_{C1}(RR_{CD}-1)+1}{P_{C0}(RR_{CD}-1)+1}, \text{ if } RR_{CD} \geq 1$$

$$ARR = RR \times \frac{P_{C1}(\frac{1}{RR_{CD}}-1)+1}{P_{C0}(\frac{1}{RR_{CD}}-1)+1}, \text{ if } RR_{CD} < 1$$

The *p***n**3 covariates were sorted by the magnitude of the log of the multiplicative bias term (fraction on the right side of the equation) in descending order.

5. Selecting covariates

The top *k* covariates were chosen from step four with a maximum number as *p***n**3 covariates. *d* binary demographic covariates of age, gender, and race were inputted in the model, as well as *l* pre-defined covariates. *l* pre-defined covariates included Charlson comorbidity index (CCI), presence of one of more clinically-relevant comorbidities, presence of at least 1 hospitalization, number of outpatient visits, number of unique prescription drugs, liver disease severity (NCD, CC, and ESLD), and baseline healthcare costs. A complete description of the pre-defined covariates can be found in Section 2.3.9.

6. Estimating exposure propensity score

In the next step, a propensity score were estimated as the predicted probability of exposure conditional on *d* + *l* + *k* covariates.

Compared to traditional propensity score methods, high dimensional propensity scoring allows for the exploitation of database information that is usually untapped rather than just considering investigator-defined variables. Schneeweiss et al. found that in

several drug-outcome relationship studies, using this method produced results closer to the expected findings of a randomized trial. [92]

Once a propensity score was calculated for each patient, a 2:1 (untreated:treated) matching algorithm was employed to match cohorts by propensity scores using a greedy matching algorithm. This algorithm matches a set of X cases to a set of Y controls in a set of X decisions. The algorithm makes the best matches first as determined by those with the highest digit match on propensity score. The next-best matches next and so forth until no more matches can be made.

2.3.2 Objective 1: Comparison of Baseline Characteristics

Baseline demographic characteristics, including gender, race, and age, were compared between treated and untreated cohorts before and after matching. Clinical characteristics, such as Charlson Comorbidity Index (CCI), baseline total healthcare costs (log-transformed), baseline number of hospitalizations, baseline number of medications, and the presence of important comorbidities (e.g. diabetes) were compared. Descriptive statistics were conducted and Chi-square tests compared categorical variables and 2 sample t-tests compared continuous variables between cohorts. Standardized differences, which calculate difference in means in units of the pooled standard deviation, were also calculated to assess for baseline balance between treated and untreated cohorts. Standardized differences have an advantage over other hypothesis tests in that they are not influenced by sample size. The formula to calculate standardized differences for continuous variables is:

$$d = \frac{(\bar{x}_{\text{treatment}} - \bar{x}_{\text{control}})}{\sqrt{\frac{s^2_{\text{treatment}} + s^2_{\text{control}}}{2}}}$$

$x^2_{\text{treatment}}$ and x^2_{control} represents sample mean of the covariate in treated and control (untreated) cohorts, respectively, while the $s^2_{\text{treatment}}$ and s^2_{control} denote the sample variance in the two cohorts, respectively.

The formula for categorical variables is:

$$d = \frac{(\hat{p}_{\text{treatment}} - \hat{p}_{\text{control}})}{\sqrt{\frac{\hat{p}_{\text{treatment}}(1-\hat{p}_{\text{treatment}}) + \hat{p}_{\text{control}}(1-\hat{p}_{\text{control}})}{2}}}$$

$p_{treatment}$ *and* $p_{control}$ denote the prevalence or mean of the variable in treated and untreated groups.

Another method used to compare the univariate distribution of continuous baseline covariates between treated and untreated subjects was by graphical box plots. This graphical display allows for a broader comparison of continuous variables between two groups.

2.3.3 Objective 2: Comparison of Healthcare Costs and Resource Utilization for Treated versus Untreated Cohorts

Costs were adjusted to 2013 US dollars using the medical price index.

Healthcare costs were analyzed using unadjusted and adjusted generalized linear models with gamma distribution and log link. Inpatient visits were too infrequent to conduct adjusted analyses. The dependent variables were the total post-index costs, while the independent variable was the group (1: treated, 0: untreated). Other covariates in the adjusted model included age, gender, CCI, presence of key HCV comorbidities, baseline health care utilization, and baseline costs. These variables were included in the matching, but were also added to the regression analysis to account for residual confounding.

When cost outcomes included a large number of zero costs, then a two-part model was employed with logit model to estimate the probability of having a visit or cost, and a gamma regression model with a log link to estimate costs or visits in those with at least one visit. The first part of the model is described by the following equation: [93, 94]

$P (Y > 0 \mid X)$

Part one is governed by a parametric binary probability model like logit or probit. The second part is a linear function of x which predicts costs condition on nonzero costs:

$E (Y \mid Y > 0, X)$

Unconditional predicted costs are obtained from multiplying the probabilities of use form the first part of the model by expected levels from the second part:

$E (Y \mid X) = P (Y > 0 \mid X) E (Y \mid Y > 0, X)$

Resource utilization was analyzed using a negative binomial regression model. The dependent variable was total post-index utilization, while the independent variable was the group (1: treated, 0: untreated). Other clinically meaningful and important demographic

covariates were included, such as included age, gender, CCI, key HCV comorbidities, baseline health care utilization, and baseline costs. Negative binomial regression can be used for over-dispersed count data, which indicates that the conditional variance exceeds the conditional mean. This model has the same mean structure as Poisson regression, but has an extra parameter to model the over-dispersion.

When resource utilization outcomes included a large number of zero values, a zero-inflated Poisson regression model was utilized. Zero-inflated models attempt to account for excess zeros, and estimate two equations simultaneously: one for the count model and one for the excess zeros. The basic structure of the zero-inflated Poisson regression model is shown below [95, 96]:

$$P(Y = 0) = \phi + (1 - \phi)e^{-\lambda}$$

$$P(Y = y) = (1 - \phi)\frac{\lambda^y e^{-\lambda}}{y!}, \quad y = 1, 2, \ldots$$

Where $0 < Ø < 1$ so that it incorporates more zeros than those permitted under the Poisson assumption (Ø=0). It was assumed that a discrete count response variable Y follows a zero-inflated Poisson distribution.

In all of the adjusted analyses, the standard error and 95% confidence intervals for the dependent variable were bootstrapped for more robust estimates.

2.3.4 Objectives 3 and 4: Comparison of Healthcare Costs and Resource Utilization for Treated versus Untreated Cohorts by Liver Disease Severity

Per the above, costs were adjusted to 2013 US dollars using the medical price index. Healthcare costs and utilization for each liver disease severity (NCD, CC, ESLD, or LT) were described as small sample sizes did not allow for statistical comparisons. Means,

standard deviations (SDs), minimums, and maximums were described for each liver disease category.

2.3.5 Objective 5: Comparison of HCV-Related Healthcare Costs and Resource Utilization in Treated versus Untreated Patients

Costs and healthcare utilization were considered HCV-related if the ICD-9 or CPT codes indicated HCV or liver disease in the primary position. The previously described cost analyses in 2.3.3 were performed. The dependent variables were the total HCV-related post-index costs and utilization, while the independent variable was the group (1: treated, 0: untreated). Other independent covariates included age, gender, CCI, key HCV comorbidities, baseline health care utilization, and baseline costs.

2.3.6 Objective 6: Comparison of Adherence and Medication Discontinuation Rates in Triple Therapy versus Dual Therapy Cohorts

Adherence was defined by proportion of days covered (PDC), which is the total days of supply divided by the total days evaluated. PDC ranges from 0 to 1 with higher numbers indicating higher compliance. Excessive days of supply from the previous period were carried forward to the next month period. A 24-week analysis period was applied since the actual length of therapy depends on the genotype information and response guided protocols, which both require access to laboratory values. Mean adherence levels were compared by t-test for triple vs. dual therapy cohorts. The proportions of patients with ≥70% and ≥80% PDC were also compared between triple and dual therapy groups using Chi-square tests. The predictors of ≥70% and ≥80% PDC were estimated by logistic regression, where the dependent variables were ≥70% vs. <70% and ≥80% vs. <80%. The independent variable was the treatment status (1 for treated, 0 for untreated). Other

covariates in the adjusted model included therapy type, age, gender, CCI, key HCV comorbidities, outpatient visits and number of non-HCV medications during the analysis period (vs. baseline). Outpatient visits and non-HCV drugs during the analysis period were included as covariates since closer follow-up during treatment was hypothesized to increase adherence and persistence.

Discontinuation rates were calculated by the proportion of patients in both dual and triple therapy groups who discontinue therapy prior to week 24 and compared by Chi-square test. Discontinuation was defined as a gap in medication on-hand as determined by refill records by the days of the previous days of supply. For instance, if the previous days of supply were 30 days, then discontinuation was defined as a 30 day gap with no medication on hand. Kaplan-Meir curves graphically illustrated the time to discontinuation.

Cox proportional hazards model was used to assess for the significant predictors of medication persistence. The independent variable was the treatment status (1 for treated, 0 for untreated and other covariates in the adjusted model included therapy type (dual vs. triple), age, gender, CCI, presence of key HCV comorbidities, baseline costs, outpatient visits and number of non-HCV medications during the analysis period. The Cox model can incorporate time-dependent covariates, is effective at controlling for multiple covariates, and can easily accommodate discrete and continuous measurement of event times. [97]

2.3.7 Objective 7: Comparison of Healthcare Costs and Resource Utilization for Triple Therapy versus Dual Therapy Cohorts

Due to the small sample size of the triple therapy group, statistical comparisons between triple and dual therapy cohorts were not possible, and costs were described (mean, SD, minimum, maximum).

2.3.8 Objective 8: Comparison of HCV-Related Healthcare Costs and Resource Utilization for Triple Therapy versus Dual Therapy Cohorts

Costs and healthcare utilization was considered HCV-related if the ICD-9 or CPT codes indicated HCV or liver disease in the primary position. Due to the small sample size of the triple therapy group, statistical comparisons between triple and dual therapy cohorts were not possible, and costs were described (mean, SD, minimum, maximum).

2.3.9 Objective 9: Comparison of Longer-Term Healthcare Costs and Resource Utilization for Treated vs. Untreated Subjects

Costs and healthcare utilization were analyzed as described in Section 2.3.3. The dependent variables were the post-index costs and utilization and the independent variable was the group (1: treated, 0: untreated). This analysis evaluated the subset of patients who have 1.5 years of follow-up claims after the index date.

2.3.10 Predefined Covariates for Adjusted Analyses

2.3.10.1 Group Covariates

Treatment status, as well as triple vs. dual therapy was denoted by categorical variables. Liver disease severity was characterized as non-cirrhotic disease (NCD), compensated cirrhosis (CC), or end stage liver disease (ESLD). Liver transplant (LT) was a separate subset within ESLD considered in stratified analyses. (Table 2.3.1)

Table 2.3.1 Definitions of Group Variables

Name	Level	Definition
Treated vs. Untreated	Categorical	0: Untreated 1: Treated
Dual vs. Triple Therapy	Categorical	0: Dual therapy (PegIFN + RBV) 1: Triple therapy (PegIFN + RBV + telaprevir or boceprevir)
Liver Disease Severity	Ordinal	0: NCD 1: CC 2: ESLD

2.3.10.2 Demographic Covariates

The demographic variables available in the Texas Medicaid database include age, gender, race, insurance type, and Texas county code. Age, gender and race were included in the covariates of the adjusted analyses. (Table 2.3.2)

Table 2.3.2 Definitions of Demographic Variables

Name	Level	Definition
Age	Continuous	Age at index date
Race	Categorical	0: Non-White 1: White
Gender	Categorical	0: Female 1: Male

2.3.10.3 Clinical Covariates

The Charlson Comorbidity Index (CCI) was calculated, as well as the presence of other important comorbidities relevant in chronic HCV. The score calculation is shown in Table 2.3.3. The other clinically important comorbidities included portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity as identified by ICD-9 codes (Table 2.3.4). This list of comorbidities was generated through clinical guidance from treating hepatologists. Covariate coding and definitions are shown in Table 2.3.5.

Table 2.3.3 Charlson Comorbidity Index (CCI)

Diagnoses	ICD-9 codes	Weight
Myocardial infarction	410.xx, 412	1
Congestive heart failure	428.x	1
Peripheral vascular disease	441.x, 443.9, 785.4, V43.4, 38.48(P)	1
Cerebrovascular disease	430-437.x, 438	1
Dementia	290.x	1
Chronic pulmonary disease	490-496, 500-505, 506.4	1
Ulcer disease	531.4x-531.7x, 532.4x-532.7x, 533.4x-533.7x, 534.4x-534.7x, 531.0x-531.3x, 532.0x-532.3x, 533.0x-533.0x, 534.0x-534.3x, 531.9, 532.9, 533.9, 534.9	1
Various cirrhosis	571.2, 571.4, 571.5, 571.6	1
Diabetes	250.0x-250.3x, 250.7x	1
Connective tissue disease	710.x, 714.x, 725.x	1
Hemiplegia	342.x, 344.1	2
Moderate or severe renal disease	582.x, 583.0-583.7, 585, 586, 588.x	2
Diabetes with complications	250.4x-250.6x	2
Various cancers	140.x-172.x, 174.x-195.x, 200.x-208.x	2
Moderate or severe liver disease	572.2-572.8	3
Metastatic cancers	196.x-199.9	6
HIV/AIDS	042.x-044.9	6
	Updated Charlson Codes (2008)	
Depression	296.2x-296.3	1
Use of warfarin	Used drug data	1
Hypertension	401.x-401.9	1
Skin ulcers/cellulitis	682.x-682.9, 707.x-707.9	2

Table 2.3.4 ICD-9 Codes for Comorbidities

Diagnoses	ICD-9 codes
Portal Hypertension	572.3
Congestive heart failure	428.x
Moderate or severe renal disease	582.x, 583.0-583.7, 585, 586, 588.x
Depression	296.2x-296.3
Schizophrenia	295.x
Diabetes	250.0x-250.3x, 250.7x, 250.4x-250.6x
Bipolar	296.x
Drug abuse	304.x
Alcohol	291.0-291.5, 291.89, 303.0x, 303.9x, 305.0x
Various cirrhosis	571.2, 571.4, 571.5, 571.6
HIV/AIDS	042.x-044.9
Obesity	278.x

Table 2.3.5 Definitions of Clinical Covariates

Name	Level	Definition
CCI	Continuous	Score calculated per Table 2.3.3
Presence of comorbidities	Categorical	0: None of the comorbidities listed in Table 2.3.4 1: At least one of the comorbidities listed in Table 2.3.4 present during the baseline period

2.3.10.4 Resource Utilization and Cost Covariates

The baseline numbers of unique prescription drugs, as well as outpatient visits were included as continuous variables. For the adherence and persistence analysis, outpatient visits and non-HCV drugs during the assessment period (vs. baseline) were included as covariates since closer follow-up during treatment was hypothesized to increase adherence and persistence. The presence of at least one hospitalization vs. no hospitalization was also

included as a covariate. The baseline costs were included as a covariate after natural log transformation due to the skewed nature of cost data. (Table 2.3.6)

Table 2.3.6 Definitions of Resource Utilization and Cost Covariates

Name	Level	Definition
Baseline number of unique prescription drugs Number of non-HCV drugs	Continuous	Number of unique medications during the baseline period Number of non-HCV drugs during the analysis period
Number of outpatient visits	Continuous	Number of outpatient visits during the baseline period Number of outpatient visits during the analysis period
Baseline hospitalization	Categorical	0: No hospitalization 1: Hospitalization
Baseline all-cause healthcare costs	Continuous	LN (baseline costs + 1); 1 was added since LN(0) = -∞

2.4 POWER ANALYSIS

Sample size calculations were performed using PASS (Power Analysis & Sample Size) software (version 12; NCSS Statistical Software, Kaysville, Utah). Using the PASS 12 software and varying the parameter required for sample size calculations over a range of values, the largest sample size obtained was chosen as the required sample size for each regression.

2.4.1 Sample Size Calculation for Multiple Regression

Considering 15 independent variables, the sample size needed to obtain 80% power at a 0.05 significance level was 186 (Table 2.4.1). [98]

Table 2.4.1 Estimates of Sample Size for Multiple Regression Analysis

N	Alpha	Ind. Variables Tested [a]	R^2 [b]	Ind. Variables Controlled [c]	R^2 [b]
186	0.05	20	0.1	15	0.1
94	0.05	20	0.2	15	0.1
66	0.05	20	0.3	15	0.1
53	0.05	20	0.4	15	0.1
47	0.05	20	0.5	15	0.1

[a] Ind. Variables Tested are those variables whose regression coefficients are tested against zero.
[b] R^2 is the amount that is added to the overall R-Squared value by these variables.
[c] Ind. Variables Controlled are those variables whose influence is removed from experimental error.

2.4.2 Sample Size Calculation for Logistic Regression

Based on the estimates of sample size obtained, an estimated total sample size of 13,714 patients was required for the logistic regression to detect a change in Prob(Y=1)

from the value of 0.100 at the mean of X to 0.109 when X is increased to one standard deviation above the mean ($\alpha = 0.05$; power=0.8) (Table 2.4.2). [99]

Table 2.4.2 Estimates of Sample Size for Logistic Regression Analysis

N	P_0 [a]	P_1 [b]	Odds Ratio [c]	R-Squared [d]
4,571	0.3	0.32	1.1	0.1
603	0.3	0.358	1.3	0.1
252	0.3	0.391	1.5	0.1
147	0.3	0.421	1.7	0.1
100	0.3	0.449	1.9	0.1
5,877	0.3	0.32	1.1	0.3
775	0.3	0.358	1.3	0.3
324	0.3	0.391	1.5	0.3
189	0.3	0.421	1.7	0.3
129	0.3	0.449	1.9	0.3
13,714	0.1	0.109	1.1	0.3
1,809	0.1	0.126	1.3	0.3
757	0.1	0.143	1.5	0.3
442	0.1	0.159	1.7	0.3
302	0.1	0.174	1.9	0.3

[a] P0 is the response probability at the mean of X.
[b] P1 is the response probability when X is increased to one standard deviation above the mean.
[c] Odds Ratio is the odds ratio when P1 is on top. That is, it is [P1/(1-P1)]/[P0/(1-P0)].
[d] R-Squared is the R^2 achieved when X is regressed on the other independent variables in the regression.

2.4.2 Sample Size Calculation for Cox Proportional Regression

Based on the estimates of sample size obtained, an estimated total sample size of 449 patients was required for the cox proportional hazards model ($\alpha = 0.05$; power=0.8) (Table 2.4.3). [100, 101]

Table 2.4.3 Estimates of Sample Size for Cox Proportional Regression Analysis

Sample Size (N)	Reg. Coef. (B) [a]	Event Rate (P) [b]	R-Squared X1 vs Other X's (R^2) [c]
349	0.5	0.1	0.1
88	1	0.1	0.1
39	1.5	0.1	0.1
□2	2	0.1	0.1
449	0.5	0.1	0.3
113	1	0.1	0.3
50	1.5	0.1	0.3
29	2	0.1	0.3
175	0.5	0.2	0.1
44	1	0.2	0.1
20	1.5	0.2	0.1
11	2	0.2	0.1
225	0.5	0.2	0.3
57	1	0.2	0.3
25	1.5	0.2	0.3
15	2	0.2	0.3

[a] B is the size of the regression coefficient to be detected
[b] P is the event rate.
[c] R^2 is the R-squared achieved when X1 is regressed on the other covariates.

2.5 SUMMARY OF STATISTICAL ANALYSES

Table 2.5.1: Summary of statistical analyses for each hypothesis

Objective/Hypothesis	Dependent Variable[1]	Independent Variable	Test
Objective 1			
To compare patient characteristics for chronically infected HCV patients who are treated with HCV drug therapies versus those who are not receiving treatment before and after matching patient cohorts by high dimensional propensity scoring.			
$H_{0\ (1a)}$: Mean age will not differ significantly between treated and untreated cohorts before or after matching.	Age	Treatment status	2 sample t-test
$H_{0\ (1b)}$: The proportion of patients in each gender category will not differ significantly between treated and untreated cohorts before or after matching.	Gender	Treatment status	Pearson Chi-square (x^2)
$H_{0\ (1c)}$: The proportion of patients in each race category will not differ significantly between treated and untreated cohorts before or after matching.	Race	Treatment status	Pearson Chi-square (x^2)
$H_{0\ (1d)}$: The mean comorbidity score will not differ significantly between treated and untreated cohort before or after matching.	Charlson Comorbidity Index (CCI) scores	Treatment status	2 sample t-test

Table 2.5.1 (Continued): Summary of statistical analyses for each hypothesis

Objective/Hypothesis	Dependent Variable[1]	Independent Variable	Test
$H_{0\ (1e)}$: The proportion of patients with at least one clinically relevant comorbidity will not differ significantly between treated and untreated cohort before or after matching.	≥1 comorbidity: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity	Treatment status	Pearson Chi-square (x^2)
$H_{0\ (1f)}$: The proportion of patients with at least one hospitalization will not differ significantly between treated and untreated cohort before or after matching.	≥1 hospitalization	Treatment status	Pearson Chi-square (x^2)
$H_{0\ (1g)}$: The mean number of baseline unique non-HCV-related prescription drugs will not differ significantly between treated and untreated cohort before or after matching.	Number of non-HCV-related prescription drugs	Treatment status	2 sample t-test
$H_{0\ (1h)}$: The mean number of baseline outpatient visits will not differ significantly between treated and untreated cohort before or after matching.	Number of outpatient visits	Treatment status	2 sample t-test
$H_{0\ (1i)}$: Baseline healthcare costs will not differ significantly between treated and untreated cohort before or after matching.	Healthcare costs[2]	Treatment status	2 sample t-test

Table 2.5.1 (Continued): Summary of statistical analyses for each hypothesis

Objective/Hypothesis	Dependent Variable[1]	Independent Variable	Test
$H_{0\ (1j)}$: The proportion of patients with non-cirrhotic disease (NCD), compensated cirrhosis (CC), end stage liver disease (ESLD), and liver transplant (LT) will not differ significantly between treated and untreated cohort before or after matching.	NCD, CC, ESLD, LT	Treatment status	Pearson Chi-square (x^2)
Objective 2 To compare healthcare costs and resource utilization for HCV patients who are treated with drug therapies versus those who are not receiving treatment during the 6 month follow-up period.			
$H_{0\ (2a)}$: Total all-cause healthcare costs for HCV patients will not differ significantly for treated versus untreated patients.	All-cause healthcare costs	Treatment status	2 sample t-test Generalized linear model (GLM)
$H_{0\ (2b)}$: Hospitalization costs and number of hospitalizations will not differ significantly for treated versus untreated patients.	Hospitalization costs Number of hospitalizations	Treatment status	2 sample t-test
$H_{0\ (2c)}$: Emergency room (ER) visit costs and number of visits will not differ significantly for treated versus untreated cohorts.	ER costs Number of ER visits	Treatment status	2 sample t-test 2 part generalized linear model (GLM) Zero-inflated poisson model
$H_{0\ (2d)}$: Outpatient costs and number of outpatient visits will not be significantly different between treated and untreated cohorts.	Outpatient costs Number of outpatient visits	Treatment status	2 sample t-test Generalized linear model (GLM) Negative binomial regression model

Table 2.5.1 (Continued): Summary of statistical analyses for each hypothesis

Objective/Hypothesis	Dependent Variable[1]	Independent Variable	Test
$H_{0\ (2e)}$: Prescription drug costs and number of prescription drugs will not be significantly higher for those treated versus untreated.	Prescription drug costs Number of prescription drugs	Treatment status	2 sample t-test Generalized linear model (GLM) Negative binomial regression model
Objective 3 To compare healthcare costs and resource utilization for HCV patients who are treated by liver disease severity during the 6 month follow-up period.			
$H_{0\ (3a)}$: In treated cohort, total all-cause healthcare costs will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	All-cause healthcare costs	NCD, CC, ESLD, LT	Mean, SD, Min, Max
$H_{0\ (3b)}$: In treated cohort, hospitalization costs and number of visits will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Hospitalization costs Number of hospitalizations	NCD, CC, ESLD, LT	Mean, SD, Min, Max
$H_{0\ (3c)}$: In treated cohort, emergency room visit costs and number of visits will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	ER costs Number of ER visits	NCD, CC, ESLD, LT	Mean, SD, Min, Max
$H_{0\ (3d)}$: In treated cohort, outpatient costs and number of visits will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Outpatient costs Number of outpatient visits	NCD, CC, ESLD, LT	Mean, SD, Min, Max
$H_{0\ (3e)}$: In treated cohort, prescription drug costs and number of prescriptions will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Prescription drug costs Number of prescription drugs	NCD, CC, ESLD, LT	Mean, SD, Min, Max

Table 2.5.1 (Continued): Summary of statistical analyses for each hypothesis

Objective/Hypothesis	Dependent Variable[1]	Independent Variable	Test
Objective 4 To compare healthcare costs and resource utilization for HCV patients who are untreated by liver disease severity during the 6 month follow-up period.			
$H_{0\ (4a)}$: In treated cohort, total all-cause healthcare costs will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	All-cause healthcare costs	NCD, CC, ESLD, LT	Mean, SD, Min, Max
$H_{0\ (4b)}$: In untreated cohort, hospitalization costs and number of visits will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Hospitalization costs Number of hospitalizations	NCD, CC, ESLD, LT	Mean, SD, Min, Max
$H_{0\ (4c)}$: In untreated cohort, emergency room visit costs and number of visits will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	ER costs Number of ER visits	NCD, CC, ESLD, LT	Mean, SD, Min, Max
$H_{0\ (4d)}$: In untreated cohort, outpatient costs and number of visits will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Outpatient costs Number of outpatient visits	NCD, CC, ESLD, LT	Mean, SD, Min, Max
$H_{0\ (4e)}$: In untreated cohort, prescription drug costs and number of prescriptions will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Prescription drug costs Number of prescription drugs	NCD, CC, ESLD, LT	Mean, SD, Min, Max

Table 2.5.1 (Continued): Summary of statistical analyses for each hypothesis

Objective/Hypothesis	Dependent Variable[1]	Independent Variable	Test
Objective 5 To compare HCV-related healthcare costs and resource utilization for HCV patients who are treated with drug therapies versus those who are not receiving treatment during the 6 month follow-up period.			
$H_{0\ (5a)}$: Total HCV-related healthcare costs for HCV patients will not differ significantly for treated versus untreated patients.	HCV-related healthcare costs	Treatment status	2 sample t-test Generalized linear model (GLM)
$H_{0\ (5b)}$: HCV-related hospitalization costs and number of hospitalizations will not differ significantly for treated versus untreated patients.	HCV-related hospitalization costs Number of HCV-related hospitalizations	Treatment status	2 sample t-test
$H_{0\ (5c)}$: HCV-related emergency room visit costs and number of visits will not differ significantly for treated versus untreated cohorts.	HCV-related ER costs Number of HCV-related ER visits	Treatment status	2 sample t-test 2 part generalized linear model (GLM) Zero-inflated poisson model
$H_{0\ (5d)}$: HCV-related outpatient costs and number of outpatient visits will not be significantly different between treated and untreated cohorts.	HCV-related outpatient costs Number of HCV-related outpatient visits	Treatment status	2 sample t-test Generalized linear model (GLM) Negative binomial regression model

Table 2.5.1 (Continued): Summary of statistical analyses for each hypothesis

Objective/Hypothesis	Dependent Variable[1]	Independent Variable	Test
Objective 6			
To compare adherence and discontinuation rates for chronically infected HCV patients on triple therapy versus dual therapy during the 6 month follow-up period.			
$H_{0\,(6a)}$: Mean medication adherence for HCV drug regimens will not differ significantly for patients on triple therapy compared to patients on dual therapy.	Proportion of days covered (PDC)	Dual or triple therapy	2 sample t-test
$H_{0\,(6b)}$: The proportion of patients who are adherent (PDC ≥ 80%) to HCV drug therapy will not differ significantly for patients on triple therapy compared to patients on dual therapy.	PDC ≥ 80% or ≥ 70%	Dual or triple therapy Treatment status	Pearson Chi-square (x^2) Logistic regression analysis
$H_{0\,(6c)}$: The proportion of patients who discontinue HCV therapy prematurely will not differ significantly for patients on triple therapy compared to patients on dual therapy.	Time until gap in medication of 1 fill	Dual or triple therapy Treatment status	Pearson Chi-square (x^2) Kaplan-Meier curves Cox proportional regression
Objective 7			
To compare healthcare costs and resource utilization for chronically infected HCV patients on triple therapy versus dual therapy during the 6 month follow-up period.			
$H_{0\,(7a)}$: Total all-cause healthcare costs for treated HCV patients will not differ significantly for patients on triple therapy versus dual therapy.	All-cause healthcare costs	Dual or triple therapy	Mean, SD, Min, Max

Table 2.5.1 (Continued): Summary of statistical analyses for each hypothesis

Objective/Hypothesis	Dependent Variable[1]	Independent Variable	Test
$H_{0\,(7b)}$: Hospitalization costs and number of hospitalizations will not differ significantly for treated patients on triple therapy versus dual therapy.	Hospitalization costs Number of hospitalizations	Dual or triple therapy	Mean, SD, Min, Max
$H_{0\,(7c)}$: Emergency room visit costs and number of visits will not differ significantly for treated patients on triple therapy compared to dual therapy.	ER costs Number of ER visits	Dual or triple therapy	Mean, SD, Min, Max
$H_{0\,(7d)}$: Outpatient costs and number of outpatient visits will not be significantly different between treated patients on triple versus dual therapy cohorts.	Outpatient costs Number of outpatient visits	Dual or triple therapy	Mean, SD, Min, Max
$H_{0\,(7e)}$: Prescription drug costs and number of prescription drugs will be significantly higher for those on triple therapy versus dual therapy.	Prescription drug costs Number of prescription drugs	Dual or triple therapy	Mean, SD, Min, Max
Objective 8 To compare HCV-related healthcare costs and resource utilization for chronically infected HCV patients on triple therapy versus dual therapy during the 6 month follow-up period			
$H_{0\,(8a)}$: Total HCV-related healthcare costs for treated HCV patients will not differ significantly for patients on triple therapy versus dual therapy.	HCV-related healthcare costs	Dual or triple therapy	Mean, SD, Min, Max

Table 2.5.1 (Continued): Summary of statistical analyses for each hypothesis

Objective/Hypothesis	Dependent Variable[1]	Independent Variable	Test
$H_{0\ (8b)}$: HCV-related hospitalization costs and number of hospitalizations will not differ significantly for treated patients on triple therapy versus dual therapy.	HCV-related hospitalization costs Number of HCV-related hospitalizations	Dual or triple therapy	Mean, SD, Min, Max
$H_{0\ (8c)}$: HCV-related emergency room visit costs and number of visits will not differ significantly for treated patients on triple therapy compared to dual therapy.	HCV-related ER costs Number of HCV-related ER visits	Dual or triple therapy	Mean, SD, Min, Max
$H_{0\ (8d)}$: HCV-related outpatient costs and number of outpatient visits will not be significantly different between treated patients on triple versus dual therapy cohorts.	HCV-related outpatient costs Number of HCV-related outpatient visits	Dual or triple therapy	Mean, SD, Min, Max
$H_{0\ (8e)}$: HCV-related prescription drug costs and number of prescription drugs will not be significantly different between treated patients on triple versus dual therapy cohorts.	HCV-related prescription drug costs Number of HCV-related	Dual or triple therapy	Mean, SD, Min, Max

Table 2.5.1 (Continued): Summary of statistical analyses for each hypothesis

Objective/Hypothesis	Dependent Variable[1]	Independent Variable	Test
Objective 9 To compare healthcare costs and resource utilization for HCV patients who are treated with drug therapies versus those who are not receiving treatment during the 1.5 year follow-up period.			
$H_{0\ (9a)}$: Total all-cause healthcare costs for HCV patients will not differ significantly for treated versus untreated patients.	All-cause healthcare costs	Treatment status	2 sample t-test Generalized linear model (GLM)
$H_{0\ (9b)}$: Hospitalization costs and number of hospitalizations will not differ significantly for treated versus untreated patients.	Hospitalization costs Number of hospitalizations	Treatment status	2 sample t-test
$H_{0\ (9c)}$: Emergency room (ER) visit costs and number of visits will not differ significantly for treated versus untreated cohorts.	ER costs Number of ER visits	Treatment status	2 sample t-test 2 part generalized linear model (GLM) Zero-inflated poisson model
$H_{0\ (9d)}$: Outpatient costs and number of outpatient visits will not be significantly different between treated and untreated cohorts.	Outpatient costs Number of outpatient visits	Treatment status	2 sample t-test Generalized linear model (GLM) Negative binomial regression model
$H_{0\ (9e)}$: Prescription drug costs and number of prescription drugs will not be significantly higher for those treated versus untreated.	Prescription drug costs Number of prescription drugs	Treatment status	2 sample t-test Generalized linear model (GLM) Negative binomial regression model

NCD=Non-Cirrhotic Disease, CC=Compensated Cirrhosis, ESLD=End-Stage Liver Disease, LT=Liver Transplant[1] Other covariates included: age, gender, race, presence of medically-relevant comorbidities, CCI, baseline number of prescription drugs and outpatient visits, and baseline costs (natural log transformed)
[2] Baseline costs were natural log-transformed

Chapter 3: Results

The results are presented for each of the objectives. The results are organized in the following sections:

- 3.1 Sample Selection
- 3.2 Baseline Characteristics
- 3.3 Healthcare Costs and Resource Utilization During 6 Month Follow-Up Period:
    - Treated vs. untreated comparison
    - By liver disease severity
    - HCV-related costs in treated vs. untreated
- 3.4 Adherence and Persistence
- 3.5 Healthcare Costs and Resource Utilization During 6-Month Follow-Up Period: Dual vs. Triple Therapy Comparison
- 3.6 Healthcare Costs and Resource Utilization During 18-Month Follow-Up Period: Treated vs. Untreated Comparison

3.1 SAMPLE SELECTION

There were a total of 24,032 patients identified with chronic HCV during the study period of 1/1/07 to 9/30/11. Of the chronic HCV population, 9.4% had evidence of receiving HCV treatment as ascertained by prescription drug claims. Of those treated, 11.2% were initiated on therapy with either telaprevir or boceprevir in 2011. After excluding patients for age (<18, or >63), and non-continuous enrollment for 6 months before and 6 months after the index date, 979 patients remained in the treated group. Of these, only 28 were on either telaprevir- or boceprevir-based triple therapy. A total of 7,713 patients remained in the untreated group; however, due to the multiple possible index dates (date of HCV-related ICD-9 codes), each patient-index date pair were treated as a separate unique patient for a sample size of 27,341.

After high dimensional propensity scoring, patients were matched 2:1 using greedy matching algorithm to lend to 939 patients in the treated group and 1878 patients in the untreated group. The patient selection scheme is shown in Figure 3.1.1. Although 3:1 matching was also considered, only 730 patients were matched successfully so the analysis proceeded with 2:1 matching.

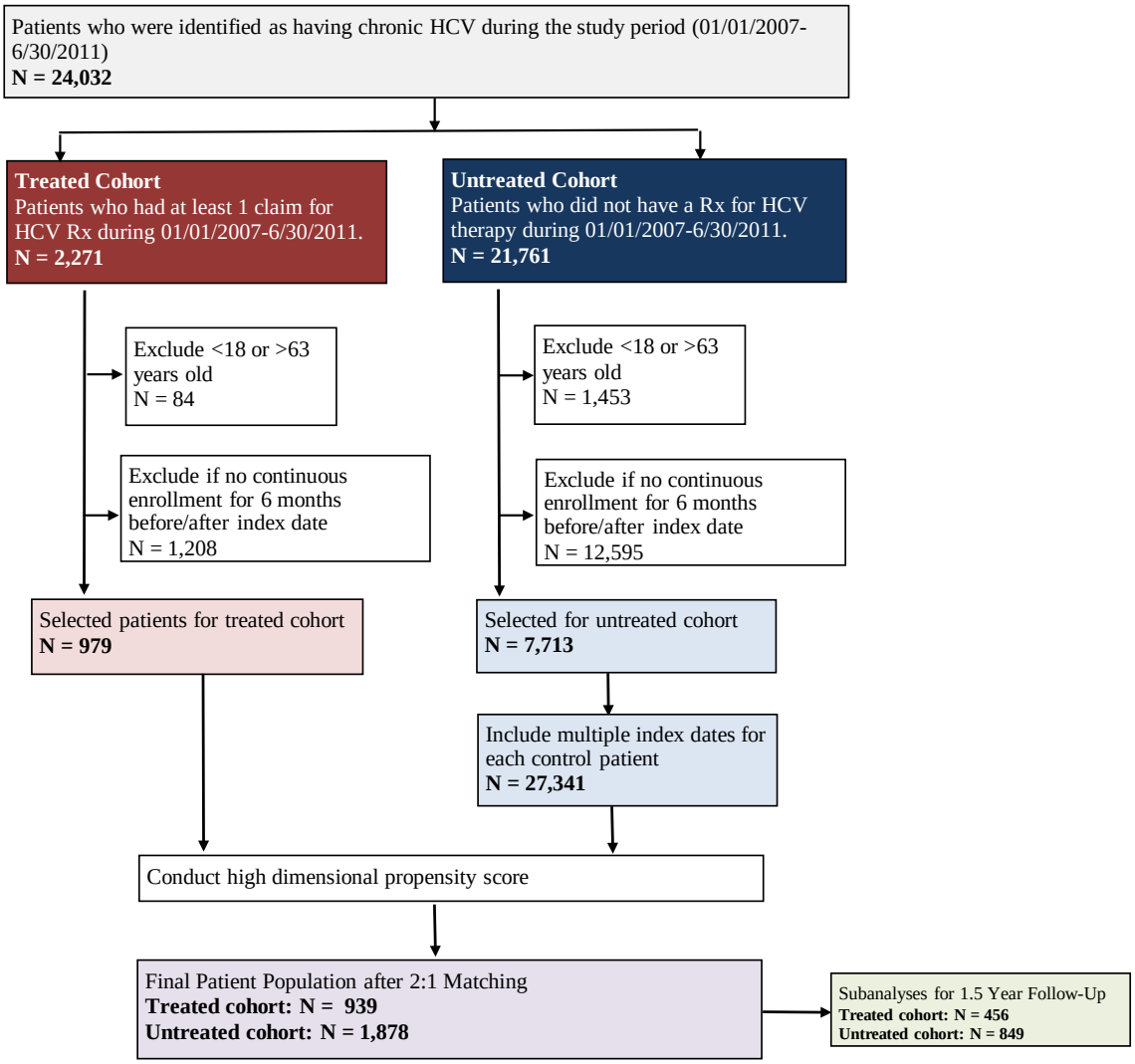


Figure 3.1.1 Patient Selection Scheme

3.2 BASELINE CHARACTERISTICS

3.2.1 Objective 1: To compare patient characteristics for chronically infected HCV patients who are treated with HCV drug therapies versus those who are not receiving treatment before and after matching patient cohorts by high dimensional propensity scoring

3.2.1.1 Age

$H_{0\ (1a)}$: In the unmatched cohort, the mean age in the treated group was 48.41 (SD 8.52) versus 50.37 (SD 7.65) in the untreated group ($p<0.001$). After matching, the mean age was 48.57 (SD 8.46) in the treated group and 48.65 (SD 8.65) in the untreated group ($p=0.865$). The standardized difference was also much smaller for the matched vs. unmatched cohorts (0.007 vs. 0.194, respectively). (Tables 3.2.1 and 3.2.2) The box plots for age for unmatched and matched samples are shown in Figure 3.2.1a.

$H_{0\ (1a)}$: Rejected for Unmatched Cohort
$H_{0\ (1a)}$: Not Rejected for Matched Cohort

3.2.1.2 Gender

$H_{0\ (1b)}$: There were 45.35% and 46.86% males in treated and untreated cohorts, respectively, before matching ($p=0.573$). After matching, the percentage was 46.11% and 44.78%, respectively ($p=0.682$). The standardized difference was smaller for the matched vs. unmatched groups (0.025 vs. 0.030, respectively). (Tables 3.2.1 and 3.2.2)

$H_{0\ (1b)}$: Not Rejected for Unmatched Cohort
$H_{0\ (1b)}$: Not Rejected for Matched Cohort

3.2.1.3 Race

$H_{0\ (1c)}$: Race was categorized by White vs. Non-white. The percentage of Whites were 50.87% vs. 42.42% in the treated and untreated cohorts prior to matching ($p=0.001$).

After matching the percentages were 49.95% and 51.28%, respectively (p=0.703). Standardized differences were 0.170 for the unmatched vs. 0.025 for the matched groups. (Tables 3.2.1 and 3.2.2)

$H_{0\ (1c)}$: Rejected for Unmatched Cohort
$H_{0\ (1c)}$: Not Rejected for Matched Cohort

3.2.1.4 Comorbidities

$H_{0\ (1d)}$: In the unmatched group, the mean CCI was 0.36 (SD 0.74) and 0.42 (0.92) in the treated and untreated cohorts (standardized difference=0.061; p=0.045). In the matched group, the mean scores were 0.36 (SD 0.75) and 0.37 (SD 0.79) (standardized difference=0.016; p=0.706). (Tables 3.2.1 and 3.2.2)

$H_{0\ (1d)}$: Rejected for Unmatched Cohort
$H_{0\ (1d)}$: Not Rejected for Matched Cohort

$H_{0\ (1e)}$: Another baseline covariate was measured by the presence of one of the following comorbidities: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity. In the unmatched sample, 16.24% had at least one of these comorbidities compared to 18.03% (p=0.228) in the treated and untreated cohorts, respectively. After matching, 16.61% of treated patients and 17.84% of untreated patients had at least one of the relevant comorbidities (p=0.498). The standardized differences were 0.048 and 0.034 in unmatched and matched groups, respectively. (Tables 3.2.1 and 3.3.2)

$H_{0\ (1e)}$: Not Rejected for Unmatched Cohort
$H_{0\ (1e)}$: Not Rejected for Matched Cohort

3.2.1.5 Resource utilization

$H_{0\ (1f)}$: The percentage of patients with at least 1 hospitalization was significantly lower in the treated vs. untreated cohorts of the unmatched sample (0.61% vs. 3.18%, respectively, p<0.001). However, in the matched sample, there was no significant difference (0.63% vs. 0.48%, p=0.585).

$H_{0\ (1f)}$: Rejected for Unmatched Cohort
$H_{0\ (1f)}$: Not Rejected for Matched Cohort

$H_{0\ (1g)}$: In the unmatched sample, the mean number of baseline unique non-HCV-related prescription drugs was 19.64 (SD 16.61) in the treated vs. 15.72 (SD 22.63) in the untreated group (p<0.001). In the matched sample, the mean number of baseline prescription drugs was 19.75 (SD 16.79) vs. 20.98 (SD 15.44) (p=0.055). Standardized differences were 0.170 and 0.061 in unmatched and matched samples, respectively. The box plots of the mean numbers of prescription drugs are displayed in Figure 3.2.1b.

$H_{0\ (1g)}$: Rejected for Unmatched Cohort
$H_{0\ (1g)}$: Not Rejected for Matched Cohort

$H_{0\ (1h)}$: The number of outpatient visits was similar in both treated and untreated groups of the unmatched sample (7.77, SD 10.57 vs. 7.41, SD 12.17, respectively; p=0.353), and for the matched sample (7.88, SD 10.70 vs. 8.24, SD 8.29, respectively; p=0.355). The standardized difference was similar in both samples: 0.027 in the unmatched sample and 0.029 in the matched sample. (Tables 3.2.1 and 3.2.2) Figure 3.2.1c shows the box plots for mean number of outpatient visits at baseline.

$H_{0\ (1h)}$: Not Rejected for Unmatched Cohort
$H_{0\ (1h)}$: Not Rejected for Matched Cohort

3.2.1.6 Baseline Healthcare Costs

$H_{0\ (1i)}$: Baseline healthcare costs were evaluated after natural log transformation. These baseline costs totaled the outpatient, inpatient, and prescription drug costs during the 6 month baseline period. The transformed baseline costs were significantly different between treated and untreated groups ($8.57, SD 0.52 vs. $6.25, SD 2.14, respectively; $p<0.001$). In the matched group, the transformed baseline costs were similar between groups ($8.54, SD 0.49 vs. $8.57, SD 0.80, respectively; $p=0.365$). The standardized differences were 1.451 in the unmatched cohort and 0.034 in the matched cohort. (Tables 3.2.1 and 3.2.2) The box plots of the transformed baseline costs are shown in Figure 3.2.1d.

$H_{0\ (1g)}$: Rejected for Unmatched Cohort
$H_{0\ (1g)}$: Not Rejected for Matched Cohort

3.2.1.7 Liver Disease Severity

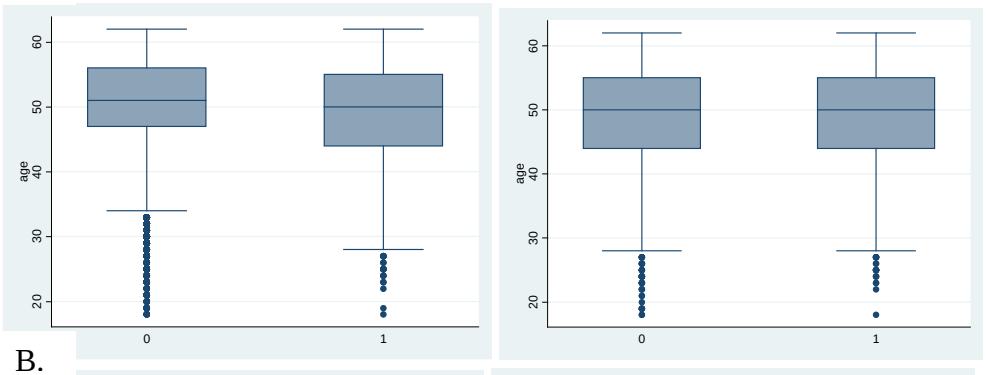
In the unmatched sample, 2.66% of patients had non-cirrhotic disease (NCD), no paitients had compensated cirrhosis (CC), and 97.34% of patients had end stage liver disease (ESLD), and 0.10% (1 patient) had a prior liver transplant in the treated cohort. In the untreated cohort, the corresponding percentages were 21.33%, 8.62%, 0.05%, and 0.18%. There was a significant difference between the proportions of those with ESLD and NCD. In the matched sample, there were no significant differences between proportions of NCD, CC, ESLD and LT between groups: 2.77% and 1.92%, 0% and 0%, 97.23% and 98.08%, 0.11% and 0.05% of treated and untreated patients, respectively, had evidence of the corresponding liver disease severity indicators. (Tables 3.2.1 and 3.2.2) Since 98% of patients had ESLD, liver disease severity was not considered in the regression analyses as a covariate.

$H_{0\ (1j)}$: Rejected for Unmatched Cohort
$H_{0\ (1j)}$: Not Rejected for Matched Cohort

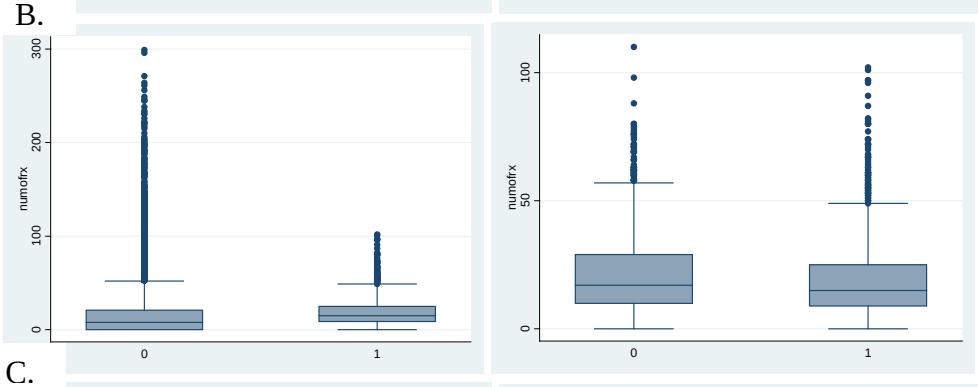
3.2.1.7 Balance Between Matched and Unmatched Samples

The comparison between the significance tests and standardized differences of the baseline covariates indicate that the high dimensional propensity scoring resulted in a better balance between treated and untreated cohorts. In the unmatched sample, there were significant differences in the proportion of patients with at least one inpatient visit, with ESLD, and NCD. In addition, there were significant differences in the continuous covariates of age, CCI, number of baseline prescription drugs, and baseline costs (natural log of costs). In contrast, after matching, there were no significant differences between groups and for any of the covariates. The baseline number of unique medications was approaching significance at p=0.055, but as shown by Figure 3.2.1c and standardized differences, the matched sample was more balanced than the unmatched sample.

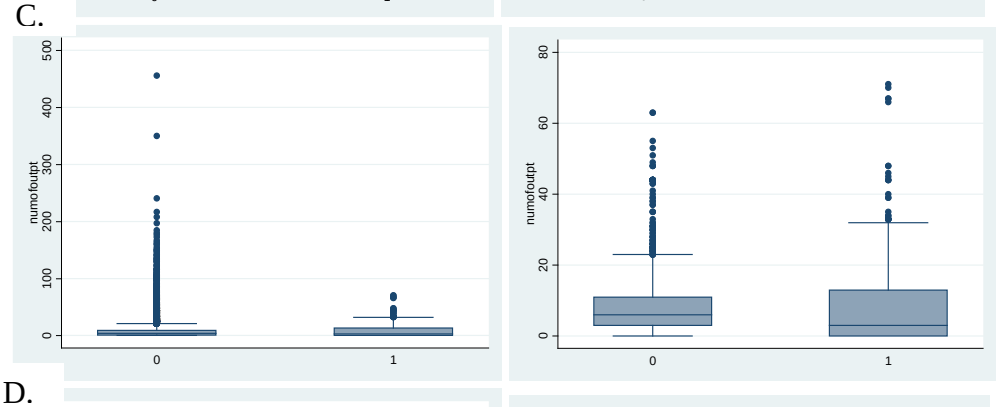
A.



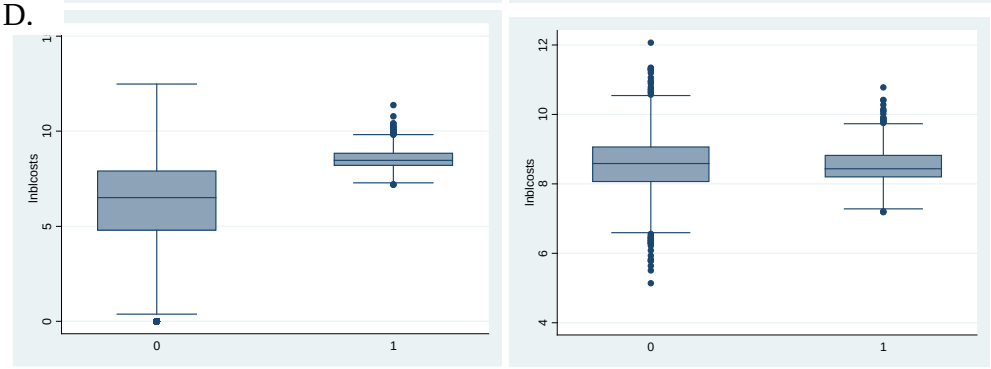
B.



C.



D.



A. Age, B. Number of Prescription Drugs, C. Number of Outpatient Visits, D. Natural Log of Baseline Costs

Figure 3.2.1: Box Plots of Covariates in Unmatched (Left) and Matched (Right) Group

Table 3.2.1: Baseline Characteristics of Unmatched Group

Categorical Variables	Treated					Untreated				Standardized Difference	p-value
	n	Percent	SE	95% CI		n	Percent	SE	95% CI		
Gender											
- Male	444	45.35%	0.016	0.515-0.578		12813	46.86%	0.003	0.525-0.537	0.030	0.573
Race											
- White	498	50.87%	0.016	0.46-0.523		11599	42.42%	0.003	0.57-0.582	0.170	0.001
Comorbidities											
-≥ 1 Comorbidit(ies)	159	16.24%	0.012	0.814-0.861		4930	18.03%	0.002	0.815-0.824	0.048	0.228
Resource Utilization											
-≥1 Inpatient Visit(s)	6	0.61%	0.002	0.989-0.999		869	3.18%	0.001	0.966-0.97	0.189	<0.001
Liver Disease Severity											
- CC	0	0.00%	0.000			14	0.05%	0.000	0.999-1	0.032	0.479
- ESLD	953	97.34%	0.005	0.016-0.037		21495	78.62%	0.002	0.209-0.219	0.601	<0.001
- LT	1	0.10%	0.001	0.997-1.001		48	0.18%	0.000	0.998-0.999	0.020	0.588
- NCD	26	2.66%	0.005	0.963-0.984		5832	21.33%	0.002	0.782-0.792	0.600	<0.001
Continuous Variables	**Treated**					**Untreated**				**Standardized Difference**	**p-value**
	Mean	**SD**	**Min**	**Max**		**Mean**	**SD**	**Min**	**Max**		
Age											
-Age	48.41	8.52	18	62		50.37	7.65	18	62	0.194	<0.001
Comorbidities											
- Charlson Comorbidity Index	0.36	0.74	0	7		0.42	0.92	0	9	0.061	0.045
Resource Utilization											
Number of Unique Medications	19.64	16.61	0	102		15.72	22.63	0	299	0.170	<0.001
Number of Outpatient Visits	7.77	10.57	0	71		7.41	12.17	0	456	0.027	0.353
Costs											
All-Cause Costs (LN)	8.57	0.52	7.19	11.38		6.25	2.14	0	12.4774	1.451	<0.001

Table 3.2.2: Baseline Characteristics of Matched Group

Categorical Variables	Treated					Untreated				Standardized Difference	p-value
	n	Percent	SE	95% CI		N	Percent	SE	95% CI		
Gender											
- Male	433	46.11%	0.016	0.507-0.571		841	44.78%	0.011	0.529-0.574	0.025	0.682
Race											
- White	469	49.95%	0.016	0.469-0.533		963	51.28%	0.012	0.465-0.51	0.026	0.703
Comorbidities											
≥ 1 Comorbidit(ies)	156	16.61%	0.012	0.81-0.858		335	17.84%	0.009	0.804-0.838	0.034	0.498
Resource Utilization											
≥1 Inpatient Visit(s)	6	0.64%	0.003	0.989-0.999		9	0.48%	0.002	0.992-0.998	0.022	0.585
Liver Disease Severity											
- CC	0	0.00%				0	0.00%				
- ESLD	913	97.23%	0.005	0.017-0.038		1842	98.08%	0.003	0.013-0.025	0.057	0.878
- LT	1	0.11%	0.001	0.997-1.001		1	0.05%	0.001	0.998-1.001	0.019	0.617
- NCD	26	2.77%	0.005	0.962-0.983		36	1.92%	0.003	0.975-0.987	0.057	0.156
Continuous Variables	**Treated**					**Untreated**				**Standardized Difference**	**p-value**
	Mean	**SD**	**Min**	**Max**		**Mean**	**SD**	**Min**	**Max**		
Age											
-Age	48.57	8.46	18	62		48.65	8.72	18	62	0.007	0.865
Comorbidities											
- Charlson Comorbidity Index	0.36	0.75	0	7		0.37	0.79	0	5	0.014	0.706
Resource Utilization											
Number of Unique Medications	19.75	16.79	0	102		20.98	15.44	0	110	0.061	0.055
Number of Outpatient Visits	7.88	10.70	0	71		8.24	8.29	0	63	0.029	0.355
Costs											
All-Cause Costs (LN)	8.63	0.49	7.23	10.82		8.66	0.80	5.26	12.11	0.036	0.346

3.2.1.8 Predictors of Treatment

The following variables were independently associated with lower odds of being treated: age (OR=0.985), male gender (OR=0.733), at least one inpatient visit (OR=0.209), number of unique medications (OR=0.950), and number of outpatient visits (OR=0.954). The variables independently associated with higher odds of being treated include: white race (OR=1.766), and higher baseline costs (OR=4.267). (Table 3.2.3)

Table 3.2.3: Logistic Regression Model Evaluating Predictors of Treatment

Variable	Odds Ratio	Standard Error	z	p-value	95% Confidence Interval	
Age	0.985	0.004	-3.520	<0.001	0.977	0.993
Gender (Male vs. Female)	0.733	0.053	-4.290	<0.001	0.636	0.845
Race (White vs. Non-White)	1.766	0.128	7.860	<0.001	1.533	2.036
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	1.036	0.118	0.310	0.758	0.829	1.295
CCI	0.946	0.051	-1.010	0.311	0.851	1.053
Number of Unique Medications	0.950	0.002	-20.490	<0.001	0.945	0.955
Number of Outpatient Visits	0.954	0.004	-11.150	<0.001	0.946	0.962
≥1 Inpatient Visit (Yes vs. No)	0.209	0.089	-3.670	<0.001	0.091	0.482
Liver disease severity[2] - NCD vs. CC	0.392	0.417	-0.880	0.379	0.048	3.164
- ESLD vs. CC	4.937	5.154	1.530	0.126	0.638	38.204
Baseline Costs[3]	4.267	0.172	36.020	<0.001	3.943	4.618
Intercept	0.000	0.000	-12.380	<0.001	0.000	0.000

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] NCD=Non-Cirrhotic Disease, CC=Compensated Cirrhosis, ESLD=End Stage Liver Disease; CC is the reference

[3] Baseline costs were natural log transformed

3.3 HEALTHCARE COSTS AND RESOURCE UTILIZATION DURING 6-MONTH FOLLOW-UP PERIOD: TREATED VS. UNTREATED COHORTS

3.3.1 Objective 2: To compare healthcare costs and resource utilization for HCV patients who are treated with drug therapies versus those who are not receiving treatment

3.3.1.1 All-Cause Healthcare Costs

$H_{0\ (2a)}$: Total mean healthcare costs during the 6-month follow-up period were compared for treated vs. untreated patients in unadjusted and adjusted analyses. The unadjusted mean costs were $18,322 (SD $11,406) in the treated group, and significantly less in the untreated group ($7,655, SD $10,711; $p<0.001$). (Table 3.3.8) After adjusting for baseline covariates of age, gender, race, presence of medically-relevant comorbidities, CCI, therapy type, baseline number of prescription drugs and outpatient visits, and baseline costs (natural log transformed), the differences remained significant when evaluated by a generalized linear model (GLM). This model indicated that the adjusted mean costs for all-cause services were $20,998 for patients in the treated cohort, $13,960 higher the mean for those in the untreated group (mean=$7,038) ($p<0.001$). (Table 3.3.1) Appendix B1 shows the results of the regression model with all predictors.

$H_{0\ (2a)}$: Rejected

Table 3.3.1: A Generalized Linear Model (GLM) Adjusted All-Cause Costs (A) and Differences (B) among Cohorts while Controlling for Covariates (N=2,817)

(A) A GLM model adjusted all-cause costs

All-Cause Costs	Mean	SE	Z	p-value	95% Confidence Interval	
Untreated	$7,037.64	120.70	58.31	<0.001	$6,801.08	$7,274.20
Treated	$20,998.02	461.24	45.52	<0.001	$20,094.00	$21,902.03

(B) Differences in adjusted all-cause costs between treated and untreated cohorts

	Mean	SE	Z	p-value	95% Confidence Interval	
Difference in All-Cause Costs	$13,960.38	457.94	30.49	<0.001	$13,062.84	$14,857.92

3.3.1.2 Inpatient Costs and Utilization

$H_{0\ (2b)}$: The costs of inpatient services was $49 (SD $645) in the treated group. None of the patients in the untreated cohort had a hospitalization, leading to $0 inpatient costs. The differences between groups were statistically significant with $p<0.001$.

There were only 6 patients experiencing at least one inpatient visit in the treated group vs. 0 patients with inpatient services in the untreated group ($p<0.001$). The small number of inpatient hospitalizations did not allow for adjusted analyses.

$H_{0\ (2b)}$: Rejected for costs
$H_{0\ (2b)}$: Rejected for utilization

3.3.1.3 Emergency Room (ER) Costs and Utilization

$H_{0\ (2c)}$: ER visit costs were lower in the treated vs. untreated cohorts. The mean costs for ER services was $97 (SD $319) in the treated patients and $137 (SD $414) in the untreated patients ($p<0.001$). After adjusting for covariates in a GLM analysis, the mean costs for ER services in the treated cohort were $90 (SE $9) vs. $144 (SE $11) in the

untreated cohort. The difference of -$55 (treated vs. untreated) was significant (p<0.001). (Table 3.3.2) A two-part generalized linear model was used due to the large number of 0 values.

The numbers of patients who had at least one ER visit during the 6-month follow-up period were 272 patients (29.0%) in the treated cohort and 532 patients (28.3%) in the untreated cohort. In contrast to ER costs, the mean numbers of ER visits were statistically higher in the treated vs. untreated cohorts. The mean number of ER visits was 1.21 (SD 2.77) in treated patients compared to 0.57 (SD 1.30) in untreated patients (p<0.001). In an adjusted zero-inflated poisson regression model, the difference in the number of ER visits was 0.62 (p<0.001). (Table 3.3.3) Zero-inflated poisson model was chosen to compare adjusted counts due to the large number of 0 values. Appendices B2 and B3 show the results of the regression models with all predictors.

$H_{0\ (2c)}$: Rejected for costs
$H_{0\ (2c)}$: Rejected for utilization

Table 3.3.2: A Two-Part Generalized Linear Model (GLM) Adjusted ER Costs (A) and Differences (B) among Cohorts while Controlling for Covariates (N=2,817)

(A) A GLM model adjusted ER costs

ER Costs	Mean	SE	z	p-value	95% Confidence Interval	
Untreated	$144.41	10.84	13.32	<0.001	$123.17	$165.66
Treated	$89.64	8.76	10.23	<0.001	$72.47	$106.81

(B) Differences in adjusted ER costs between treated and untreated cohorts

	Mean	SE	z	p-value	95% Confidence Interval	
Difference in ER Costs	-$54.77	13.85	-3.95	<0.001	-$81.93	-$27.62

Table 3.3.3: A Zero-Inflated Poisson Model Adjusted Number of ER Visits (A) and Differences (B) among Cohorts while Controlling for Covariates (N=2,817)

(A) A zero-inflated poisson model adjusted number of ER visits

Number of ER Visits	Mean	SE	Z	p-value	95% Confidence Interval	
Untreated	0.55	0.02	23.44	<0.001	0.50	0.59
Treated	1.17	0.06	20.89	<0.001	1.06	1.27

(B) Difference in adjusted number of ER visits in treated and untreated cohorts

	Mean	SE	z	p-value	95% Confidence Interval	
Difference in Number of ER Visits	0.62	0.06	11.06	0.00	0.51	0.73

3.3.1.4 Outpatient Costs and Utilization

$H_{0\ (2d)}$: In the treated group, the mean cost for outpatient services was $620 (SD $947) compared to $1,782 (SD $2,974) in the untreated group (p=0.010). After adjusting for baseline covariates in a GLM, the mean adjusted cost for outpatient services was $890 vs. $1,528 in treated vs. untreated patients, respectively (difference=$638). (Table 3.3.4)

The majority of patients in both groups had at least one outpatient visit. Most patients had at least one outpatient visit: 94.0% and 99.1% of patients had at least 1 outpatient visit treated and untreated cohorts, respectively. The mean numbers of outpatient visits were significantly higher in the treated vs. untreated cohorts (6.53, SD 4.88 vs. 4.69, SD 4.42; p<0.001). In the adjusted analysis, the difference remained significant; the model estimated 2.45 (SE 0.21) more visits in treated vs. untreated patients. (Table 3.3.5) Due to the small number of zero values, a negative binomial regression model was chosen to run the comparison. Appendices B4 and B5 show the results of the regression models with all predictors.

$H_{0\ (2d)}$: Rejected for costs
$H_{0\ (2d)}$: Rejected for utilization

Table 3.3.4: A Generalized Linear Model (GLM) Adjusted Outpatient Service Costs (A) and Differences (B) among Cohorts while Controlling for Covariates (N=2,817)

(A) A GLM model adjusted outpatient service costs

Outpatient Costs	**Mean**	**SE**	**z**	**p-value**	**95% Confidence Interval**	
Untreated	$1,527.94	48.90	31.25	<0.001	$1,432.11	$1,623.78
Treated	$890.19	49.61	17.94	<0.001	$792.96	$987.43

(B) Difference in adjusted outpatient service costs in treated and untreated cohorts

	Mean	**SE**	**z**	**p-value**	**95% Confidence Interval**	
Difference in Outpatient Costs	-$637.75	65.31	-9.76	<0.001	-$765.76	-$509.74

Table 3.3.5: A Negative Binomial Regression Model Adjusted Number of Outpatient Visits (A) and Differences (B) among Cohorts while Controlling for Covariates (N=2,817)

(A) A negative binomial regression model adjusted number of outpatient visits

Number of Outpatient Visits	Mean	SE	Z	p-value	95% Confidence Interval	
Untreated	4.57	0.09	52.47	<0.001	4.40	4.74
Treated	7.01	0.19	36.32	<0.001	6.64	7.39

(B) Difference in adjusted number of outpatient visits in treated and untreated cohorts

	Mean	SE	z	p-value	95% Confidence Interval	
Difference in Number of Outpatient Visits	2.45	0.21	11.78	<0.001	2.04	2.85

3.3.1.5 Prescription Drug Costs and Utilization

$H_{0\,(2e)}$: Mean prescription drug costs during the follow-up period were significantly higher in the treated ($17,653, SD $11,204) vs. untreated ($5,873, SD $10,796) cohorts ($p<0.001$). After adjusting for relevant covariates, the mean costs in the treated cohort were estimated to be $23,458, $18,341 higher than mean costs in the untreated cohort. (Table 3.3.6)

The mean number of prescription drugs was also higher in the treated patients compared to untreated patients (30.28, SD 20.65 vs. 23.89, SD 19.33, respectively; $p<0.001$). In the adjusted analysis, the mean number of prescriptions drugs in the treated cohort was 34.49 (SE 0.78) compared to 24.46 (SE 0.35) in the untreated cohort, resulting in a mean difference of 10.03 prescriptions ($p<0.001$). (Table 3.3.7) Appendices B6 and B7 show the results of the regression models with all predictors.

$H_{0\ (2e)}$: Rejected for costs
$H_{0\ (2e)}$: Rejected for utilization

Table 3.3.6: A Generalized Linear Model (GLM) Adjusted Prescription Drug Costs (A) and Differences (B) among Cohorts while Controlling for Covariates (N=2,817)

(A) A GLM model adjusted prescription drug costs

Prescription Drug Costs	Mean	SE	z	p-value	95% Confidence Interval	
Untreated	$5,116.81	122.64	41.72	<0.001	$4,876.43	$5,357.18
Treated	$23,457.91	767.78	30.55	<0.001	$21,953.09	$24,962.74

(B) Difference in adjusted prescription drug costs in treated and untreated cohorts

	Mean	SE	z	p-value	95% Confidence Interval	
Difference in Prescription Drug Costs	$18,341.11	767.38	23.9	<0.001	$16,837.06	$19,845.15

Table 3.3.7: A Negative Binomial Regression Model Adjusted Number of Prescription Drugs (A) and Differences (B) among Cohorts while Controlling for Covariates (N=2,817)

(A) A negative binomial regression model adjusted number of prescription drugs

Prescription Drugs	Mean	SE	z	p-value	95% Confidence Interval	
Untreated	24.46	0.35	69.91	<0.001	23.77	25.14
Treated	34.49	0.78	44.09	<0.001	32.95	36.02

(B) Difference in adjusted number of prescription drug in treated and untreated cohorts

	Mean	SE	z	p-value	95% Confidence Interval	
Difference in Number of Prescription Drugs	10.03	0.76	13.24	<0.001	8.54	11.51

Table 3.3.8: Unadjusted Healthcare Costs in Treated and Untreated Cohorts

	Treated					Untreated				
Type of Cost	**Mean**	**Standard Deviation**	**Min**	**Max**		**Mean**	**Standard Deviation**	**Min**	**Max**	**p-value**
Total All-Cause Costs	$18,322	$11,406	$1,529	$98,522		$7,655	$10,711	$5	$185,821	<0.001
Inpatient Costs	$49	$645	$0	$12,178		$0	$0	$0	$0	<0.001
Emergency Room Costs	$97	$319	$0	$5,635		$137	$414	$0	$4,467	<0.001
Outpatient Costs[1]	$620	$947	$0	$15,707		$1,782	$2,974	$0	$27,437	0.010
Rx Costs	$17,653	$11,204	$1,013	$98,264		$5,873	$10,796	$0	$185,767	<0.001

[1]Outpatient costs are inclusive of emergency visit costs

Table 3.3.9: Unadjusted Healthcare Utilization in Treated and Untreated Cohorts

	Treated					Untreated				
Type of Service	**Mean**	**Standard Deviation**	**Min**	**Max**		**Mean**	**Standard Deviation**	**Min**	**Max**	**P-value**
Inpatient	0.01	0.08	0.00	1.00		0.00	NA	NA	NA	<0.001
Emergency Room	1.21	2.77	0.00	21.00		0.57	1.30	0.00	13.00	<0.001
Outpatient[1]	6.53	4.88	0.00	34.00		4.69	4.42	0.00	50.00	<0.001
Prescription Drugs	30.28	20.65	2.00	127.00		23.89	19.33	0.00	255.00	<0.001

[1]Outpatient visits are inclusive of emergency room visits

3.3.2 Objective 3: To compare healthcare costs and resource utilization for HCV patients who are treated by liver disease severity

3.3.2.1 All-Cause Healthcare Costs

$H_{0\ (3a)}$: In the treated group, 26 (2.8%) of the patients had ICD-9 codes indicating NCD, none of the patients had codes indicative of compensated cirrhosis and those with cirrhosis also had codes indicating ESLD. 912 (97.1%) had ICD-9 codes indicating ESLD, and 1 patient had a prior liver transplant. Since the majority of patients fell into the ESLD category, statistical comparisons by liver disease categories were not possible.

In the treated cohort, the average total all-cause healthcare costs for those with NCD were $22,318 (SD $17,096) vs. $18,121 (SD $10,885) for ESLD. The total healthcare costs for the one patient with liver transplant were $97,869. (Table 3.3.10)

$H_{0\ (3a)}$: NA

3.3.2.2 Inpatient Costs and Utilization

$H_{0\ (3b)}$: There were no inpatient costs and visits for those with NCD or prior liver transplant. For those with ESLD, there were 6 hospitalizations in the treated cohort with mean costs of $50 (SD $654). (Tables 3.3.10 and 3.3.11)

$H_{0\ (3b)}$: NA

3.3.2.3 Emergency Room (ER) Costs and Utilization

$H_{0\ (3c)}$: The mean costs due to ER services were $81 (SD $182) for patients with NCD vs. $98 (SD $322) for patients with ESLD. There were no ER costs and visits for the patient with a prior liver transplant. (Table 3.3.10)

The numbers of ER visits during the 6-month follow-up period was 0.69 (SD 1.46) in patients with NCD vs. 1.22 (SD 2.80) in patients with ESLD. (Table 3.3.11)

$H_{0\ (3c)}$: NA

3.3.2.4 Outpatient Costs and Utilization

$H_{0\ (3d)}$: The mean outpatients costs were $454 (SD $568) for those with NCD, $625 (SD $956) for those with ESLD, and $614 for the patient with prior liver transplant. (Table 3.3.10)

The mean numbers of outpatient visits were 4.46 (SD 3.82) for those with NCD, 96.58 (SD 4.88) for those with ESLD, and 18 visits for the patient with prior liver transplant. (Table 3.3.11)

$H_{0\ (3d)}$: NA

3.3.2.5 Prescription Drugs Costs and Utilization

$H_{0\ (3e)}$: The mean prescription drug costs were highest in the patient with prior liver transplant $97,256. In the patients with NCD, mean prescription drug costs were $21,865 (SD $16,954). In patients with ESLD, mean prescription drug costs were $17,446 (SD $10,671). (Table 3.3.10)

The mean numbers of prescription drugs were 36.69 (SD 22.81), 30.08 (SD 20.57), and 48, in patients with NCD, ESLD, and prior liver transplant, respectively. (Table 3.3.11)

$H_{1\ (30)}$: NA

Table 3.3.10: Mean Costs by Liver Disease Severity in the Treated Cohort

Type of Cost	NCD				
	n	Mean	Standard Deviation	Min	Max
Total All-Cause Costs	26	$22,318	$17,096	$5,374	$80,771
Inpatient Costs	26	$0	$0	$0	$0
ER Costs	26	$81	$182	$0	$749
Outpatient Costs[1]	26	$454	$568	$0	$2,293
Prescription Drug Costs	26	$21,865	$16,954	$4,984	$79,459
Type of Cost	**ESLD**				
	n	**Mean**	**Standard Deviation**	**Min**	**Max**
Total All-Cause Costs	912	$18,121	$10,885	$1,529	$98,522
Inpatient Costs	912	$50	$654	$0	$12,178
Emergency Room Costs	912	$98	$322	$0	$5,635
Outpatient Costs[1]	912	$625	$956	$0	$15,707
Prescription Drug Costs	912	$17,446	$10,671	$1,013	$98,264
Type of Cost	**LT**				
	n	**Mean**	**Standard Deviation**	**Min**	**Max**
Total All-Cause Costs	1	$97,869	NA	$97,869	$97,869
Inpatient Costs	1	$0	NA	$0	$0
Emergency Room Costs	1	$0	NA	$0	$0
Outpatient Costs[1]	1	$614	NA	$614	$614
Prescription Drug Costs	1	$97,256	NA	$97,256	$97,256

[1]Outpatient costs are inclusive emergency room costs

Table 3.3.11: Mean Resource Utilization by Liver Disease Severity in the Treated Cohort

Type of Service	NCD				
	n	Mean	Standard Deviation	Min	Max
Inpatient	26	0.00	0.00	0.00	0.00
Emergency Room	26	0.69	1.46	0.00	5.00
Outpatient[1]	26	4.46	3.82	0.00	17.00
Prescription Drugs	26	36.69	22.81	13.00	88.00
Type of Service	**ESLD**				
	n	**Mean**	**Standard Deviation**	**Min**	**Max**
Inpatient	912	0.01	0.08	0.00	1.00
Emergency Room	912	1.22	2.80	0.00	21.00
Outpatient[1]	912	6.58	4.88	0.00	34.00
Prescription Drugs	912	30.08	20.57	2.00	127.00
Type of Service	**LT**				
	n	**Mean**	**Standard Deviation**	**Min**	**Max**
Inpatient	1	0.00	NA	0.00	0.00
Emergency Room	1	0.00	NA	0.00	0.00
Outpatient[1]	1	18.00	NA	18.00	18.00
Prescription Drugs	1	48.00	NA	48.00	48.00

[1]Outpatient visits are inclusive of emergency room visits

3.3.3 Objective 4: To compare healthcare costs and resource utilization for HCV patients who are not treated by liver disease severity

3.3.3.1 All-Cause Healthcare Costs

$H_{1\ (4a)}$: In the untreated group, 36 (1.9%) patients had NCD, no patients had compensated cirrhosis, 1841 (98.0%) had ESLD, and 1 patient had a prior liver transplant as indicated by ICD-9 codes. Since the majority of patients fell into the ESLD category, statistical comparisons by liver disease categories were not possible.

In the untreated cohort, the mean total all-cause healthcare costs were $17,385 (SD $31,557) for those with NCD, $7,461 (SD 9,807) for those with ESLD, and $14,133 for the one patient with prior liver transplant. (Table 3.3.12)

$H_{1\ (4a)}$: NA

3.3.3.2 Inpatient Costs and Utilization

$H_{1\ (4b)}$: There were no inpatient visits for any patients in the untreated cohort. (Tables 3.3.12 and 3.3.13)

$H_{1\ (4b)}$: NA

3.3.3.3 Emergency Room (ER) Costs and Utilization

$H_{1\ (4c)}$: Mean ER costs were highest in patients with ESLD ($118, SD $343) and lowest in the patient with prior liver transplant ($63). ER costs were $137 (SD $415) in patients with NCD. (Table 3.3.12)

Mean numbers of ER visits were 0.53 (SD 1.11) for those with NCD, 0.57 (SD 1.63) for those with ESLD, and 2 visits for the patient with a prior liver transplant. (Table 3.3.13)

$H_{1\ (4c)}$: NA

3.3.3.4 Outpatient Costs and Utilization

$H_{1\ (4d)}$: The mean costs for outpatient services were $423 (SD $867), $1,810 (SD $2,995), and $63 for patients with NCD, ESLD, and prior liver transplant, respectively. (Table 3.3.12)

The mean numbers of outpatient visits in patients with NCD was lowest at 2.17 (SD 1.63) vs. 4.74 (SD 4.44) and 2 in patients with ESLD and liver transplant. (Table 3.3.13)

$H_{1\ (4d)}$: NA

3.3.3.4 Prescription Drugs Costs and Utilization

$H_{1\ (4e)}$: The mean costs for prescription drugs were $16,962 (SD $31,616) for patients with NCD, $5,652 (SD $9,869) for those with ESLD, and $14,070 for the patient with prior liver transplant. (Table 3.3.12)

The mean numbers of prescription drugs were 17.58 (SD 13.14), 24.01 (SD 19.42), and 14 in patients with NCD, ESLD, and prior liver transplant, respectively. (Table 3.3.13)

$H_{1\ (4e)}$: NA

Table 3.3.12: Mean Costs by Liver Disease Severity in the Untreated Cohort

Type of Cost	NCD				
	n	Mean	Standard Deviation	Min	Max
Total All-Cause Costs	36	$17,385	$31,557	$115	$164,581
Inpatient Costs	36	$0	$0	$0	$0
Emergency Room Costs	36	$118	$343	$0	$1,848
Outpatient Costs[1]	36	$423	$867	$0	$4,284
Prescription Drug Costs	36	$16,962	$31,616	$0	$164,326
Type of Cost	**ESLD**				
	n	**Mean**	**Standard Deviation**	**Min**	**Max**
Total All-Cause Costs	1841	$7,461	$9,807	$5	$185,821
Inpatient Costs	1841	$0	$0	$0	$0
Emergency Room Costs	1841	$137	$415	$0	$4,467
Outpatient Costs[1]	1841	$1,810	$2,995	$0	$27,437
Prescription Drug Costs	1841	$5,652	$9,869	$0	$185,767
Type of Cost	**LT**				
	n	**Mean**	**Standard Deviation**	**Min**	**Max**
Total All-Cause Costs	1	$14,133	NA	$14,133	$14,133
Inpatient Costs	1	$0	NA	$0	$0
Emergency Room Costs	1	$63	NA	$63	$63
Outpatient Costs[1]	1	$63	NA	$63	$63
Prescription Drug Costs	1	$14,070	NA	$14,070	$14,070

[1]Outpatient costs are inclusive emergency room costs

Table 3.3.13: Mean Resource Utilization by Liver Disease Severity in the Untreated Cohort

Type of Service	NCD				
	n	Mean	Standard Deviation	Min	Max
Inpatient	36	0.00	0.00	0.00	0.00
Emergency Room	36	0.53	1.11	0.00	6.00
Outpatient	36	2.17	1.63	0.00	7.00
Prescription Drugs	36	17.58	13.14	0.00	55.00
Type of Service	**ESLD**				
	n	**Mean**	**Standard Deviation**	**Min**	**Max**
Inpatient	1841	0.00	0.00	0.00	0.00
Emergency Room	1841	0.57	1.30	0.00	13.00
Outpatient	1841	4.74	4.44	0.00	50.00
Prescription Drugs	1841	24.01	19.42	0.00	255.00
Type of Service	**LT**				
	n	**Mean**	**Standard Deviation**	**Min**	**Max**
Inpatient	1	0.00	NA	0.00	0.00
Emergency Room	1	2.00	NA	2.00	2.00
Outpatient	1	2.00	NA	2.00	2.00
Prescription Drugs	1	14.00	NA	14.00	14.00

[1]Outpatient visits are inclusive emergency room visits

3.3.4 Objective 5: To compare HCV-related healthcare costs and resource utilization for HCV patients who are treated with drug therapies versus those who are not receiving treatment

3.3.4.1 HCV-Related Total Costs

$H_{0\ (5a)}$: Total mean HCV-related costs were $11,753 (SD $9,005) in the treated cohort compared to $1,679 (SD $2,828) in the untreated cohort ($p<0.001$). (Table 3.3.19)

In an adjusted analysis, the mean costs were $14,547 higher in treated vs. untreated patients; mean costs in untreated patients were $1,494 (SE $50). (Table 3.3.14) Appendix C1 shows the results of the regression analysis with all predictors.

$H_{0\ (5a)}$: Rejected

Table 3.3.14: A Generalized Linear Model (GLM) Adjusted HCV-Related Costs (A) and Differences (B) among Cohorts while Controlling for Covariates (N=2,817)

(A) A GLM model adjusted HCV-related total costs

HCV-Related Total Costs	Mean	SE	z	p-value	95% Confidence Interval	
Untreated	$1,494.37	50.40	29.65	<0.001	$1,395.58	$1,593.15
Treated	$16,041.24	618.16	25.95	<0.001	$14,829.67	$17,252.81

(B) Difference in HCV-related total costs for treated vs. untreated cohorts

	Mean	SE	z	p-value	95% Confidence Interval	
Difference in HCV-Related Total Costs	$14,546.87	615.94	23.62	<0.001	$13,339.65	$15,754.10

3.3.4.2 HCV-Related Inpatient Costs and Utilization

$H_{0\ (5b)}$: All of the hospitalizations were HCV-related. The mean costs of inpatient services were $49 (SD $645) in the treated group. None of the patients in the untreated cohort had a hospitalization, leading to $0 inpatient costs. The differences between groups were statistically significant with p=0.001. (Table 3.3.19)

There were only 6 patients experiencing at least one inpatient visit vs. 0 in the untreated group (p<0.001). Small number of inpatient hospitalizations did not allow for adjusted analyses. (Table 3.3.20)

$H_{0\ (5b)}$: Rejected for costs
$H_{0\ (5b)}$: Rejected for utilization

3.3.4.3 HCV-Related Emergency Room (ER) Costs and Utilization

$H_{0\ (5c)}$: Mean HCV-related ER costs were $96 (SD $318) in treated vs. $137 (SD $414) in untreated patients (p=0.008). (Table 3.3.19) In a two-part adjusted analysis using a generalized linear regression model, mean costs were estimated to be $88 (SE $9) in the treated cohort vs. $144 (SE $11) in the untreated cohort. The difference of $56 (SE $14) was statistically significant (p<0.001). (Table 3.3.15)

Of treated patients, 270 (28.8%) had at least one HCV-related ER visit; of untreated patients, 532 (28.3%) had a HCV-related ER visit. The mean number of ER visits for treated patients was 1.18 (SD 2.74) compared to 0.57 (SD 1.30) for untreated patients (p<0.001). (Table 3.3.20) After adjusting for covariates, the mean number of ER visits was 0.59 higher in the treated vs. untreated cohorts. (Table 3.3.16) Appendices C2 and C3 show the results of the regression analyses with all predictors.

$H_{0\ (5c)}$: Rejected for costs
$H_{0\ (5c)}$: Rejected for utilization

Table 3.3.15: A Two-Part Generalized Linear Model (GLM) Adjusted HCV-Related ER Costs (A) and Differences (B) among Cohorts while Controlling for Covariates (N=2,817)

(A) A GLM model adjusted ER costs

HCV-Related ER Costs	Mean	SE	Z	p-value	95% Confidence Interval	
Untreated	$144.44	10.62	13.60	<0.001	$123.63	$165.26
Treated	$88.08	8.62	10.22	<0.001	$71.18	$104.98

(B) Differences in adjusted ER costs between treated and untreated cohorts

	Mean	SE	Z	p-value	95% Confidence Interval	
Difference in HCV-Related ER Costs	-$56.36	13.56	-4.16	<0.001	-$82.94	-$29.79

Table 3.3.16: A Zero-Inflated Poisson Model Adjusted Number of HCV-Related ER Visits (A) and Differences (B) among Cohorts while Controlling for Covariates (N=2,817)

(A) A zero-inflated poisson model adjusted number of ER visits

ER Visits	Mean	SE	z	p-value	95% Confidence Interval	
Untreated	0.55	0.02	23.38	<0.001	0.50	0.60
Treated	1.14	0.05	20.77	<0.001	1.03	1.25

(B) Difference in adjusted number of ER visits in treated and untreated cohorts

	Mean	SE	z	p-value	95% Confidence Interval	
Difference in Number of ER Visits	0.59	0.06	10.72	<0.001	0.48	0.70

3.3.4.4 HCV-Related Outpatient Costs and Utilization

$H_{0\ (5d)}$: The mean HCV-related outpatient costs were significantly lower in the treated vs. untreated groups ($609, SD $938 vs. $1,679, SD $2,828, respectively, p<0.001). (Table 3.3.19) After adjusting for covariates, the adjusted difference between cohorts was $615 ($850, SE $29 in treated vs. $1,465, SE $52 in untreated cohorts; p<0.001). (Table 3.3.17)

The mean numbers of HCV-related outpatient visits were 6.44 (SD 4.85) in treated patients compared to 4.53 (SD 4.30) in untreated patients (p<0.001). (Table 3.3.20) In the adjusted analysis, treated patients were estimated to have 2.43 (SE 0.19) more visits than the untreated patients (p<0.001). (Table 3.3.18) Appendices C4 and C5 show the results of the regression analyses with all predictors.

$H_{0\ (5d)}$: Rejected for costs
$H_{0\ (5d)}$: Rejected for utilization

Table 3.3.17: A Generalized Linear Model (GLM) Adjusted HCV-Related Outpatient Service Costs (A) and Differences (B) among Cohorts while Controlling for Covariates (N=2,817)

(A) A GLM model adjusted outpatient service costs

HCV-Related Outpatient Costs	Mean	SE	z	p-value	95% Confidence Interval	
Untreated	$1,465.33	51.78	28.30	<0.001	$1,363.85	$1,566.82
Treated	$850.11	48.82	17.41	<0.001	$754.43	$945.79

(B) Difference in adjusted outpatient service costs in treated and untreated cohorts

	Mean	SE	z	p-value	95% Confidence Interval	
Difference in HCV-Related Outpatient Costs	-$615.22	67.27	-9.15	<0.001	-$747.07	-$483.38

Table 3.3.18: A Negative Binomial Regression Model Adjusted Number of Outpatient Visits (A) and Differences (B) among Cohorts while Controlling for Covariates (N=2,817)

(A) A negative binomial regression model adjusted number of outpatient visits

Outpatient Visits	**Mean**	**SE**	**z**	**p-value**	**95% Confidence Interval**	
Untreated	4.43	0.09	50.86	<0.001	4.26	4.60
Treated	6.86	0.18	38.35	<0.001	6.51	7.22

(B) Difference in adjusted number of outpatient visits in treated and untreated cohorts

	Mean	**SE**	**z**	**p-value**	**95% Confidence Interval**	
Difference in Number of Outpatient	2.43	0.19	12.48	<0.001	2.05	2.81

Table 3.3.19: Unadjusted HCV-Related Healthcare Costs in Treated and Untreated Cohorts

Type of Cost	Treated					Untreated				p-value
	Mean	Standard Deviation	Min	Max		Mean	Standard Deviation	Min	Max	
Total HCV-Related Costs	$11,753	$9,005	$0	$88,047		$1,679	$2,828	$0	$27,437	<0.001
HCV-Related Inpatient Costs	$49	$645	$0	$12,178		$0	$0	$0	$0	0.001
HCV-Related Emergency Room Costs	$96	$318	$0	$5,635		$137	$414	$0	$4,467	0.008
HCV-Related Outpatient Costs[1]	$609	$938	$0	$15,707		$1,679	$2,828	$0	$27,437	<0.001
HCV-Related Prescription Drug Costs	$11,095	$8,886	$0	$87,789		NA				

[1]Outpatient costs are inclusive of emergency room costs

Table 3.3.20: Unadjusted HCV-Related Healthcare Costs in Treated and Untreated Cohorts

Type of Service	Treated					Untreated				P-value
	Mean	Standard Deviation	Min	Max		Mean	Standard Deviation	Min	Max	
Inpatient	0.01	0.08	0.00	1.00		0	NA	NA	NA	<0.001
Emergency Room	1.18	2.74	0	21		0.57	1.30	0.00	13.00	<0.001
Outpatient[1]	6.44	4.85	0	34		4.53	4.30	0.00	50.00	<0.001
Prescription Drugs	4.61	2.95	0	15		NA				

[1]Outpatient visits are inclusive of emergency room visits

3.4 ADHERENCE AND PERSISTENCE

3.4.1 Objective 6: To compare adherence and discontinuation rates for chronically infected HCV patients on triple therapy versus dual therapy

3.4.1.1 Adherence

$H_{0\ (6a)}$: After adjusting for continuous enrollment, only 28 patients were on triple therapy. As such, statistical comparisons were not possible. The mean PDC for the first 12 weeks, second 12 weeks, and overall 24 weeks for dual and triple therapy can be found in Table 3.4.1. A 24-week analysis period was applied since the actual length of therapy depends on the genotype information and response guided protocols, which require access to laboratory values. The average PDC was 71% with a significant difference between the first 12 weeks and the following 12 weeks of therapy (80% vs. 62%, $p<0.001$).

$H_{0\ (6a)}$: NA

Table 3.4.1: Proportion of Days Covered (PDC) for HCV Dual and Triple Therapy

Dual Therapy			
	n	Mean	Standard Deviation
PDC for first 12 weeks	951	0.80	0.24
PDC for second 12 weeks	951	0.62	0.40
Overall 24-week PDC	951	0.71	0.29
Triple Therapy			
	n	Mean	Standard Deviation
PDC for first 12 weeks	28	0.61	0.36
PDC for second 12 weeks	28	0.61	0.45
Overall 24-week PDC	28	0.61	0.30
All			
	n	Mean	Standard Deviation
PDC for first 12 weeks	979	0.80	0.25
PDC for second 12 weeks	979	0.62	0.40
Overall 24-week PDC	979	0.71	0.29

$H_{0\ (6b)}$: The proportion of patients with at least a PDC of 80% during the 24-week analysis period was 36% for patients on triple therapy and 52% for patients on dual therapy; overall, the proportion was 52% (p=0.307). The proportion of patients with at least a PDC of 70% was 43% for patients on triple therapy and 58% for patients on dual therapy; overall, the proportion was 57% (p=0.395). (Table 3.4.2)

$H_{0\ (6b)}$: Not Rejected

Table 3.4.2: Proportion of Patients with Proportion of Days Covered (PDC) of At Least 70% or 80% by HCV Regimen

	Dual Therapy					**Triple Therapy**					**p-value**
	n	%	SE	95% Confidence Interval		n	%	SE	95% Confidence Interval		
PDC ≥80%	496	0.52	0.02	0.49	0.55	10	0.36	0.09	0.18	0.54	0.307
PDC ≥70%	548	0.58	0.02	0.54	0.61	12	0.43	0.10	0.24	0.62	0.395

	All				
	n	%	SE	95% Confidence Interval	
PDC ≥80%	506	0.52	0.02	0.49	0.55
PDC ≥70%	560	0.57	0.02	0.54	0.60

In an adjusted multivariate analysis, the following predictors for PDC of at least 70% and 80% were evaluated: therapy type (dual vs. triple), age, gender, CCI, race (whites vs. non-whites), presence of medical/psychosocial comorbidities, baseline costs, and number of prescription drugs and office visits during the analysis period (intervals of 10). Intervals of 10 were considered for the number of prescription drugs and office visits for

easier interpretation as the odds ratio were very small (~1.01) when including continuous number of prescriptions drugs and office visits. In addition, intervals of 10 were more clinically-relevant since these patients had numerous outpatient visits and prescription drugs. Adherence levels to coronary artery disease and diabetes medications were considered, but omitted due to missing observations and lack of significance. Significant positive independent predictors of HCV medication PDC greater than 70% included white race (OR=1.62, 95% CI=1.25-2.11), higher number of non-HCV prescription drugs (OR=1.14, 95% CI=1.03-1.25) and higher number of outpatient visits (OR=1.14, 95% CI= 1.04-1.25). Age, CCI, therapy type, presence of relevant comorbidities, baseline costs, and gender were not significant independent predictors for having a PDC of greater than 70%. Significant positive independent predictors of HCV medication PDC greater than 80% included white race (OR=1.51, 95% CI=1.16-1.95), and higher number of non-HCV prescription drugs (OR=1.14, 95% CI=1.04-1.26). (Table 3.4.4)

Table 3.4.3: Logistic Regression Model Comparing the Proportion of Patients with PDC ≥ 70% in Patients while Controlling for Covariates (N= 979)

Variable	Odds Ratio	Standard Error	z	p-value	95% Confidence Interval	
Intercept	5.410	6.711	1.360	0.174	0.476	61.537
Protease Inhibitor (Yes vs. No)	0.634	0.258	-1.120	0.263	0.285	1.408
CCI	1.049	0.110	0.450	0.651	0.853	1.288
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	0.968	0.201	-0.160	0.874	0.644	1.453
Gender (Male vs. Female)	1.102	0.149	0.720	0.471	0.846	1.436
Age	0.990	0.008	-1.250	0.211	0.974	1.006
Race (White vs. Non-White)	1.621	0.217	3.600	0.000	1.246	2.108
Number of Non-HCV Drugs	1.135	0.056	2.580	0.010	1.031	1.250
Number of Outpatient Visits	1.139	0.056	2.680	0.007	1.036	1.254
Baseline Costs (Ln transformed)	0.822	0.117	-1.380	0.167	0.622	1.086

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

Table 3.4.4: Logistic Regression Model Comparing the Proportion of Patients with PDC ≥ 80% in Patients while Controlling for Covariates (N= 979)

Variable	Odds Ratio	Standard Error	z	p-value	95% Confidence Interval	
Intercept	2.161	2.645	0.630	0.529	0.196	23.791
Protease Inhibitor (Yes vs. No)	0.547	0.228	-1.450	0.147	0.242	1.237
CCI	0.999	0.103	-0.010	0.990	0.815	1.224
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	1.092	0.224	0.430	0.668	0.730	1.633
Gender (Male vs. Female)	1.092	0.146	0.660	0.509	0.841	1.418
Age	0.985	0.008	-1.830	0.068	0.970	1.001
Race (White vs. Non-White)	1.505	0.200	3.080	0.002	1.161	1.952
Number of Non-HCV Drugs	1.142	0.055	2.760	0.006	1.039	1.256
Number of Outpatient Visits	1.086	0.050	1.770	0.077	0.991	1.189
Baseline Costs (Ln transformed)	0.922	0.129	-0.580	0.564	0.701	1.214

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

3.4.1.2 Persistence

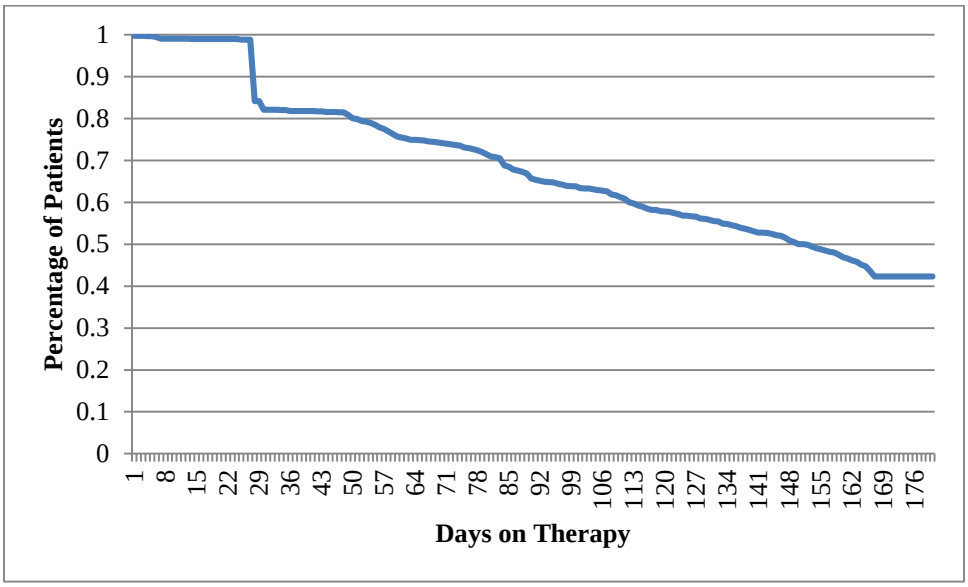
$H_{0\ (6c)}$: Discontinuation was defined as missing one or more fills and assessed for the first 24 weeks of therapy. By the end of 24 weeks, 42.3% of patients remained on dual or triple therapy. (Figure 3.4.1) The percentage remaining on therapy in the dual therapy

cohort was 43.0% vs. 17.9% of patients remaining on triple therapy at the end of 24 weeks (p=0.064).

Predictors of discontinuation were evaluated by a Cox proportional hazards regression model. In the model, being on triple vs. dual therapy was associated with a higher risk of discontinuing treatment (HR=1.74, 95% CI=1.13-2.68). White race was associated with decreased risk of discontinuing treatment (HR=0.79; 95% CI=0.67-0.94). In addition, having more outpatient visits in intervals of 10 was associated with a 9% decrease in the risk of discontinuation (HR=0.91, 95% CI=0.86-0.98). No other covariates considered (gender, age, presence of at least one relevant comorbidity, CCI, number of non-HCV prescription drugs, and baseline costs) had a significant association with the risk of discontinuation.[1] (Table 3.4.5)

$H_{0\ (6c)}$: Rejected

Figure 3.4.1: Kaplan Meir Curve of Percentage of Patients Remaining on Dual or Triple Therapy



[1] Select data from this adherence and persistence analysis was presented at the International Society of Pharmacoeconomics and Outcomes Research International Meeting, Montreal, QC, June 4, 2014.

Table 3.4.5: Cox Proportional Hazards Regression Model Evaluating Predictors of Therapy Discontinuation while Controlling for Covariates (N=979)

Variable	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Interval	
Triple Therapy (Yes vs. No)	0.554	0.220	6.325	0.012	1.740	1.130	2.680
Age	0.007	0.005	1.777	0.183	1.007	0.997	1.017
Gender (Male vs. Female)	-0.098	0.087	1.271	0.260	0.907	0.765	1.075
Race (White vs. Non-White)	-0.230	0.087	6.994	0.008	0.794	0.670	0.942
CCI	0.079	0.063	1.579	0.209	1.082	0.957	1.225
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	-0.095	0.136	0.490	0.484	0.909	0.697	1.186
Number of Non-HCV Drugs	-0.035	0.032	1.227	0.268	0.966	0.908	1.027
Number of Outpatient Visits	-0.090	0.033	7.485	0.006	0.914	0.857	0.975
Baseline Cost (Ln transformed)	0.069	0.089	0.596	0.440	1.071	0.900	1.275

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

3.5 HEALTHCARE COSTS AND RESOURCE UTILIZATION DURING THE 6-MONTH FOLLOW-UP PERIOD: DUAL VS. TRIPLE THERAPY

3.5.1 Objective 7: To compare healthcare costs and resource utilization for chronically infected HCV patients on triple therapy versus dual therapy

3.5.1.1 All-Cause Healthcare Costs

$H_{0\ (7a)}$: Due to the small number of patients receiving triple therapy, statistical comparisons between dual therapy and triple therapy were not possible. In the cost analyses, the only patients who were matched were considered (n=939 in the treated group).

Patients on dual therapy had mean total all-cause healthcare costs of $17,363 (SD $8,701) while patients on triple therapy had total costs of $54,898 (SD $29,401). (Table 3.5.1)

$H_{0\ (7a)}$: NA

3.5.1.2 Inpatient Costs and Utilization

$H_{0\ (7b)}$: For patients on dual therapy, the mean costs of inpatient services was $50 (SD $653) during the 6-month follow-up period. There were no inpatient visits for those on triple therapy. (Table 3.5.1)

There were six inpatient visits in dual therapy patients, resulting in a mean number of 0.01 visits (SD 0.08), and no inpatient visits for those on triple therapy. (Table 3.5.2)

$H_{0\ (7b)}$: NA

3.5.1.3 ER Costs and Utilization

$H_{0\ (7c)}$: The mean costs for ER services were $99 (SD $322) and $48 (SD $119) for dual and triple therapy patients, respectively. (Table 3.5.1)

The mean number of ER visits were 1.22 (SD 2.79) and 0.92 (SD 1.77) for dual and triple therapy patients, respectively. (Table 3.5.2)

$H_{0\ (7c)}$: NA

3.5.1.4 Outpatient Costs and Utilization

$H_{0\ (7d)}$: The average costs for outpatient services were $615 (SD $924) in patients on dual therapy, and $802 (SD $1,610) in patients on triple therapy. (Table 3.5.1)

The mean number of outpatient visits was 6.53 (SD 4.86) vs. 6.75 (SD 5.60) in dual vs. triple therapy patients, respectively. (Table 3.5.2)

$H_{0\ (7d)}$: NA

3.5.1.5 Prescription Drugs Costs and Utilization

$H_{0\ (7e)}$: The mean costs for prescription drugs during the follow-up period were lower for patients on dual therapy ($16,697, SD $8,486) compared to patients on triple therapy ($54,096, SD $28,915). (Table 3.5.1)

The average numbers of prescription drugs were 30.02 (SD 20.43) and 40.29 (SD 26.44) in patients on dual and triple therapy, respectively. (Table 3.5.2)

$H_{0\ (7e)}$: NA

Table 3.5.1: Healthcare Costs for Patients by Dual and Triple Therapy

Dual Therapy					
Type of Cost	n	Mean	Standard Deviation	Minimum	Maximum
Total All-Cause Costs	915	$17,363	$8,701	$1,529	$54,013
Inpatient Costs	915	$50	$653	$0	$12,178
ER Costs	915	$99	$322	$0	$5,635
Outpatient Costs	915	$615	$924	$0	$15,707
Rx Costs	915	$16,697	$8,486	$1,013	$52,351
Triple Therapy					
Type of Cost	n	Mean	Standard Deviation	Minimum	Maximum
Total All-Cause Costs	24	$54,898	$29,401	$4,584	$98,522
Inpatient Costs	24	$0	$0	$0	$0
ER Costs	24	$48	$119	$0	$494
Outpatient Costs	24	$802	$1,610	$0	$7,522
Rx Costs	24	$54,096	$28,915	$4,584	$98,264

Table 3.5.2: Resource Utilization for Patients by Dual and Triple Therapy

Dual Therapy					
Type of Service	n	Mean	Standard Deviation	Minimum	Maximum
Inpatient Visits	915	0.01	0.08	0.00	1.00
ER Visits	915	1.22	2.79	0.00	21.00
Outpatient Visits	915	6.53	4.86	0.00	34.00
Rx Costs	915	30.02	20.43	2.00	127.00
Triple Therapy					
Type of Service	n	Mean	Standard Deviation	Minimum	Maximum
Inpatient Costs	24	0.00	0.00	0.00	0.00
ER Costs	24	0.92	1.77	0.00	6.00
Outpatient Costs	24	6.75	5.60	0.00	18.00
Rx Costs	24	40.29	26.44	13.00	127.00

3.5.2 Objective 8: To compare HCV-related healthcare costs and resource utilization for chronically infected HCV patients on triple therapy versus dual therapy

3.5.2.1 HCV-Related Healthcare Costs

$H_{0\ (7a)}$: Mean HCV-related healthcare costs were $10,925 (SD $6,210) in patients on dual therapy compared to $43,336 (SD $26,577) in patients on triple therapy. (Table 3.5.3)

$H_{0\ (8a)}$: NA

3.5.2.2 HCV-Related Inpatient Costs and Utilization

$H_{0\ (7b)}$: All inpatient visits were HCV-related. For patients on dual therapy, the mean costs of inpatient services was $50 (SD $653) during the 6-month follow-up period. There were no inpatient visits for those on triple therapy. (Table 3.5.3)

There were 6 inpatient visits in dual therapy patients, resulting in a mean number of 0.01 visits (SD 0.08), and no inpatient visits for those on triple therapy. (Table 3.5.4)

$H_{0\ (8b)}$: NA

3.5.2.3 HCV-Related ER Costs and Utilization

$H_{0\ (7c)}$: The mean costs for ER services were $97 (SD $321) and $48 (SD $119) for dual and triple therapy patients, respectively. (Table 3.5.3)

The mean number of ER visits were 1.19 (SD 2.77) and 0.92 (SD 1.77) for dual and triple therapy patients, respectively. (Table 3.5.4)

$H_{0\ (8c)}$: NA

3.5.2.4 HCV-Related Outpatient Costs and Utilization

$H_{0\ (7d)}$: The average costs for outpatient services were $607 (SD $920) in patients on dual therapy, and $698 (SD $1,495) in patients on triple therapy. (Table 3.5.3)

The mean number of outpatient visits was 6.44 (SD 4.84) vs. 6.50 (SD 5.44) in dual vs. triple therapy patients, respectively. (Table 3.5.4)

$H_{0\ (8d)}$: NA

3.5.2.5 HCV-Related Prescription Drugs Costs and Utilization

$H_{0\ (8e)}$: The mean costs for prescription drugs during the follow-up period were significantly lower for patients on dual therapy ($10,268, SD $6,096) compared to patients on triple therapy ($42,637, SD $26,036; $p<0.001$). (Table 3.5.3)

The average numbers of prescription drugs were 4.58 (SD 2.94) and 5.71 (SD 3.10) in patients on dual and triple therapy, respectively. (Table 3.5.4)

$H_{0\ (8e)}$: NA

Table 3.5.3: HCV-Related Healthcare Costs for Patients by Dual and Triple Therapy

Dual Therapy					
Type of Cost	n	Mean	Standard Deviation	Minimum	Maximum
Total All-Cause Costs	915	$10,925	$6,210	$0	$26,580
Inpatient Costs	915	$50	$653	$0	$12,178
ER Costs	915	$97	$321	$0	$5,635
Outpatient Costs	915	$607	$920	$0	$15,707
Rx Costs	915	$10,268	$6,096	$0	$26,149
Triple Therapy					
Type of Cost	n	Mean	Standard Deviation	Minimum	Maximum
Total All-Cause Costs	24	$43,336	$26,577	$2,620	$88,047
Inpatient Costs	24	$0	$0	$0	$0
ER Costs	24	$48	$119	$0	$494
Outpatient Costs	24	$698	$1,495	$0	$7,522
Rx Costs	24	$42,637	$26,036	$2,620	$87,789

Table 3.5.4: HCV-Related Resource Utilization for Patients by Dual and Triple Therapy

Dual Therapy					
Type of Service	n	Mean	Standard Deviation	Minimum	Maximum
Inpatient Visits	915	0.01	0.08	0.00	1.00
ER Visits	915	1.19	2.77	0.00	21.00
Outpatient Visits	915	6.44	4.84	0.00	34.00
Prescription Drugs	915	4.58	2.94	0.00	15.00
Triple Therapy					
Type of Service	n	Mean	Standard Deviation	Minimum	Maximum
Inpatient Visits	24	0.00	0.00	0.00	0.00
ER Visits	24	0.92	1.77	0.00	6.00
Outpatient Visits	24	6.50	5.44	0.00	18.00
Prescription Drugs	24	5.71	3.10	1.00	11.00

3.6 FOLLOW-UP COSTS AND UTILIZATION

3.6.1 Objective 9: To compare longer term healthcare costs and resource utilization for chronically infected HCV patients in treated compared to untreated patients

3.6.1.1 All-Cause Healthcare Costs

$H_{0\ (9a)}$: There were 456 patients in the treated cohort and 849 patients in the untreated cohort with 1.5 years of follow-up claims data. Total mean healthcare costs during the 1.5 year follow-up period were compared for treated vs. untreated patients in unadjusted and adjusted analyses. The unadjusted costs were $31,379 (SD $22,618) in the treated group and $21,905 (SD $29,467) in the untreated cohort ($p<0.001$). (Table 3.6.8) The GLM model indicated that adjusted mean costs for all-cause services were $40,591 for patients in the treated cohort, $20,834 higher than the mean for those in the untreated group (mean=$19,757) ($p<0.001$). (Table 3.6.1) Appendix D1 shows the results of the regression analysis with all predictors.

$H_{0\ (9a)}$: Rejected

Table 3.6.1: A Generalized Linear Model (GLM) Adjusted All-Cause Costs 18 Months Post-Index Date (A) and Differences (B) among Cohorts while Controlling for Covariates (N=1,305)

(A) A GLM model adjusted all-cause costs

All-Cause Costs	Mean	SE	z	p-value	95% Confidence Interval	
Untreated	$19,756.98	410.27	48.16	<0.001	$18,952.87	$20,561.09
Treated	$40,590.61	1,431.05	28.36	<0.001	$37,785.80	$43,395.41

(B) Differences in adjusted all-cause costs between treated and untreated cohorts

	Mean	SE	z	p-value	95% Confidence Interval	
Difference in All-Cause Costs	$20,833.63	1,459.09	14.28	<0.001	$17,973.87	$23,693.38

3.6.1.2 Inpatient Costs and Utilization

$H_{0\ (9b)}$: The costs of inpatient services was $161 (SD $1,206) in the treated group vs. $0 in the untreated group. The differences between groups were statistically significant with $p<0.001$.

10 patients had one hospitalization in the treated group vs. 0 patients with inpatient services in the untreated group ($p<0.001$). The small number of inpatient hospitalizations did not allow for adjusted analyses. (Tables 3.6.8 and 3.6.9)

$H_{0\ (9b)}$: Rejected for costs
$H_{0\ (9b)}$: Rejected for utilization

3.6.1.3 Emergency Room Costs and Utilization

$H_{0\ (9c)}$: ER visit costs were lower in the treated vs. untreated cohorts. The mean costs for ER services were $154 (SD $363) in the treated patients and $245 (SD $681) in

the untreated patients (p=0.008). (Table 3.6.8) After adjusting for covariates in a GLM analysis, the mean costs for ER services in the untreated cohort were $244 (SE $24) vs. $158 (SE $18) in the treated cohort. The difference of -$86 (treated vs. untreated) was significant (p=0.004). (Table 3.6.2) A two-part generalized linear model was used due to the large number of 0 values.

The mean numbers of ER visits were statistically higher in the treated vs. untreated cohorts. During the 1.5 years of follow-up, the mean number of ER visits was 2.04 (SD 4.74) in treated patients compared to 1.11 (SD 2.43) in untreated patients (p<0.001). (Table 3.6.9) In an adjusted zero-inflated poisson regression model, the difference in the number of ER visits was 0.97 (p<0.001). (Table 3.6.3) Zero-inflated poisson model was chosen to compare adjusted counts due to the large number of 0 values. Appendices D2 and D3 show the results of the regression analyses with all predictors.

$H_{0\ (9C)}$: Rejected for costs
$H_{0\ (9C)}$: Rejected for utilization

Table 3.6.2: A Two-Part Generalized Linear Model (GLM) Adjusted ER Costs 18 Months Post-Index Date (A) and Differences (B) among Cohorts while Controlling for Covariates (N=1,305)

(A) A GLM model adjusted ER costs

ER Costs	Mean	SE	z	p-value	95% Confidence Interval	
Untreated	$244.26	24.13	10.12	<0.001	$196.97	$291.55
Treated	$158.23	18.45	8.58	<0.001	$122.07	$194.39

(B) Differences in adjusted ER costs between treated and untreated cohorts

	Mean	SE	z	p-value	95% Confidence Interval	
Difference in ER Costs	-$86.03	29.8258	-2.88	0.004	-$144.49	-$27.57

Table 3.6.3: A Zero-Inflated Poisson Model Adjusted Number of ER Visits 18 Months Post-Index Date (A) and Differences (B) among Cohorts while Controlling for Covariates (N=1,305)

(A) A zero-inflated poisson model adjusted number of ER visits

Number of ER Visits	Mean	SE	Z	p-value	95% Confidence Interval	
Untreated	1.09	0.06	19.29	<0.001	0.98	1.20
Treated	2.06	0.11	18.01	<0.001	1.84	2.29

(B) Difference in adjusted number of ER visits in treated and untreated cohorts

	Mean	SE	z	p-value	95% Confidence Interval	
Difference in Number of ER Visits	0.97	0.10	9.63	<0.001	0.77	1.17

3.6.1.4 Outpatient Costs and Utilization

$H_{0\ (2d)}$: In the treated group, the mean cost for outpatient services was $1,432 (SD $2,485) compared to $5,169 (SD $8,091) in the untreated group ($p<0.001$). (Table 3.6.8) After adjusting for baseline covariates in a GLM, the mean adjusted costs for outpatient services were $2,296 vs. $4,190 in treated vs. untreated patients, respectively (difference= $1,894). (Table 3.6.4)

The mean numbers of outpatient visits were significantly higher in the treated vs. untreated cohorts (14.25, SD 10.11 vs. 13.24, SD 12.56; $p=0.154$). (Table 3.6.9) Although the unadjusted analyses did not show a significant difference, the difference was significant in the adjusted analysis; the model estimated 3.65 visits more in the treated vs. untreated patients. (Table 3.6.5) Due to the small number of zero values, a negative binomial regression model was chosen to run the comparison. Appendices D5 and D6 show the results of the regression analyses with all predictors.

$H_{0\ (2d)}$: Rejected for costs
$H_{0\ (2d)}$: Rejected for utilization

Table 3.6.4: A Generalized Linear Model (GLM) Adjusted Outpatient Service Costs 18 Months Post-Index Date (A) and Differences (B) among Cohorts while Controlling for Covariates (N=1,305)

(A) A GLM model adjusted outpatient service costs

Outpatient Costs	Mean	SE	Z	p-value	95% Confidence Interval	
Untreated	$4,189.84	198.72	$21.08	<0.001	$3,800.37	$4,579.32
Treated	$2,295.64	202.33	$11.35	<0.001	$1,899.08	$2,692.19

(B) Difference in adjusted outpatient service costs in treated and untreated cohorts

	Mean	SE	Z	p-value	95% Confidence Interval	
Difference in Outpatient Costs	-$1,894.20	273.93	-6.91	<0.001	-$2,431.10	-$1,357.31

Table 3.6.5: A Negative Binomial Regression Model Adjusted Number of Outpatient Visits 18 Months Post-Index Date (A) and Differences (B) among Cohorts while Controlling for Covariates (N=1,305)

(A) A negative binomial regression model adjusted number of outpatient visits

Number of Outpatient Visits	Mean	SE	z	p-value	95% Confidence Interval	
Untreated	12.50	0.36	34.60	<0.001	11.79	13.21
Treated	16.15	0.62	26.13	<0.001	14.94	17.36

(B) Difference in adjusted number of outpatient visits in treated and untreated cohorts

	Mean	SE	z	p-value	95% Confidence Interval	
Difference in Number of Outpatient Visits	3.65	0.72	5.04	<0.001	2.23	5.07

3.3.1.5 Prescription Drug Costs and Utilization

$H_{0\ (2e)}$: Mean prescription drug costs during the follow-up period were significantly higher in the treated ($32,885, SD $22,022) vs. untreated ($16,735, SD $29,980) cohorts ($p<0.001$). (Table 3.6.8) After adjusting for relevant covariates, the mean costs in the treated cohort were estimated to be $45,259, $30,781 higher than mean costs in the untreated cohort. (Table 3.6.6)

The mean number of prescription drugs was also higher in the treated patients compared to untreated patients (85.68, SD 62.51 vs. 72.40, SD 54.83, respectively; $p<0.001$). (Table 3.6.9) In the adjusted analysis, the mean number of prescriptions drugs in the treated cohort was 95.79 compared to 75.79 in the untreated cohort, resulting in a mean difference of 20.00 prescriptions ($p<0.001$). (Table 3.6.7) Appendices D6 and D7 show the results of the regression analyses with all predictors.

$H_{0\ (2e)}$: Rejected for costs
$H_{0\ (2e)}$: Rejected for utilization

Table 3.3.6: A Generalized Linear Model (GLM) Adjusted Prescription Drug Costs 18 Months Post-Index Date (A) and Differences (B) among Cohorts while Controlling for Covariates (N=1,305) (A) A GLM model adjusted prescription drug costs

Prescription Drug Costs	Mean	SE	z	p-value	95% Confidence Interval	
Untreated	$14,477.38	458.38	$31.58	<0.001	$13,578.98	$15,375.78
Treated	$45,258.85	2,121.36	$21.33	<0.001	$41,101.07	$49,416.63

(B) Difference in adjusted prescription drug costs in treated and untreated cohorts

	Mean	SE	z	p-value	95% Confidence Interval	
Difference in Prescription Drug Costs	$30,781.47	2,077.03	14.82	<0.001	$26,710.56	$34,852.37

Table 3.3.7: A Negative Binomial Regression Model Adjusted Number of Prescription Drugs 18 Months Post-Index Date (A) and Differences (B) among Cohorts while Controlling for Covariates (N=1,305)

(A) A negative binomial regression model adjusted number of prescription drugs

Prescription Drugs	Mean	SE	Z	p-value	95% Confidence Interval	
Untreated	75.79	1.56	48.64	<0.001	72.73	78.84
Treated	95.79	3.05	31.40	<0.001	89.81	101.77

(B) Difference in adjusted number of prescription drug in treated and untreated cohorts

	Mean	SE	Z	p-value	95% Confidence Interval	
Difference in Number of Prescription Drugs	20.00	2.99	6.69	<0.001	14.14	25.86

Overall, the costs were still significantly higher in treated vs. untreated subjects in the analysis considering longer follow-up evaluation period of 1.5 years.

Table 3.6.8: Unadjusted Healthcare Costs in Treated and Untreated Cohorts During 18-Month Follow-Up Period

	Treated					Untreated				
Type of Cost	**Mean**	**Standard Deviation**	**Min**	**Max**		**Mean**	**Standard Deviation**	**Min**	**Max**	**p-value**
Total All-Cause Costs	$34,479	$22,618	$2,604	$152,090		$21,905	$29,467	$21	$527,826	<0.001
Inpatient Costs	$161	$1,206	$0	$12,977		$0	$0	$0	$0	<0.001
ER Costs	$154	$363	$0	$3,221		$245	$681	$0	$8,319	0.008
Outpatient Costs	$1,433	$2,485	$0	$37,812		$5,169	$8,091	$12	$32,131	<0.001
Rx Costs	$32,885	$22,022	$2,507	$149,265		$16,735	$29,980	$0	$526,786	<0.001

Table 3.6.9: Unadjusted Healthcare Utilization in Treated and Untreated Cohorts During 18-Month Follow-Up Period

	Treated					Untreated				
Type of Service	**Mean**	**Standard Deviation**	**Min**	**Max**		**Mean**	**Standard Deviation**	**Min**	**Max**	**P-value**
Inpatient	0.008	0.087	0.00	1.00		0.00	NA	NA	NA	<0.001
ER	2.04	4.74	0.00	35.00		1.11	2.43	0.00	19.00	<0.001
Outpatient	14.25	10.11	0.00	80.00		13.24	12.56	1.00	107.00	0.154
Prescription Drugs	85.68	62.51	4.00	391.00		72.40	54.83	0.00	370.00	<0.001

3.7 SUMMARY OF RESULTS

Table 3.7.1: Results for Each Hypothesis

Objective/Hypothesis	Objective/Hypothesis	Result
Objective 1	To compare patient characteristics for chronically infected HCV patients who are treated with HCV drug therapies versus those who are not receiving treatment before and after matching patient cohorts by high dimensional propensity scoring	
$H_{0\ (1a)}$	Mean age will not differ significantly between treated and untreated cohorts before or after matching.	Rejected for Unmatched Cohort Not Rejected for Matched Cohort
$H_{0\ (1b)}$	The proportion of patients in each gender category will not differ significantly between treated and untreated cohorts before or after matching.	Rejected for Unmatched Cohort Not Rejected for Matched Cohort
$H_{0\ (1c)}$	The proportion of patients in each race category will not differ significantly between treated and untreated cohorts before or after matching.	Rejected for Unmatched Cohort Not Rejected for Matched Cohort
$H_{0\ (1d)}$	The mean comorbidity score will not differ significantly between treated and untreated cohort before or after matching.	Rejected for Unmatched Cohort Not Rejected for Matched Cohort
$H_{0\ (1e)}$	The proportion of patients with at least one clinically relevant comorbidity will not differ significantly between treated and untreated cohort before or after matching.	Not Rejected for Unmatched Cohort Not Rejected for Matched Cohort
$H_{0\ (1f)}$	The proportion of patients with at least one hospitalization will not differ significantly between treated and untreated cohort before or after matching.	Rejected for Unmatched Cohort Not Rejected for Matched Cohort

Table 3.7.1 (continued): Results for Each Hypothesis

Objective/Hypothesis	Objective/Hypothesis	Result
$H_{0\ (1g)}$	The mean number of baseline unique non-HCV-related prescription drugs will not differ significantly between treated and untreated cohort before or after matching.	Rejected for Unmatched Cohort Not Rejected for Matched Cohort
$H_{0\ (1h)}$	The mean number of baseline outpatient visits will not differ significantly between treated and untreated cohort before or after matching.	Not Rejected for Unmatched Cohort Not Rejected for Matched Cohort
$H_{0\ (1i)}$	Baseline healthcare costs will not differ significantly between treated and untreated cohort before or after matching.	Rejected for Unmatched Cohort Not Rejected for Matched Cohort
$H_{0\ (1j)}$	The proportion of patients with non-cirrhotic disease (NCD), compensated cirrhosis (CC), end stage liver disease (ESLD), and liver transplant (LT) will not differ significantly between treated and untreated cohort before or after matching.	Rejected for Unmatched Cohort Not Rejected for Matched Cohort
Objective 2	To compare healthcare costs and resource utilization for HCV patients who are treated with drug therapies versus those who are not receiving treatment during the 6 month follow-up period.	
$H_{0\ (2a)}$	Total all-cause healthcare costs for HCV patients will not differ significantly for treated versus untreated patients.	Rejected
$H_{0\ (2b)}$	Hospitalization costs and number of hospitalizations will not differ significantly for treated versus untreated patients.	Rejected for Costs Rejected for Utilization Sample size too small for adjusted analyses
$H_{0\ (2c)}$	Emergency room (ER) visit costs and number of visits will not differ significantly for treated versus untreated cohorts.	Rejected for Costs Rejected for Utilization

Table 3.7.1 (continued): Results for Each Hypothesis

Objective/Hypothesis	Objective/Hypothesis	Result
$H_{0\ (2d)}$	Outpatient costs and number of outpatient visits will not be significantly different between treated and untreated cohorts.	Rejected for Costs Rejected for Utilization
$H_{0\ (2e)}$	Prescription drug costs and number of prescription drugs will not be significantly higher for those treated versus untreated.	Rejected for Costs Rejected for Utilization
Objective 3	To compare healthcare costs and resource utilization for HCV patients who are treated by liver disease severity during the 6 month follow-up period.	
$H_{0\ (3a)}$	In treated cohort, total all-cause healthcare costs will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Sample size too small for statistical analyses
$H_{0\ (3b)}$	In treated cohort, hospitalization costs and number of visits will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Sample size too small for statistical analyses
$H_{0\ (3c)}$	In treated cohort, emergency room visit costs and number of visits will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Sample size too small for statistical analyses
$H_{0\ (3d)}$	In treated cohort, outpatient costs and number of visits will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Sample size too small for statistical analyses
$H_{0\ (3e)}$	In treated cohort, prescription drug costs and number of prescriptions will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Sample size too small for statistical analyses
Objective 4	To compare healthcare costs and resource utilization for HCV patients who are untreated by liver disease severity during the 6 month follow-up period.	
$H_{0\ (4a)}$	In treated cohort, total all-cause healthcare costs will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Sample size too small for statistical analyses

Table 3.7.1 (continued): Results for Each Hypothesis

Objective/Hypothesis	Objective/Hypothesis	Result
$H_{0\ (4b)}$	In untreated cohort, hospitalization costs and number of visits will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Sample size too small for statistical analyses
$H_{0\ (4c)}$	In untreated cohort, emergency room visit costs and number of visits will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Sample size too small for statistical analyses
$H_{0\ (4d)}$	In untreated cohort, outpatient costs and number of visits will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Sample size too small for statistical analyses
$H_{0\ (4e)}$	In untreated cohort, prescription drug costs and number of prescriptions will not differ significantly for those with more severe liver disease compared to those without cirrhosis.	Sample size too small for statistical analyses
Objective 5	To compare HCV-related healthcare costs and resource utilization for HCV patients who are treated with drug therapies versus those who are not receiving treatment during the 6 month follow-up period.	
$H_{0\ (5a)}$	Total HCV-related healthcare costs for HCV patients will not differ significantly for treated versus untreated patients.	Rejected
$H_{0\ (5b)}$	HCV-related hospitalization costs and number of hospitalizations will not differ significantly for treated versus untreated patients.	Rejected for Costs Rejected for Utilization Sample size too small for adjusted analyses
$H_{0\ (5c)}$	HCV-related emergency room visit costs and number of visits will not differ significantly for treated versus untreated cohorts.	Rejected for Costs Rejected for Utilization
$H_{0\ (5d)}$	HCV-related outpatient costs and number of outpatient visits will not be significantly different between treated and untreated cohorts.	Rejected for Costs Rejected for Utilization

Table 3.7.1 (continued): Results for Each Hypothesis

Objective/Hypothesis	Objective/Hypothesis	Result
Objective 6	To compare adherence and discontinuation rates for chronically infected HCV patients on triple therapy versus dual therapy during the 6 month follow-up period.	
$H_{0\ (6a)}$	Mean medication adherence for HCV drug regimens will not differ significantly for patients on triple therapy compared to patients on dual therapy.	Sample size too small for statistical analyses
$H_{0\ (6b)}$	The proportion of patients who are adherent (PDC $\geq$ 80%) to HCV drug therapy will not differ significantly for patients on triple therapy compared to patients on dual therapy.	Not Rejected
$H_{0\ (6c)}$	The proportion of patients who discontinue HCV therapy prematurely will not differ significantly for patients on triple therapy compared to patients on dual therapy.	Not Rejected in Unadjusted Analysis Rejected in Adjusted Analysis
Objective 7	To compare healthcare costs and resource utilization for chronically infected HCV patients on triple therapy versus dual therapy during the 6 month follow-up period.	
$H_{0\ (7a)}$	Total all-cause healthcare costs for treated HCV patients will not differ significantly for patients on triple therapy versus dual therapy.	Sample size too small for statistical analyses
$H_{0\ (7b)}$	Hospitalization costs and number of hospitalizations will not differ significantly for treated patients on triple therapy versus dual therapy.	Sample size too small for statistical analyses
$H_{0\ (7c)}$	Emergency room visit costs and number of visits will not differ significantly for treated patients on triple therapy compared to dual therapy.	Sample size too small for statistical analyses
$H_{0\ (7d)}$	Outpatient costs and number of outpatient visits will not be significantly different between treated patients on triple versus dual therapy cohorts.	Sample size too small for statistical analyses
$H_{0\ (7e)}$	Prescription drug costs and number of prescription drugs will be significantly higher for those on triple therapy versus dual therapy.	Sample size too small for statistical analyses

Table 3.7.1 (continued): Results for Each Hypothesis

Objective/Hypothesis	Objective/Hypothesis	Result
Objective 8	To compare HCV-related healthcare costs and resource utilization for chronically infected HCV patients on triple therapy versus dual therapy during the 6 month follow-up period	
$H_{0\ (8a)}$	Total HCV-related healthcare costs for treated HCV patients will not differ significantly for patients on triple therapy versus dual therapy.	Sample size too small for statistical analyses
$H_{0\ (8b)}$	HCV-related hospitalization costs and number of hospitalizations will not differ significantly for treated patients on triple therapy versus dual therapy.	Sample size too small for statistical analyses
$H_{0\ (8c)}$	HCV-related emergency room visit costs and number of visits will not differ significantly for treated patients on triple therapy compared to dual therapy.	Sample size too small for statistical analyses
$H_{0\ (8d)}$	HCV-related outpatient costs and number of outpatient visits will not be significantly different between treated patients on triple versus dual therapy cohorts.	Sample size too small for statistical analyses
$H_{0\ (8e)}$	HCV-related prescription drug costs and number of prescription drugs will not be significantly different between treated patients on triple versus dual therapy cohorts.	Sample size too small for statistical analyses
Objective 9	To compare healthcare costs and resource utilization for HCV patients who are treated with drug therapies versus those who are not receiving treatment during the 1.5 year follow-up period.	
$H_{0\ (9a)}$	Total all-cause healthcare costs for HCV patients will not differ significantly for treated versus untreated patients.	Rejected
$H_{0\ (9b)}$	Hospitalization costs and number of hospitalizations will not differ significantly for treated versus untreated patients.	Rejected for Costs Rejected for Utilization Sample size too small for adjusted analyses

Table 3.7.1 (continued): Results for Each Hypothesis

Objective/Hypothesis	Objective/Hypothesis	Result
$H_{0\ (9c)}$	Emergency room (ER) visit costs and number of visits will not differ significantly for treated versus untreated cohorts.	Rejected for Costs Rejected for Utilization
$H_{0\ (9d)}$	Outpatient costs and number of outpatient visits will not be significantly different between treated and untreated cohorts.	Rejected for Costs Rejected for Utilization
$H_{0\ (9e)}$	Prescription drug costs and number of prescription drugs will not be significantly higher for those treated versus untreated.	Rejected for Costs Rejected for Utilization

Chapter 4: Discussion

This section presents a detailed evaluation of the results and their implications by each objective. The purpose of this study was to evaluate the resource utilization and healthcare costs in treated versus untreated chronically hepatitis C patients within the Texas Medicaid system. One of the key questions the state is currently considering with the rising costs of HCV treatment is whether the upfront investment in treatment will reduce healthcare costs downstream.

4.1 PATIENT SELECTION

The continuous enrollment requirement of 6 months before and after the index date limited sample size substantially. 62.4% (13,568 out of 21,761) of the untreated subjects and 53.2% (1,208 out of 2,271) of the treated subjects were excluded due to non-continuous enrollment. Although a longer follow-up period was desired for the analysis, the intermittent eligibility of the Medicaid population did not allow for a longer analysis period. In addition, since telaprevir and boceprevir entered the market in May 2011, only 6 months of follow-up data were available for patients on triple therapy. The balance and compromise between sample size and follow-up time was carefully considered to determine the analysis period of 6 months. To examine the potential impact of longer term follow-up on costs and utilization, sub-analyses with a subset of patients with 18 months of follow-up were conducted.

4.2 BASELINE CHARACTERISTICS

4.2.1 Objective 1: To compare patient characteristics for chronically infected HCV patients who are treated with HCV drug therapies versus those who are not receiving treatment before and after matching patient cohorts by high dimensional propensity scoring

The first objective lent insight to characteristics and health status of the treated and untreated groups before matching. In addition, this objective was an important one to evaluate the success of the high dimensional score matching.

The predictors of treatment included white race and higher baseline costs. Those with higher baseline costs (in multiples of 2.72 due to natural log transformation) had over 4 times greater odds of receiving treatment. One would expect that those who are higher utilizers of care would be more likely to receive treatment. White race as a predictor is also

expected since treatment response varies by race. For instance, African-Americans have an Il-28B genotype which predisposes them to lower SVR rates. [30] Predictors of no treatment included female gender, higher number of baseline medications and outpatient visits and the presence of at least 1 inpatient visit. It seemed counterintuitive that higher baseline numbers of medications and outpatient visits were associated with lower odds of receiving treatment; however, the odds ratios were over 0.95 and the majority of chronic HCV patients, regardless of treatment status, have higher numbers of prescriptions and visits compared to patients without HCV. [72] Presence of other relevant comorbidities, CCI scores, and liver disease severity status were not significant indicators of treatment status. Liver disease was not significant since most patients had an indication of more advanced disease. Since the patient population was filtered based on having on ICD-9 code for a visit, mostly those patients who were symptomatic and/or came to seek care for a complication were included in the study. Furthermore, HCV screening was previously targeted to higher risk patients so many chronic HCV patients remain undiagnosed and those identified have symptomatic disease. [34]

Since only a select small percentage of chronic HCV patients receive treatment, the use of high dimensional propensity score matching was especially important. For instance, only 11.6% of patients received therapy with PegIFN + RBV at the VA, which has a disproportionately higher prevalence of HCV. [14] The high dimensional propensity scoring allows use of all of the codes in the claims record, without the need to predefine all variables, while traditional propensity score methods require the investigator to identify the predictors of treatment at the outset. The high dimensional propensity score involves the following steps: (1) collecting as many codes as possible, (2) identifying the codes that could possibly bias the treatment/outcome relation, (3)

combining variables identified a priori with these other codes in a propensity score, and (4) using the estimated propensity score to match treated and untreated patients. [92] Overall, the high dimensional propensity scoring seemed to match patients successfully. In the unmatched sample, there were significant differences in the proportion of patients with at least one inpatient visit, with ESLD, and NCD. In addition, there were significant differences in the continuous covariates of age, CCI, number of baseline prescription drugs, and baseline costs. In contrast, after matching, there were no significant differences between groups and for any of the covariates. As shown by Figure 3.2.1, all of the continuous characteristics were much more balanced between untreated and treated groups after matching.

4.3 HEALTHCARE COSTS AND RESOURCE UTILIZATION

4.3.1 Objective 2: To compare healthcare costs and resource utilization for HCV patients who are treated with drug therapies versus those who are not receiving treatment

As expected, healthcare costs were significantly higher in the treated subjects compared to untreated subjects. The major contributor of these higher costs was the prescription drug costs. Based on adjusted analyses of total costs, the mean difference between the costs in the treated vs. untreated patients was $13,960 (SE $458). The adjusted analyses for just the pharmacy portion of costs estimated a larger difference of $18,341 (SE $767). Overall, pharmacy costs accounted for 95.9% of total costs in the treated patients, and 70.5% of costs in those untreated. These higher costs in the treated patients are expected given the cost of HCV therapies: the whole acquisition costs (WAC) of PegIFN + RBV ranges from $18,000 to $39,000 for 24 to 48 weeks of treatment; telaprevir-

based triple therapy ranges from $85,000 to $104,000 for 24 to 48 weeks; and boceprevir-based triple therapy ranges from $59,000 to $88,000 for 24 to 48 weeks. The newer regimens, such as sofosbuvir and simeprevir, which just entered the market in December 2013 are also costly. Sofosbuvir + PegIFN + RBV costs $93,000 and simeprevir + PegIFN + RBV costs up to $104,000. [102] Although these newer therapies still require significant investment, these regimens are highly efficacious, more tolerable, and have shorter durations of therapy (12-24 weeks). [103, 104]

Even though the prescription drug costs were higher, the costs associated with outpatient visits was lower in treated patients by $638 (SE $65) compared to patients who did not receive treatment. Interestingly, even though the costs were lower, the number of outpatient visits was higher in the treated group by 2.45 (SE 0.21) visits. Many of these extra visits may have been due to viral load and other laboratory monitoring required during treatment, instead of disease complications.

No conclusions can be drawn from the inpatient visits since they occurred very infrequently during the 6-month observation. Only 6 patients had an inpatient visit in the treated group and no patients were hospitalized in the untreated group.

Total mean direct medical costs were similar in the Texas Medicaid HCV population to costs in the commercially-insured population. For instance, the average 6-month costs estimated by McAdam-Marx et al. were around $10,000 [$US 2009]. [72] In this population, average 6-month costs were $11,211 (SD $12,045).

4.3.2 Objectives 3 and 4: To compare healthcare costs and resource utilization for HCV patients who are treated and untreated by liver disease severity.

Due to the small number of patients with NCD, CC, ESLD, and LT, statistical analyses comparing costs and utilization by liver disease severity were not feasible. Trends were also difficult to assess given the small sample sizes. In the treated cohort, as expected, the patient with liver transplant had very high total costs of $97,869. However, contrary to expected results, the 26 patients with NCD had higher costs ($22,318, SD $17,096) than those with ESLD ($18,121, SD $10,885). As typically seen in healthcare costs, the standard deviations were large.

In the untreated cohort, the total cost for the patient with prior liver transplant was the lowest at $14,133. These low costs indicate that the liver transplant most likely occurred prior to the baseline 6-month period. The total mean costs for the ESLD patients were $7,461 (SD $9,807). Those with NCD (n=36) had costs of $17,385 (SD $31,557). For the total cohort, the average costs were $19,454 (SD $26,405) for NCD, $10,993 (SD $11,345) for ESLD, and $56,001 (SD $59,210) for liver transplant. The average cost of NCD in this cohort was substantially higher than the cost for NCD estimated by Gordon et al. ($8,639, $US 2009). [73] Gordon et al. and McAdam-Marx et al. estimated the 6-month all-cause costs for ESLD to range from $7,000 to over $50,000. [72, 73]

The discrepancies between the studies may be due to sample sizes and the populations being studied. The Gordon et al. and McAdam-Marx et al. studies evaluated over 34,000 chronic HCV patients using a large commercial payer database. This study evaluates a much smaller Texas Medicaid population with different demographics. In addition, practice patterns may differ in Texas. One other explanation could be that the patients in the sample were mis-categorized as NCD since ICD-9 codes during the 6-month baseline period identified their liver disease category.

4.3.3 Objective 5: To compare HCV-related healthcare costs and resource utilization for HCV patients who are treated with drug therapies versus those who are not receiving treatment

Another observation was that most of the visits were HCV-related. All of the inpatient claims were HCV-related and over 90% of the total outpatient and ER claims were HCV-related. Since most of these patients had evidence of ESLD, the high percentage of HCV-related resource utilization was expected.

The adjusted differences in healthcare costs and resource utilization were consistent with the results in objective 2, which outline the all-cause costs and utilization. The mean adjusted HCV-related total costs were $14,545 (SE $616) more in the treated patients compared to untreated patients.

4.4 Adherence and Persistence

4.4.1 Objective 6: To compare adherence and discontinuation rates for chronically infected HCV patients on triple therapy versus dual therapy

In the adherence analysis, average HCV medication PDC was 71% with a significant difference between the first 12 weeks and the following 12 weeks of therapy (80% vs. 62%, $p<0.001$). There were only 28 patients who received triple therapy, so analyses comparing triple vs. dual therapy was limited. In general, the proportion of patients with good adherence (PDC $\geq$80%) was higher for patients on dual therapy vs. triple therapy (52% vs. 36%, respectively).

In an effort to see if adherence to other chronic medications predicted adherence to HCV medications, PDC was also calculated for diabetes and CAD medications. There was no association identified in the multivariate logistic regression analysis, so these variables

were omitted from the final analysis. Other significant positive independent predictors of HCV medication PDC greater than 70% or 80% included white race, higher number of non-HCV prescription drugs and higher number of outpatient visits. These results suggest that closer follow-up and management of other comorbidities may improve readiness to HCV therapy and improve treatment adherence.

Only 43.0% and 17.9% of patients remained on dual and triple therapy, respectively, at the end of 24 weeks (p=0.064); overall, 42.3% of patients discontinued by week 24. The results of the Cox proportional hazards model were consistent with the predictors for good adherence (PDC ≥70% or 80%). However, due to the smaller sample size requirements in the Cox proportional hazards model, triple vs. dual therapy was also a significant predictor for persistence. Being on triple vs. dual therapy was associated with a higher chance of discontinuing treatment, as well as non-white race. These findings were unsurprising as triple therapy is associated with more side effects than dual therapy. [51] In addition, some non-white races, namely African-Americans or those of African descent, have a IL-38B genotype predisposing them to have a poor response to therapy. Having more outpatient visits (in intervals of 10) was associated with a 9% decrease in the risk of discontinuation (HR=0.91, 95% CI=0.86-0.98), also indicating that closer follow-up improves treatment persistence.

4.5 Healthcare Costs and Resource Utilization During the 6-Month Follow-Up Period: Dual vs. Triple Therapy

4.5.1 Objectives 7 and 8: To compare all-cause and HCV-related healthcare costs and resource utilization for chronically infected HCV patients on triple therapy versus dual therapy

Statistical comparisons between dual therapy and triple therapy were not possible due to the small number of patients on triple therapy. Patients on dual therapy had mean total all-cause healthcare costs of $17,363 (SD $8,701) while patients on triple therapy had total costs of $54,898 (SD $29,401). Pharmacy cost differences accounted for the majority of this difference: the mean costs for prescription drugs during the follow-up period were higher for patients on triple therapy ($54,096, SD $28,915) compared to patients on dual therapy ($16,697, SD $8,486). (Table 3.5.1) The large difference in prescription drug costs is expected due to the over 2 times higher cost of triple vs. dual therapy.

HCV-related costs accounted for over 90% of all claims. As stated previously, this large proportion of HCV related-costs may be due to the more advanced liver disease of these patients. Mean HCV-related healthcare costs were $10,925 (SD $6,210) in patients on dual therapy compared to $43,336 (SD $26,577) in patients on triple therapy. (Table 3.5.3) The mean costs for prescription drugs during the follow-up period were higher for patients on triple therapy ($42,637, SD $26,036) compared to patients on dual therapy $10,268 (SD $6,096).

4.6 FOLLOW-UP COSTS AND UTILIZATION

4.6.1 Objective 9: To compare longer term healthcare costs and resource utilization for chronically infected HCV patients in treated compared to untreated patients

Due to the continuous enrollment requirement and transient eligibility of the Texas Medicaid population, most patients did not meet the continuous enrollment requirement. As such, the main analysis was limited to 6 months. The 6-month analysis was an "on-treatment" perspective since the index date was the date of the first fill and treatment duration ranges from 24 to 48 weeks. In order to evaluate whether the upfront investment of treatment was offset by lower downstream costs, a sub-analysis of fewer patients with 18 months of follow-up was added.

There were 456 patients in the treated cohort and 849 patients in the untreated cohort included in the follow-up analysis. The GLM model indicated that the adjusted mean costs for all-cause services during the 18 month follow-up period were $20,834 (SE $1,459) higher than mean for those in the untreated group (mean=$19,757) ($p<0.001$). The prescription drug costs were $30,781 (SE $2,077) higher than mean costs in the untreated cohort, which is around $6,000 more than cost difference in the 6-month period. This higher difference is expected during the longer follow-up period since treatment may be required for up to 48 weeks. As in the 6-month analysis, mean outpatient visits were more frequent in the 18 months (3.65 more visits), but mean costs were $1,894 (SE $274) less in treated vs. untreated patients. These results indicate that the pattern of less costly outpatient visits continued even after treatment.

Another analysis was performed to look at the costs incurred after treatment. Since treatment can required up to 48 weeks, costs from month 12 to 18 were analyzed. In this analysis, the adjusted total all-cause costs were not significantly different between treated and untreated patients; the difference was $233 (SE $534) ($p=0.656$). Numerous studies

have shown the benefits of achieving SVR on HCV morbidity and mortality. Achievement of SVR is also associated with benefits on the extraheptic manifestations of HCV, such as reduction in diabetes and myocardial injury. [55-62] Gordon et al. found that mean all-cause per person per month (PPPM) health-care costs were 29% higher for non-treated patients compared to those completing treatment using data from a large commercial claims database with mean follow-up of 634 days. [87] Manos et al. found total adjusted costs were significantly higher in the non-SVR group than in the SVR group, with rate ratios (RRs) and 95% CIs ranging from 1.26 (95% CI=1.13-1.40) to 1.64 (95% CI=1.38-1.96), driven mostly by hospital and outpatient pharmacy costs. [88] Both of these studies, however, did not include the costs of HCV treatment since the objective was to look at solely post-treatment costs.

In this analysis, cost offsets in outpatient visits did not counterbalance the costs of HCV treatment; however, the continuing decrease in outpatient costs over time may be an indication that the cost offsets will continue to accumulate over a longer period of time. In addition to the short follow-up period, another reason for the smaller cost offsets may have been the advanced liver disease nature of these patients. Over 90% of patients had some evidence of end stage liver disease as indicated by ICD-9 codes for ascites, encephalopathy, variceal bleeding and hepatorenal syndrome. SVR rates are 10-20% lower in patients with advanced disease of compensated cirrhosis or beyond, and longer treatment duration is required. [30, 51] For instance, SVR rates for cirrhotic genotype 1 treatment-naïve patients treated with PegIFN + RBV was 33% in a published meta-analysis of 3 large-scale clinical trials. [105] As such, the majority of the patients in this study cohort who received treatment most likely did not achieve SVR.

4.7 LIMITATIONS

The main two limitations of this study were the small sample size and short follow-up period. These were both largely due to the continuous enrollment criteria restrictions. Due to the small sample size, statistical inferences by liver disease severity and dual vs. triple therapy were not possible. Due to the short follow-up period, evaluation of downstream costs was limited; however, some trends in lower outpatient costs were noted in the treated patients. The balance and compromise between sufficient sample size for matching and follow-up time was carefully considered to determine the analysis period of 6 months. In addition, a sub-analysis of patients with 18 months of follow-up was added.

Another limitation was that each control (untreated) patient was considered multiple times with multiple index dates being the dates of ICD-9 codes indicating chronic HCV diagnosis. This multiplication of controls was necessary to increase the sample size for matching. In addition, since HCV is a slowly progressing disease and treatment is expensive, treatment rates are very low and treatment is usually reserved for those who are sicker. If only the first index date was considered, more mild disease patients would be in the untreated group, making matching more difficult. Each control was included in the analysis an average of two times with two different index dates. Of note, when duplicates were removed from the control group, the differences in costs were not significantly different. For instance, the adjusted mean 6-month follow-up costs were $12,653 (SE $424, 95% CI=$11,821-$13,484) higher in the treated vs. untreated cohorts when removing duplicates. The 95% confidence interval overlapped with confidence interval of the analysis with the duplicates ($13,063-$14,858).

Since this study uses observational data on a nonrandomized intervention, there still may be unobservable differences that our methods cannot account for despite attempts to

adjust for selection bias. Despite these limitations, the use of robust statistical methods to match patients via high dimensional propensity scoring and greedy matching algorithms was a key strength of this study. After matching, key demographic and clinical characteristics were more balanced between the treated and untreated cohorts. The few studies that look at downstream costs in treated vs. untreated patients adjusted for confounders, but did not match patients at baseline.

Furthermore, the external generalizability of this study is also limited as only one state's Medicaid population is evaluated. However, Texas was the first state to launch a hepatitis C initiative, and the prevalence of HCV in Texas was estimated to be 1.8% or 387,395 Texans infected in 2000, which is higher than the prevalence in the overall country (1.6%). [90, 91]

Another limitation was that clinical data were unavailable. Important variables, such as genotype and viral load were in Medicaid claims data. Consequently, the achievement of SVR was unknown in the treated cohort and low SVR rates may be a reason why more cost offsets were not seen.

In addition, the calculation of adherence and persistence using pharmacy refill data contributed to the study limitations. This method assumes that if patients obtain their prescription, they will take all the medication as directed.

4.8 IMPLICATIONS

This study is very timely given the recent media on the cost of the newer HCV treatments. Congressman Waxman recently wrote a letter for the Chief Executive Officer of Gilead expressing concern regarding the $84,000 price of the sofosbuvir regimen – "our concern is that a treatment will not cure patients if they cannot afford it." The letter states

that “Because Hepatitis C is ‘concentrated in low-income, minority patients,’ the affordability problems are likely to be particularly acute for state Medicaid programs and those patients served by these programs.” [106] Initially, Texas considered imposing strict limits to sofosbuvir drug access due to the high price, but as of April 2014, they are again deliberating whether to loosen access barriers and prior authorization requirements. [107]

One should not take these results at face value and assume that downstream costs do not offset HCV treatment costs. This study had a shorter time period that did not allow an adequate evaluation of downstream costs. In addition, inpatient visits, which are usually the cost drivers, were infrequent in this time frame so trends in costly complications were difficult to assess. Despite these limitations, the unmet needs in HCV treatment were evident – only a very small percentage of patients in the Texas Medicaid population have ever received treatment (9.4%). Furthermore, most patients have advanced to more severe liver diseases, reducing the chances of achieving SVR and averting liver disease sequelae. If anything, this study emphasizes the importance of earlier treatment to increase the chance of offsetting downstream costs. The benefits of successful treatment on HCV-related mortality and morbidity, as well as extrahepatic manifestations are clear from numerous studies. [56-62] Even in the VA population, a population similar to Medicaid, SVR was associated with a substantial mortality benefit (genotype-1 hazard ratio, 0.70; $p<0.001$; genotype-2 hazard ratio, 0.64; $p=0.006$; genotype-3 hazard ratio, 0.51; $p<0.001$). [60] Both Davis K et al. and Manos et al. found significantly lower costs in those who achieved SVR vs. those who did not, [71, 88] and Gordon et al. found significantly lower costs in a treated cohort.[87] When assessing 6-month costs, this study did not show short-term cost offsets, but the sub-analysis following patients for 18 months showed trends in downstream cost offsets. One other important consideration is that HCV treatment is one-

time therapy if successful with the possibility of lifetime cure. The lifetime cost of biologics for chronic illnesses far exceed the one-time cost of HCV. For instance, the lifetime treatment costs for relapsing-remitting multiple sclerosis is more than $430,000, almost four times the cost of HCV treatment. [108] The more pertinent questions are 'when to treat' and 'who to treat,' rather than 'if to treat.' Since discontinuation rates are high and adherence rates are low, one possible screening criterion is to consider the patients' previous adherence patterns to other drugs and provider appointments. Another criterion should also be abstinence from alcohol or drugs, which are risk factors for worsening liver disease and also increase risk of being re-infected.

Future studies with longer follow-up may show that this gap continues to close. As mentioned previously, earlier treatment could bend the cost curve before patients reached the more advanced stages seen in this costly cohort. With the new birth cohort screening guidelines, those with earlier disease could be identified more readily.

4.9 CONCLUSIONS

The Texas Medicaid chronic HCV population had advanced disease, with the majority having indication of end stage liver disease and high costs. The costs of treatment were high, leading to significantly higher costs in those receiving treatment compared to those who did not in the 6- and 18-month follow-up periods studied. Moreover, the majority of those who were treated did not adhere or persist on therapy, reducing the chances of successfully being cured. Despite higher overall costs, trends in decreasing outpatient service costs were seen with treatment, especially when followed for a longer period of time.

The chronic HCV population in the Texas Medicaid system clearly demands attention. The white paper of the Texas Hepatitis C Initiative concluded the executive summary with the following statement, “What must be realized is that ultimately the cost to society of not providing screening, counseling, and treatment will be much higher.” [91]

Future studies should examine the Medicaid population in multiple states to see if the vulnerability of these patients is consistent with that seen in Texas. In addition, longer-term follow-up using a population more likely to be continuously enrolled and using a database with SVR information would lend greater insights on downstream costs. This study can also be repeated within the Texas Medicaid population once the new screening recommendations are implemented in order to identify patients earlier. Also importantly, new HCV therapies are now available that are highly efficacious and tolerable so those treated will have a higher chance of successful cure and averting downstream complications.

Appendices

Appendix A List of Acronyms

AASLD = American Association for the Study of Liver Diseases

CC = Compensated Cirrhosis

CCI = Charlson Comorbidity Index

DAA = Direct Acting Antiviral

Dual therapy = Pegylated Interferon + Ribavirin

ESLD = End Stage Liver Disease

EVR = Early Virological Response

GLM = Generalized Linear Model

HCC = Hepatocellular Carcinoma

HBV = Hepatitis B Virus

HCV = Hepatitis C Virus

LT = Liver Transplant

NCD = Non-Cirrhotic Disease

NPV = Negative Predictive Value

PDC = Proportion of Days Covered

PegIFN = Pegylated Interferon Alfa

RBV = Ribavirin

RVR = Rapid Viral Response

SVR = Sustained Virologic Response

Triple therapy = Pegylated Interferon + Ribavirin + Telaprevir or Boceprevir

Appendix B1: A Generalized Linear Model (GLM) Comparing Adjusted All-Cause Costs Between Treated and Untreated Cohorts: 6 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	0.000	0.002	0.140	0.888	-0.004	0.004
Gender (Male vs. Female)	0.121	0.028	4.240	0.000	0.065	0.176
Race (White vs. Non-White)	-0.048	0.026	-1.830	0.067	-0.099	0.003
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	-0.073	0.040	-1.840	0.065	-0.151	0.005
CCI	0.008	0.020	0.380	0.704	-0.032	0.048
Number of Medications	0.002	0.001	1.910	0.057	0.000	0.004
Number of Outpatient Visits	-0.003	0.001	-2.550	0.011	-0.006	-0.001
≥1 Inpatient Visit	0.195	0.204	0.960	0.339	-0.204	0.594
Group (Treated vs. Untreated)	1.093	0.026	42.630	0.000	1.043	1.143
Baseline Costs[2]	0.730	0.036	20.270	0.000	0.660	0.801
Protease Inhibitor (Yes vs. No)[3]	0.809	0.159	5.070	0.000	0.496	1.121
Intercept	2.326	0.332	7.010	0.000	1.676	2.976

Model parameters: *Log likelihood= -29742.2; AIC=21.12; BIC= -20997.7.*

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

[3] Protease inhibitors include telaprevir or boceprevir

Appendix B2: Two-Part Generalized Linear Model (GLM) Comparing Adjusted Emergency Room Costs Between Treated and Untreated Cohorts: 6 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Probit						
Age	0.005	0.003	1.820	0.069	0.000	0.011
Gender (Male vs. Female)	-0.162	0.052	-3.150	0.002	-0.264	-0.061
Race (White vs. Non-White)	0.490	0.052	9.340	0.000	0.388	0.593
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	0.220	0.078	2.830	0.005	0.067	0.372
CCI	-0.153	0.041	-3.690	0.000	-0.234	-0.072
Number of Medications	-0.007	0.002	-3.590	0.000	-0.011	-0.003
Number of Outpatient Visits	0.015	0.003	5.410	0.000	0.010	0.021
≥1 Inpatient Visit	0.805	0.357	2.260	0.024	0.106	1.504
Group (Treated vs. Untreated)	-0.101	0.046	-2.210	0.027	-0.190	-0.011
Baseline Costs[3]	0.006	0.055	0.110	0.911	-0.101	0.113
Intercept	-0.146	0.387	-0.380	0.707	-0.904	0.613
GLM						
Age	0.008	0.005	1.570	0.116	-0.002	0.018
Gender (Female vs. Male)	-0.131	0.095	-1.380	0.168	-0.317	0.055
Race (Non-White vs. White)	-0.094	0.106	-0.890	0.374	-0.302	0.113
Presence of ≥1 comorbidi(ties) (No vs. Yes)[1]	0.002	0.147	0.010	0.991	-0.287	0.291
CCI	0.141	0.081	1.740	0.081	-0.018	0.300

Number of Medications	0.001	0.004	0.140	0.886	-0.008	0.009
Number of Outpatient Visits	0.017	0.006	2.850	0.004	0.005	0.029
≥1 Inpatient Visit	0.295	0.685	0.430	0.667	-1.047	1.637
Group (Treated vs. Untreated)	-0.082	0.092	-0.890	0.371	-0.262	0.098
Baseline Costs[3]	-0.484	0.108	-4.500	0.000	-0.695	-0.273
Intercept	6.406	0.766	8.370	0.000	4.906	7.907

Model parameters: *Wald chi^2 =165.2; p<0.001.*

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

Appendix B3: Zero-Inflated Poisson Regression Model Comparing Adjusted Number of Emergency Room Visits Between Treated and Untreated Cohorts: 6 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	0.012	0.003	4.290	0.000	0.007	0.018
Gender (Male vs. Female)	-0.148	0.049	-2.990	0.003	-0.245	-0.051
Race (White vs. Non-White)	0.186	0.055	3.420	0.001	0.079	0.293
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	0.251	0.070	3.610	0.000	0.115	0.388
CCI	0.121	0.037	3.220	0.001	0.047	0.194
Number of Medications	-0.008	0.002	-3.250	0.001	-0.012	-0.003
Number of Outpatient Visits	0.018	0.002	8.120	0.000	0.014	0.023
Group (Treated vs. Untreated)	-0.395	0.251	-1.570	0.115	-0.886	0.097
Baseline Costs[2]	0.753	0.057	13.210	0.000	0.641	0.865
Intercept	-0.034	0.042	-0.820	0.412	-0.116	0.048
Inflate						
Intercept	0.648	0.049	13.300	0.000	0.552	0.743

Model parameters: *Inflation model=logit; Log Likelihood=-3195.64; LR chi^2 =570.17; p<0.001*.

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

Appendix B4: A Generalized Linear Model (GLM) Comparing Adjusted Outpatient Costs Between Treated and Untreated Cohorts: 6 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	0.017	0.003	5.230	0.000	0.010	0.023
Gender (Male vs. Female)	-0.153	0.058	-2.650	0.008	-0.266	-0.040
Race (White vs. Non-White)	-0.727	0.062	-11.820	0.000	-0.848	-0.607
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	0.141	0.095	1.490	0.136	-0.045	0.327
CCI	-0.087	0.044	-1.960	0.050	-0.174	0.000
Number of Medications	-0.011	0.002	-4.940	0.000	-0.015	-0.007
Number of Outpatient Visits	0.033	0.003	10.290	0.000	0.026	0.039
≥1 Inpatient Visit	-0.791	0.300	-2.640	0.008	-1.380	-0.203
Group (Treated vs. Untreated)	-0.540	0.061	-8.880	0.000	-0.659	-0.421
Baseline Costs[2]	0.411	0.065	6.280	0.000	0.282	0.539
Protease Inhibitor (Yes vs. No)	0.095	0.415	0.230	0.819	-0.719	0.909
Intercept	3.155	0.569	5.550	0.000	2.040	4.271

Model parameters: *Log likelihood= -22310.5; AIC=15; BIC=-17614.7.*

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

Appendix B5: A Negative Binomial Regression Model Comparing Adjusted Outpatient Visits Between Treated and Untreated Cohorts: 6 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	0.005	0.002	2.860	0.004	0.002	0.008
Gender (Male vs. Female)	-0.064	0.032	-1.980	0.048	-0.127	-0.001
Race (White vs. Non-White)	-0.264	0.031	-8.410	0.000	-0.326	-0.203
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	0.063	0.047	1.340	0.182	-0.029	0.155
CCI	-0.070	0.027	-2.570	0.010	-0.123	-0.016
Number of Medications	-0.005	0.001	-4.040	0.000	-0.007	-0.002
Number of Outpatient Visits	0.027	0.002	14.770	0.000	0.023	0.030
≥1 Inpatient Visit	-0.470	0.170	-2.760	0.006	-0.803	-0.137
Group (Treated vs. Untreated)	0.429	0.033	13.130	0.000	0.365	0.493
Baseline Costs[2]	0.152	0.031	4.910	0.000	0.091	0.212
Protease Inhibitor (Yes vs. No)	0.101	0.213	0.480	0.635	-0.316	0.518
Intercept	-0.034	0.272	-0.130	0.900	-0.567	0.499

Model parameters: *Log likelihood= -7226.3; Wald Chi^2=669.18; p<0.001.*

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

Appendix B6: A Generalized Linear Model (GLM) Comparing Adjusted Prescription Drug Costs Between Treated and Untreated Cohorts: 6 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	-0.004	0.003	-1.330	0.184	-0.009	0.002
Gender (Male vs. Female)	0.218	0.041	5.350	0.000	0.138	0.299
Race (White vs. Non-White)	0.217	0.038	5.770	0.000	0.143	0.290
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	0.000	0.058	0.000	0.997	-0.114	0.114
CCI	0.020	0.032	0.620	0.537	-0.043	0.083
Number of Medications	0.011	0.002	6.910	0.000	0.008	0.015
Number of Outpatient Visits	-0.023	0.002	-9.980	0.000	-0.027	-0.018
≥1 Inpatient Visit	0.173	0.237	0.730	0.465	-0.291	0.637
Group (Treated vs. Untreated)	1.523	0.039	39.120	0.000	1.446	1.599
Baseline Costs[2]	0.738	0.044	16.790	0.000	0.652	0.824
Protease Inhibitor (Yes vs. No)[3]	0.693	0.170	4.080	0.000	0.361	1.026
Intercept	1.815	0.399	4.550	0.000	1.032	2.597

Model parameters: *Log likelihood= -27601.3; AIC=19.60; BIC= -20101.2.*

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

[3] Protease inhibitors include telaprevir or boceprevir

Appendix B7: A Negative Binomial Regression Model Comparing Adjusted Number of Prescription Drug Between Treated and Untreated Cohorts: 6 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	0.002	0.001	1.620	0.106	0.000	0.004
Gender (Male vs. Female)	0.003	0.021	0.140	0.892	-0.038	0.044
Race (White vs. Non-White)	0.014	0.020	0.690	0.489	-0.026	0.054
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	0.039	0.031	1.270	0.203	-0.021	0.100
CCI	0.012	0.016	0.770	0.442	-0.019	0.043
Number of Medications	0.035	0.001	34.010	0.000	0.033	0.037
Number of Outpatient Visits	-0.008	0.001	-5.560	0.000	-0.010	-0.005
≥1 Inpatient Visit	0.174	0.169	1.030	0.304	-0.158	0.506
Group (Treated vs. Untreated)	0.344	0.023	14.940	0.000	0.299	0.389
Baseline Costs[2]	-0.042	0.023	-1.790	0.074	-0.088	0.004
Protease Inhibitor (Yes vs. No)[3]	-0.042	0.102	-0.410	0.682	-0.241	0.158
Intercept	2.570	0.195	13.190	0.000	2.188	2.951

Model parameters: *Log likelihood= -10779.6; Wald Chi^2=1680.96; p<0.001.*

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity
[2] Baseline costs were natural log transformed
[3] Protease inhibitors include telaprevir or boceprevir

Appendix C1: A Generalized Linear Model (GLM) Comparing Adjusted HCV-Related Costs Between Treated and Untreated Cohorts: 6 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	0.011	0.003	4.120	0.000	0.006	0.016
Gender (Male vs. Female)	-0.113	0.047	-2.420	0.016	-0.204	-0.021
Race (White vs. Non-White)	-0.696	0.052	-13.330	0.000	-0.799	-0.594
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	-0.133	0.066	-2.010	0.045	-0.263	-0.003
CCI	-0.045	0.039	-1.160	0.247	-0.121	0.031
Number of Medications	-0.010	0.002	-5.460	0.000	-0.014	-0.006
Number of Outpatient Visits	0.036	0.003	12.290	0.000	0.030	0.041
≥1 Inpatient Visit	-0.603	0.353	-1.710	0.087	-1.295	0.088
Group (Treated vs. Untreated)	2.373	0.049	48.420	0.000	2.277	2.470
Baseline Costs[3]	0.337	0.060	5.570	0.000	0.218	0.455
Protease Inhibitor (Yes vs. No)	1.402	0.224	6.270	0.000	0.963	1.840
Intercept	3.975	0.505	7.870	0.000	2.986	4.965

Model parameters: *Log likelihood= -24986.9; AIC=17.75; BIC= -17972.5.*

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity
[2] Baseline costs were natural log transformed
[3] Protease inhibitors include telaprevir or boceprevir

Appendix C2: Two-Part Generalized Linear Model (GLM) Comparing Adjusted HCV-Related Emergency Room Costs Between Treated and Untreated Cohorts: 6 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Probit						
Age	0.005	0.003	1.730	0.083	-0.001	0.011
Gender (Male vs. Female)	-0.167	0.053	-3.170	0.002	-0.270	-0.064
Race (White vs. Non-White)	0.486	0.054	9.010	0.000	0.380	0.592
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	0.221	0.078	2.830	0.005	0.068	0.374
CCI	-0.152	0.041	-3.730	0.000	-0.232	-0.072
Number of Medications	-0.007	0.002	-3.370	0.001	-0.011	-0.003
Number of Outpatient Visits	0.015	0.003	5.310	0.000	0.010	0.021
≥1 Inpatient Visit	0.806	0.340	2.370	0.018	0.139	1.473
Group (Treated vs. Untreated)	-0.100	0.046	-2.160	0.031	-0.191	-0.009
Baseline Costs[2]	0.000	0.053	-0.010	0.996	-0.105	0.104
Intercept	-0.141	0.393	-0.360	0.720	-0.912	0.630
GLM						
Age	0.009	0.005	1.640	0.101	-0.002	0.019
Gender (Male vs. Female)	-0.127	0.096	-1.320	0.186	-0.315	0.061
Race (White vs. Non-White)	-0.095	0.103	-0.920	0.358	-0.297	0.107
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	0.007	0.143	0.050	0.958	-0.273	0.288
CCI	0.135	0.078	1.720	0.086	-0.019	0.289
Number of Medications	0.000	0.004	0.110	0.911	-0.008	0.009
Number of Outpatient Visits	0.017	0.006	2.800	0.005	0.005	0.029

≥1 Inpatient Visit	0.290	0.682	0.430	0.671	-1.046	1.626
Group (Treated vs. Untreated)	-0.083	0.090	-0.920	0.358	-0.260	0.094
Baseline Costs[2]	-0.494	0.109	-4.520	0.000	-0.709	-0.280
Intercept	6.394	0.770	8.310	0.000	4.885	7.902

Model parameters: *Wald chi^2 =167.18; p<0.001*.

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

Appendix C3: Zero-Inflated Poisson Regression Model Comparing Adjusted HCV-Related Number of Emergency Room Visits Between Treated and Untreated Cohorts: 6 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	0.013	0.003	4.550	0.000	0.008	0.019
Gender (Male vs. Female)	-0.146	0.050	-2.930	0.003	-0.244	-0.049
Race (White vs. Non-White)	0.182	0.055	3.320	0.001	0.074	0.289
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	0.260	0.070	3.720	0.000	0.123	0.397
CCI	0.115	0.038	3.050	0.002	0.041	0.189
Number of Medications	-0.008	0.002	-3.390	0.001	-0.012	-0.003
Number of Outpatient Visits	0.019	0.002	8.240	0.000	0.014	0.023
≥1 Inpatient Visit	-0.382	0.251	-1.520	0.127	-0.874	0.109
Group (Treated vs. Untreated)	0.730	0.057	12.700	0.000	0.617	0.842
Baseline Costs[3]	-0.035	0.042	-0.840	0.400	-0.118	0.047
Intercept	-0.031	0.371	-0.080	0.934	-0.758	0.696
Inflate						
Intercept	0.649	0.049	13.280	0.000	0.553	0.744

Model parameters: *Inflation model=logit; Log Likelihood=-3186.65; LR chi^2 =557.48; p<0.001*.

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

Appendix C4: A Generalized Linear Model (GLM) Comparing Adjusted HCV-Related Outpatient Costs Between Treated and Untreated Cohorts: 6 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	0.016	0.003	4.980	0.000	0.010	0.022
Gender (Male vs. Female)	-0.114	0.058	-1.970	0.049	-0.227	0.000
Race (White vs. Non-White)	-0.713	0.064	-11.090	0.000	-0.839	-0.587
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	0.135	0.095	1.420	0.157	-0.052	0.321
CCI	-0.075	0.044	-1.690	0.090	-0.161	0.012
Number of Medications	-0.010	0.002	-4.150	0.000	-0.014	-0.005
Number of Outpatient Visits	0.032	0.003	9.970	0.000	0.025	0.038
≥1 Inpatient Visit	-0.789	0.299	-2.640	0.008	-1.376	-0.203
Group (Treated vs. Untreated)	-0.544	0.064	-8.490	0.000	-0.670	-0.419
Baseline Costs[2]	0.380	0.063	6.030	0.000	0.257	0.504
Protease Inhibitor (Yes vs. No)	-0.023	0.410	-0.060	0.955	-0.826	0.780
Intercept	3.373	0.572	5.890	0.000	2.251	4.494

Model parameters: *Log likelihood= -22241.3; AIC=15.80; BIC=-17646.8.*

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

Appendix C5: A Negative Binomial Regression Model Comparing Adjusted HCV-Related Outpatient Visits Between Treated and Untreated Cohorts: 6 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	0.004	0.002	2.450	0.014	0.001	0.008
Gender (Male vs. Female)	-0.033	0.031	-1.060	0.290	-0.094	0.028
Race (White vs. Non-White)	-0.250	0.032	-7.820	0.000	-0.313	-0.188
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	0.066	0.047	1.390	0.163	-0.027	0.159
CCI	-0.060	0.028	-2.170	0.030	-0.115	-0.006
Number of Medications	-0.003	0.001	-2.830	0.005	-0.006	-0.001
Number of Outpatient Visits	0.026	0.002	14.150	0.000	0.022	0.029
≥1 Inpatient Visit	-0.473	0.171	-2.770	0.006	-0.808	-0.138
Group (Treated vs. Untreated)	0.437	0.032	13.750	0.000	0.375	0.499
Baseline Costs[2]	0.128	0.031	4.060	0.000	0.066	0.189
Protease Inhibitor (Yes vs. No)	0.069	0.195	0.350	0.723	-0.313	0.450
Intercept	0.137	0.270	0.510	0.612	-0.393	0.666

Model parameters: *Log likelihood= -7256.49; Wald Chi^2=681.05; p<0.001.*

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

Appendix D1: A Generalized Linear Model (GLM) Comparing Adjusted All-Cause Costs Between Treated and Untreated Cohorts: 18 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	0.003	0.002	1.540	0.124	-0.001	0.008
Gender (Male vs. Female)	0.163	0.035	4.600	0.000	0.094	0.232
Race (White vs. Non-White)	-0.029	0.037	-0.780	0.436	-0.102	0.044
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	-0.036	0.054	-0.670	0.502	-0.141	0.069
CCI	0.022	0.024	0.890	0.372	-0.026	0.069
Number of Medications	0.003	0.001	1.860	0.062	0.000	0.005
Number of Outpatient Visits	-0.005	0.002	-2.930	0.003	-0.009	-0.002
≥1 Inpatient Visit	-0.650	0.325	-2.000	0.046	-1.287	-0.012
Group (Treated vs. Untreated)	0.720	0.040	18.200	0.000	0.642	0.798
Baseline Costs[3]	0.754	0.052	14.380	0.000	0.651	0.857
Protease Inhibitor (Yes vs. No)	2.963	0.435	6.810	0.000	2.110	3.816
Intercept	2.839	0.306	9.280	0.000	2.239	3.438

Model parameters: *Log likelihood= -14333.9; AIC=21.98; BIC= -8810.66.*

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

[3] Protease inhibitors include telaprevir or boceprevir

Appendix D2: Two-Part Generalized Linear Model (GLM) Comparing Adjusted Emergency Room Costs Between Treated and Untreated Cohorts: 18 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Probit						
Age	0.014	0.004	3.130	0.002	0.005	0.023
Gender (Male vs. Female)	-0.216	0.077	-2.810	0.005	-0.367	-0.065
Race (White vs. Non-White)	0.535	0.083	6.460	0.000	0.373	0.697
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	0.263	0.115	2.290	0.022	0.038	0.489
CCI	-0.224	0.061	-3.700	0.000	-0.343	-0.106
Number of Medications	-0.010	0.003	-3.160	0.002	-0.017	-0.004
Number of Outpatient Visits	0.013	0.004	3.070	0.002	0.005	0.022
≥1 Inpatient Visit	1.059	0.579	1.830	0.068	-0.077	2.194
Group (Treated vs. Untreated)	-0.037	0.070	-0.530	0.596	-0.174	0.100
Baseline Costs[2]	-0.064	0.076	-0.840	0.400	-0.212	0.084
Intercept	-0.841	0.608	-1.380	0.166	-2.032	0.350
GLM						
Age	0.000	0.007	-0.060	0.951	-0.014	0.013
Gender (Female vs. Male)	-0.261	0.111	-2.350	0.019	-0.479	-0.043
Race (Non-White vs. White)	-0.077	0.123	-0.630	0.528	-0.317	0.163
Presence of ≥1 comorbidi(ties) (No vs. Yes)[1]	-0.057	0.184	-0.310	0.755	-0.417	0.303

CCI	0.282	0.089	3.160	0.002	0.107	0.457
Number of Medications	0.007	0.008	0.980	0.327	-0.007	0.022
Number of Outpatient Visits	0.013	0.007	1.940	0.053	0.000	0.026
≥1 Inpatient Visit	-0.177	0.467	-0.380	0.704	-1.091	0.737
Group (Treated vs. Untreated)	0.048	0.126	0.380	0.705	-0.200	0.295
Baseline Costs[2]	-0.368	0.127	-2.890	0.004	-0.617	-0.118
Intercept	5.945	1.003	5.930	0.000	3.979	7.911

Model parameters: *Wald chi^2 =90.61; p<0.001.*

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

Appendix D3: Zero-Inflated Poisson Regression Model Comparing Adjusted Number of Emergency Room Visits Between Treated and Untreated Cohorts: 18 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	0.006	0.003	1.910	0.056	0.000	0.012
Gender (Male vs. Female)	-0.115	0.051	-2.280	0.022	-0.214	-0.016
Race (White vs. Non-White)	-0.131	0.052	-2.510	0.012	-0.232	-0.029
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	-0.021	0.075	-0.280	0.780	-0.168	0.126
CCI	0.202	0.039	5.180	0.000	0.126	0.279
Number of Medications	-0.006	0.002	-2.960	0.003	-0.010	-0.002
Number of Outpatient Visits	0.013	0.002	5.460	0.000	0.008	0.017
≥1 Inpatient Visit	-0.026	0.230	-0.110	0.911	-0.477	0.425
Group (Treated vs. Untreated)	0.635	0.055	11.550	0.000	0.527	0.743
Baseline Costs[2]	-0.100	0.042	-2.370	0.018	-0.183	-0.017
Intercept	1.742	0.371	4.700	0.000	1.016	2.468
Inflate						
Intercept	0.639	0.060	10.570	0.000	0.520	0.757

Model parameters: *Inflation model=logit; Log Likelihood=2929.22; LR chi^2 =337.04; p<0.001*.

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

Appendix D4: A Generalized Linear Model (GLM) Comparing Adjusted Outpatient Costs Between Treated and Untreated Cohorts: 18 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	0.015	0.005	3.190	0.001	0.006	0.025
Gender (Male vs. Female)	0.052	0.087	0.590	0.554	-0.119	0.223
Race (White vs. Non-White)	-0.824	0.101	-8.190	0.000	-1.021	-0.627
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	0.005	0.144	0.030	0.974	-0.277	0.287
CCI	-0.101	0.072	-1.400	0.162	-0.242	0.040
Number of Medications	-0.009	0.004	-2.340	0.019	-0.016	-0.001
Number of Outpatient Visits	0.031	0.005	5.900	0.000	0.021	0.041
≥1 Inpatient Visit	-0.472	0.541	-0.870	0.383	-1.531	0.588
Group (Treated vs. Untreated)	-0.602	0.097	-6.190	0.000	-0.792	-0.411
Baseline Costs[2]	0.427	0.116	3.690	0.000	0.200	0.653
Intercept	3.971	1.017	3.910	0.000	1.978	5.964

Model parameters: *Log likelihood= -11606.1; AIC=17.80; BIC=-7176.87.*

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

Appendix D5: A Negative Binomial Regression Model Comparing Adjusted Outpatient Visits Between Treated and Untreated Cohorts: 18 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	0.003	0.003	1.240	0.216	-0.002	0.008
Gender (Male vs. Female)	0.031	0.047	0.670	0.505	-0.060	0.123
Race (White vs. Non-White)	-0.345	0.047	-7.350	0.000	-0.437	-0.253
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	0.057	0.074	0.770	0.442	-0.088	0.202
CCI	-0.059	0.045	-1.310	0.189	-0.147	0.029
Number of Medications	-0.005	0.002	-2.840	0.005	-0.008	-0.002
Number of Outpatient Visits	0.025	0.003	9.060	0.000	0.019	0.030
≥1 Inpatient Visit	-0.131	0.469	-0.280	0.780	-1.051	0.788
Group (Treated vs. Untreated)	0.256	0.049	5.280	0.000	0.161	0.352
Baseline Costs[2]	0.123	0.053	2.320	0.021	0.019	0.228
Intercept	1.286	0.451	2.850	0.004	0.401	2.170

Model parameters: *Log likelihood= -4554.4; Wald Chi^2=255.37; p<0.001*.

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

Appendix D6: A Generalized Linear Model (GLM) Comparing Adjusted Prescription Drug Costs Between Treated and Untreated Cohorts: 18 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	-0.001	0.003	-0.310	0.758	-0.007	0.005
Gender (Male vs. Female)	0.203	0.048	4.210	0.000	0.108	0.297
Race (White vs. Non-White)	0.301	0.046	6.480	0.000	0.210	0.392
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	-0.010	0.071	-0.130	0.893	-0.149	0.130
CCI	0.060	0.037	1.620	0.105	-0.012	0.132
Number of Medications	0.013	0.003	5.210	0.000	0.008	0.018
Number of Outpatient Visits	-0.025	0.003	-8.570	0.000	-0.031	-0.019
≥1 Inpatient Visit	-0.847	0.459	-1.850	0.065	-1.746	0.052
Group (Treated vs. Untreated)	1.140	0.051	22.380	0.000	1.040	1.240
Baseline Costs[2]	0.788	0.058	13.690	0.000	0.675	0.901
Intercept	2.210	0.449	4.920	0.000	1.330	3.089

Model parameters: *Log likelihood= -13970.8; AIC=21.43; BIC= -8291.2.*

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

Appendix D7: A Negative Binomial Regression Model Comparing Adjusted Number of Prescription Drug Between Treated and Untreated Cohorts: 18 Months of Follow-Up

Variable	Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Age	0.003	0.002	2.140	0.033	0.000	0.007
Gender (Male vs. Female)	-0.027	0.030	-0.900	0.371	-0.086	0.032
Race (White vs. Non-White)	0.059	0.031	1.890	0.059	-0.002	0.120
Presence of ≥1 comorbidi(ties) (Yes vs. No)[1]	-0.036	0.045	-0.810	0.415	-0.124	0.051
CCI	0.026	0.022	1.180	0.238	-0.017	0.070
Number of Medications	0.035	0.002	22.980	0.000	0.032	0.038
Number of Outpatient Visits	-0.006	0.002	-3.240	0.001	-0.010	-0.002
≥1 Inpatient Visit	-0.332	0.289	-1.150	0.250	-0.897	0.234
Group (Treated vs. Untreated)	0.234	0.032	7.220	0.000	0.171	0.298
Baseline Costs[2]	-0.029	0.034	-0.830	0.404	-0.096	0.039
Intercept	3.498	0.286	12.240	0.000	2.938	4.057

Model parameters: *Log likelihood= -6458.45; Wald Chi^2=891.43; p<0.001.*

[1] Comorbidities considered include: portal hypertension, congestive heart failure, renal insufficiency, depression, schizophrenia, diabetes, bipolar, drug or alcohol abuse, cirrhosis, HIV/AIDs, and/or obesity

[2] Baseline costs were natural log transformed

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