CLINICAL EFFECTIVENESS AND COST OF ANTIVIRAL THERAPY IN PATIENTS WITH HEPATITIS C INFECTION IN A MANAGED CARE SETTING

By

CHIEN-NING HSU

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2010

To my family

ACKNOWLEDGMENTS

I express my gratitude to my supervisory committee chair, Dr. Teresa Kauf, for her guidance and support all the time. This study would not have been completed without her guidance. I give my sincere thanks to my supervisory committee members, Drs. Almut Winterstein, Earlene Lipowski, David Nelson, Jeffery Harman, and Zhou Yang for their expertise, instruction in research methodology development, and encouragement. With their help, I have greatly extended my knowledge in outcomes research area, which will greatly benefit me in my future research. I thank Mr. Huazhi Liu and Dr. Ning Li for their help with SAS programming. I am grateful for having them around for friendship and assistance.

I express my gratitude to the Department of Pharmaceutical Outcomes and Policy for their support. I appreciate the support of Dr. Richard Segal and Dr. Carole Kimberlin from the beginning of my study here. Finally, I thank my fellow graduate students for their emotional support and company in the process of completing our dissertations. I wish them all the best in their journey to success.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

CEA	Cost Effectiveness Analysis
ESLD	End-stage liver disease
EVR	Early virological response
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HMO	Health Maintenance Organization
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
INB	Incremental net benefit
INF	Interferons alpha
MCO	Managed Care Organization
NB	Net benefit
NMB	Net monetary benefit
OLS	Ordinary least square
OR	Odd ratio
POS	Point of Service
PPO	Preferred Provider Organization
RBV	Ribavirin
RCT	Randomized Controlled Trial
SVR	Sustained virological response

Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

CLINICAL EFFECTIVENESS AND COST OF ANTIVIRAL THERAPY IN PATIENTS WITH HEPATITIS C INFECTION IN A MANAGED CARE SETTING

By

Chien-Ning Hsu

May 2010

Chair: Teresa Kauf
Major: Pharmaceutical Sciences

Whether initial combination antiviral therapy results a reduction in mortality and prevention of liver transplantation and hepatocellular carcinoma in a managed care organization (MCO) setting remained unclear. The sampling uncertainty in the incremental cost-effectiveness ratio (ICER) statistic has been argued regarding to the ambiguous interpretation of negative ICERs. To overcome the statistical problems inherited in the ratio statistic and reflect current patterns of HCV care in the practice setting, the present study are: to evaluate the effectiveness of treatment in terms of end-stage liver disease (ESLD) development; to evaluate the total health care costs of treatment; to evaluate the cost-effectiveness for treatment relative to no treatment by employing the regression method in the net benefit framework.

We conducted a retrospective cohort study among managed care organization (MCO) members using the Integrated Health Care Information Services (IHCIS) National Managed Care Benchmark Database in the period January 1997 to June 2007. With the base case (≥1 claims of combination prescriptions), usual care (12 months of continued combination therapy) and extended care (>12 months of continued combination therapy) analyses, the results of present study revealed that both estimates of treatment effectiveness, mean time to ESLD development (in months) and hazard ratios agreed on the beneficial effect of antiviral therapy in patients with

cirrhosis in base case and usual care analyses. Study results in extended care analyses with both measures of effectiveness found no difference in treatment effect between treated and untreated groups. Statistical evidence suggests that initial combination antiviral therapy was cost-effective for cirrhotic patients in base case analysis given at the value of willingness to pay ≥ $15,000. Initial combination antiviral therapy was also cost-effective for cirrhotic patients with usual care given at the value of willing to pay ≥ $60,000.

Our study results support the current treatment strategy, regarding the continuation of antiviral therapy should take early virological responses, duration of therapy and genotype of HCV into account.

CHAPTER 1
INTRODUCTION

Background

Burden of Hepatitis C Virus Infection

Approximately 130 million people worldwide are infected with HCV.[1] HCV accounts for the majority of cases of viral hepatitis in the United States, and it has been estimated that nearly 4 million people are chronically infected with the virus.[2] A national survey showed that HCV infection was most prevalent in those 30 to 49 years of age and among African-Americans and Hispanics.[3, 4]

Chronic HCV infection is the leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC).[5] In the United States, 40% of chronic liver disease is HCV-related, accounting for 8,000 to 10,000 deaths annually.[6] And now HCV represents the most common indication for liver transplantations.[5] Use of healthcare services among HCV-infected patients increased 25 to 30% every year during 1994 to 2001, as the population of patients with HCV aged.[7]

Mathematical projections, based on the known prevalence of HCV-related liver disease and natural disease progression, estimate the direct medical costs of HCV infection from the years 2010 to 2019 to be $10.7 billion ($6.7 to 14.1 billion); societal costs related to premature death from decompensated cirrhosis and HCC were projected to be approximately $21 to $54 billion.[8] Mortality and morbidity related to HCV infection are expected to increase 2 to 3 times over the next decade, because of the expected increase in the number of patients with advanced HCV infection.[9] Improvements in the use and effectiveness of antiviral therapy have the potential to reduce HCV-related liver complications, mortality, and healthcare utilization associated with the disease.

Natural History of Hepatitis C Virus Infection

HCV was identified in 1989 as a blood-born RNA virus with 6 distinct major genotypes. Genotype is not a factor in the natural history of disease but does impact treatment response and the length of therapy. According to the Third National Health and Nutrition Examination Survey (NHANES III), nearly 80% of HCV RNA positive patients were infected with genotypes 1A and 1B in the United State.[10]

HCV infection can be detected in blood as soon as 1 to 3 weeks after initial exposure. After acute HCV infection, most of persons are asymptomatic or only mildly symptomatic; persistent infection occurs in approximately 85% of cases.[11, 12] Among those with chronic hepatitis C, approximately 20% progressed to cirrhosis within 20 years of initial infection as shown in Figure 1-1.[13, 14 15] When cirrhosis decompensation becomes severe enough to cause liver failure, a liver transplant may be the only way to save the life of a person with chronic hepatitis C. HCV-related complication is currently the leading reason for liver transplants in the U.S. [5] Factors related to increase the risk of progressive liver disease include older age at time of infection, male gender, race, alcohol consumption (>30g/day), co-infection with HIV or hepatitis B (HBV), diabetes, and obesity.[16, 17]

Treatment of Hepatitis C

The goal of HCV treatment is to prevent complications of HCV infection; this is principally achieved by eradication of the virus. Initially, interferon alfa (INF) monotherapy was first approved to treat HCV in 1991; since then, there have been substantial improvements in the success of HCV treatment[18] (Figure 1-2). In randomized controlled trials, the highest overall sustained virological response (SVR) rates have been achieved with the combination of weekly subcutaneous injections of long-acting pegylated interferon alfa (PEG-INF) and oral ribavirin (RBV).[18, 19]

Current standard of care for treatment of previously untreated (naïve) patients with HCV infection is combination PEG-INF with RBV for 48 weeks for patients with genotype 1 HCV infection and 24 weeks for patients with genotype 2 or 3. Patients are only offered the full duration of therapy if they meet early viral response (EVR) criteria, defined as at least a 2-log drop in viral load after the first 12 weeks of therapy. Current studies suggest a treatment stopping rule (discontinuation) in patients with genotype 1 not reaching a 2-log drop in HCV RNA at week 12 and in those who remain HCV RNA positive at week 24.[19] Patient-level factors associated with SVR rates include age younger than 40 years, lower weight, non-Black race, and absence of cirrhosis; virus factors include lower baseline virus RNA levels, non-genotype 1, rapid virus level (RVR) decline after the first 4 weeks of therapy, and adherence to treatment.[19]

Rationale for Economic Evaluations of Antiviral Therapy

HCV poses a substantial clinical, economic, and health-related quality of life (HRQoL) burden to the individual and the health care system in the United State.[7-9, 20-22] Economic evaluations of antiviral therapy using decision analytic models are useful for the following reasons:

1. Randomized controlled trials (RCTs) have shown that an average of 54to56% of patients achieve SVR with PEG-INF combination therapy [23, 24], SVR is an intermediate outcome measure. It is unclear if a successful response to treatment (SVR) is predictive of a positive effect on HCV-related morbidity and mortality.

2. Antiviral therapy is expensive and associated with considerable adverse effects, the management of which is commonly associated with additional medical expenditures. Severe interferon-related adverse events include depression and marrow suppression.[19] Ribavirin is contraindicated in pregnancy, and recommended to be avoided in patients with ischemic cardiovascular and cerebrovascular diseases and renal insufficiency. Also, hemolytic anemia may require ribavirin dose reduction or additional therapy.[19] Treatment decisions, therefore, should be recommended to patients when the potential benefits of treatment outweigh the potential risks and costs of therapy.

3. Only a small proportion of HCV-infected patients will progress to cirrhosis or HCC, and treatment is not 100% effective as stated above. In addition, patients who achieve SVR are not homogenous with respect to their risk of developing progressive liver disease.

Allocation of sufficient resources to cover treatment costs for those most in need and best able to benefit is imperative to health policy decision makers.

Need for Study

To offer decision makers guidance on the economically optimal course of action for a given patient group, the needed information is not only the efficacy, but all-important relevant cost, treatment outcomes, and consequences for each alternative identified. A decision analytic framework can synthesize all available sources of information to assist decision makers in the efficient allocation of health care resources.[25]

To date, most of the published hepatitis C cost-effectiveness analyses (CEAs) applied Markov modeling to evaluate the prospective long-term (over 20 years, or lifetime) cost-effectiveness of antiviral regimens. Findings from current decision analytic CEA modeling studies show that two forms of interferon (i.e., interferon and pegylated interferon) in combination with ribavirin are cost-effective in naïve patients in terms of reducing liver complications or improving quality-adjusted survival. [26-31] Although decision analytic CEA has been widely used to assist policy formation on the adoption of antiviral combination therapy, the limitations of the target population in the modeling studies and the statistical limitations of the cost-effectiveness estimates may not fully satisfy the needs of decision makers who must consider the use of therapy among a much broader population than that considered to date in randomized clinical studies.

Limitations of Randomized Controlled Trial-Based Modeling Studies

Current recommendations for treatment of HCV-infected persons are derived from data gathered in previous RCTs.[19, 32] Although RCTs represent the gold standard for establishing efficacy, the methodological approach employed in RCTs often limits the generalizability of study findings. Study inclusions and exclusions used in patient selection result in a non-

representative subset of the HCV-infected population. Patients who were involved in these trials were carefully selected so as to exclude those with conditions that might potentially compromise treatment response. Many of the exclusion criteria in these RCTs included groups at high risk for hepatitis C, such as patients with HIV infection, hemophilia, renal disease, and substance abuse problems (i.e., alcohol and injection drug use). In addition, study inclusion/exclusion criteria limited enrolled populations to a homogenous cohort of patients with a minimum number of complications and who were able and willing to complete the therapy and follow-up that assist the assessment of efficacy.[33] As a result, the majority of persons with HCV in the general population were not eligible for enrollment in these studies.[34-39] Similarly, in clinical trial settings, the treatment and the close monitoring approach limit the generalizability to routine clinical settings. Finally, the intermediate study endpoints examined in most RCTs (i.e., SVR), further limit the ability to address issues of long-term cost-effectiveness.

Evidence from community settings has shown the discrepancies from the clinical trial settings on the use of medical services for HCV care. Rates of antiviral therapy in HCV-infected patients were 10.7% to 30.3% in some populations.[34-39] Older patients or those with psychiatric diseases, HIV co-infection, alcohol and drugs use disorders, and with public-funded insurance programs were more likely to be ineligible for antiviral therapy.[36, 40-42] These findings indicate that today's major issues surrounding the treatment of HCV infection in clinical practice are (1) a broad spectrum of patients remain untreated, (2) the patient's characteristics and co-morbidities are key components of the treatment decision, and (3) the duration of treatment and medication adherence in community settings may not achieve the same level of treatment responses in clinical trials and adherent with consensus recommendations.

Limitations of Traditional Cost Effectiveness Estimates

Additional limitations of existing decision analytic cost-effective modeling studies are two major uncertainties surrounding the outcomes measure (incremental cost effectiveness ratio, ICER) in the interpretation of CEA results. First is the uncertainty of decision rule that describes if the new treatment or intervention is cost-effective in the analysis.[43] The ICER, a traditional outcome measure of CEA, generates an estimate of the extra cost for an additional unit of benefit when a CEA involves an intervention of new technology (T_1) compared to no treatment or standard care (T_0). The expected values of mean cost and mean effect for Ti (i=0 or 1) as u_{Ci} and u_{Ei} respectively, the ICER comparing T_1 to T_0 is defined in Equation 1-1.

$$ICER = \frac{u_{C1} - u_{C0}}{u_{E1} - u_{E0}} = \frac{u_{\Delta C}}{u_{\Delta E}} \tag{1-1}$$

Determination of whether a new treatment intervention is cost effective (worthwhile) relies on the decision maker's willingness to pay (λ), an unknown value from the cost and effectiveness data. Decision should be made to adopt the new technology if the ICER is less than the maximum amount of λ in Equation 1-2.

$$ICER = \frac{u_{\Delta C}}{u_{\Delta E}} < \lambda \tag{1-2}$$

Where λ is the ceiling ratio, that decision maker's maximum acceptable willingness to pay per unit of health gain. Because that λ is left entirely to the decision maker, and will presumably vary by decision makers' various preferences for health relative to other goods among the population or available budgets for health care, the precision of maximum amount of willingness to paid is taken as a uncertainty surrounding the observed ICER.

Second is the statistical uncertainty in estimation of confidence interval for ICER. Because the true μ_{Ci} and μ_{Ei} in the population are unknown, the un-observerable ICER parameter is estimated using the "analogy" estimator (Equation 1-3).[44]

$$\hat{ICER} = \frac{\overline{C_1} - \overline{C}_0}{\overline{E}_1 - \overline{E}_0} = \frac{\Delta\overline{C}}{\Delta\overline{E}} \qquad (1\text{-}3)$$

Due to uncertainty in these estimates, the bootstrapping method is most widely used to estimate the confidence interval (or variance) of ICER by multiple replications of cost and effect differences in the study samples. It denotes the joint probability (typically 0.95) of containing the true ICER parameter, and is shown like an ellipse (called confidence ellipse) on the cost-effectiveness plane (Figure 1-3). Particular concerns occur when constructing the confidence interval (CI) for the ICER, if the joint probability distribution of cost and effects extend more than one quadrant on the CE plane, the ICER confidence interval can be problematic. One example is the study results from an economic evaluation of crisis residential care (T_1) for people who have serious mental illness in need of hospital-level care.[45] A 5,000 bootstrap estimates for ICER, a negative ICER occurs 36% of time (=8%+28%), and 77% (=28/36) of the negative ICERs represent cases in which the crisis residential costs less and provides more. However, 64% of the ICER bootstrap estimates suggest that crisis residential care costs less and provides less (Figure 3). Consequently, these study results cannot provide meaningful information on the probability of implementing a program which is cost effective for the decision makers. Because negative ICER may be economically efficient, decision makers might not want to adopt intervention associated with reduced health.

However, some analysts suggested that that magnitude of a negative ICER coveys no useful statistical information,[43] and that the confidence interval of an ICER is meaningful only

when uncertainty is restricted to one of the positive quadrants of the CE plane. Recently, the net benefit regression framework of cost effectiveness was developed to manage these uncertainties surrounding the economic evaluation of treatment intervention.[46] The net benefit (i.e., net monetary benefit, NMB) approach rearranges the formulation of the cost-effectiveness ratio with a threshold value (decision rule or willingness-to-paid) to overcome the ratio problems with traditional ICER. Furthermore, in the regression framework, factors attributable to ICER can be identified and quantified the magnitude of impact on the ICER. This practical advantage of net benefit regression framework, therefore, is able to identify important subgroups of patients for the HCV therapy

In summary, regardless of the limitations of the traditional cost-effectiveness estimate, the results of CEA offer policymakers important information of a rank of a rank of ICER of antiviral therapy by their maximum amount of willingness to pay.

Purpose of Study

HCV infection poses an increasingly significant clinical, economic, and health-related quality of life burden to the individual, the health care system, and society in general, as the U.S. population with chronic HCV continues to age. In response, many innovative anti-HCV agents will be developed to meet the growing demands for more effective treatment interventions, which continue to increase costs for the treatment and prevention of liver complications. There is an increasing demand among healthcare policymakers for economic evaluations of current antiviral treatment intervention strategies to the healthcare system.

Existing decision analytic models based on clinical trial settings conducted for a managed care organization viewpoint to compare antiviral treatment strategies have served as a guide to efficient resources allocation.[30] Given the uncertainties created by the application of clinical trial data in the estimate of the cost-effectiveness ratio as mentioned above, retrospective economic

evaluation will provide valuable information to the stakeholders in the system about the impact of previous decisions and the cost-effectiveness of current HCV treatments and prevention of HCV-related complication strategies.

To achieve this purpose, this study used a managed care organization (MCO) dataset to estimate the cost-effectiveness of initial combination antiviral therapy among newly-diagnosed, HCV-infected patients and to identify what factors contribute to economically attractive antiviral therapy. This thesis will evaluate the impact of patient-level factors, provider-level factors, treatment tolerability, and treatment interruption on the efficient use of antiviral therapy. MCOs are key sites for analysis of the treatment of HCV. First, the age group most frequently diagnosed as having HCV, ages 30 to 49 years, is likely to be employed and covered by employer-provided health insurance. Approximately 93% of privately insured persons receiving coverage from their employer are enrolled in managed care.[47] Second, a MCO setting automated claims dataset will allow for assessing the possibly best efficiency of antiviral therapy that may differ in a publicly funded healthcare system (e.g., fee-for-service or Medicaid and Medicare programs). To enable efficient use of resources, in a MCO health care environment, the health plan designs involve cost-containment strategies, cost sharing and benefit coverage that may affect health service utilizations. In this thesis, employing a net benefit regression framework will be able to incorporate the impact of patient-level variability on the cost effectiveness of antiviral therapy which may not be fully explored in previous modeling studies.

Study Aims

To answer these study questions, three individual analyses were performed to address the following specific aims:

- **Objective 1:** To estimate the effectiveness of combination antiviral therapy relative to no treatment in newly-diagnosed, HCV-infected patients. Delay in time to first occurrence of end-stage liver disease (ESLD) was the primary effectiveness measure, including HCC,

liver transplantation, decompensated cirrhosis and a proxy of death. Furthermore, the secondary effectiveness measure was rate of ESLD progression.

- **Objective 2:** To estimate difference in average total health care cost between patients with and without treatment during the study period.

- **Objective 3:** To assess the cost-effectiveness of combination antiviral therapy relative to no treatment among newly-diagnosed, HCV-infected patients while controlling for patients baseline characteristics, including social demographics, comorbid conditions and health service use. The incremental net benefit (net monetary benefit, NMB) was employed as a measure of the value for the cost of antiviral therapy relative to no treatment in the regression framework. Effects of covariates on the incremental net benefit of treatment will be assessed by the interaction with treatment in the regression framework.

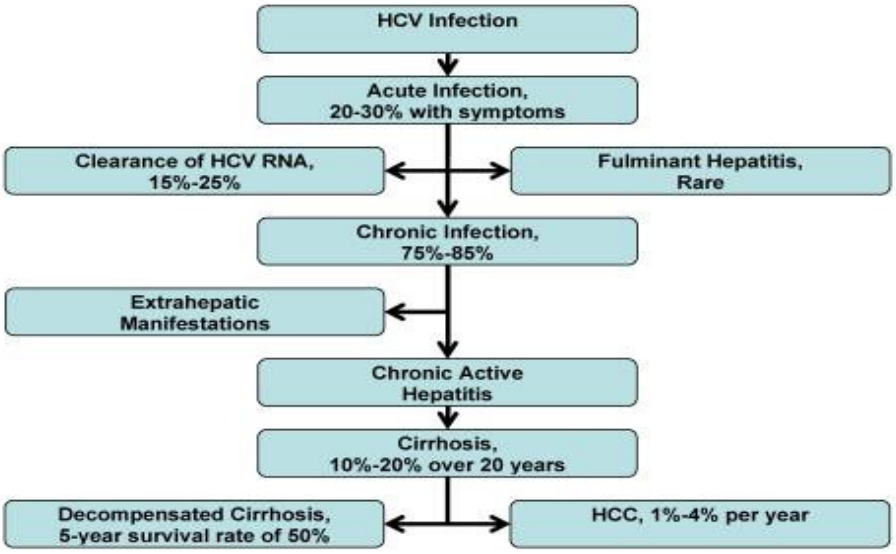

Figure 1-1. Natural history of hepatitis C virus (HCV) infection. (Source: Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci 2006;3(2):47-52).

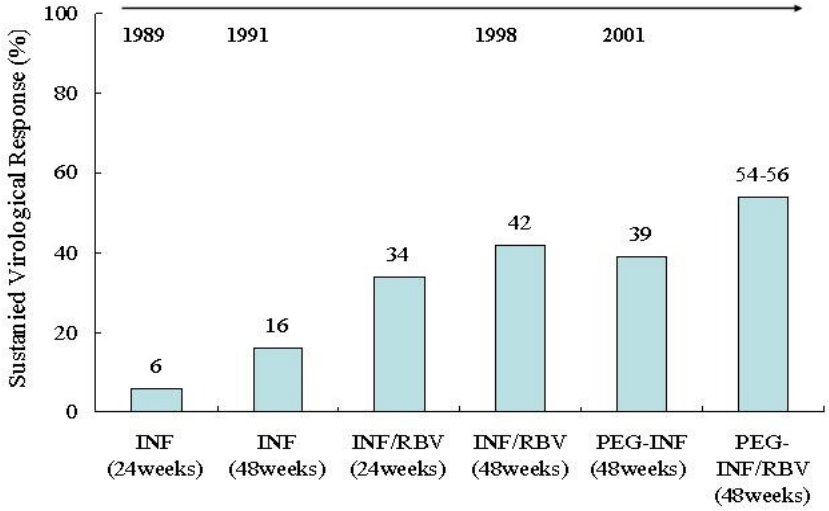

Figure 1-2. Milestones of interferon (INF)-based therapy for chronic hepatitis C. (Source: Strader DB, Wright T, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004;39(4):1147-1171).

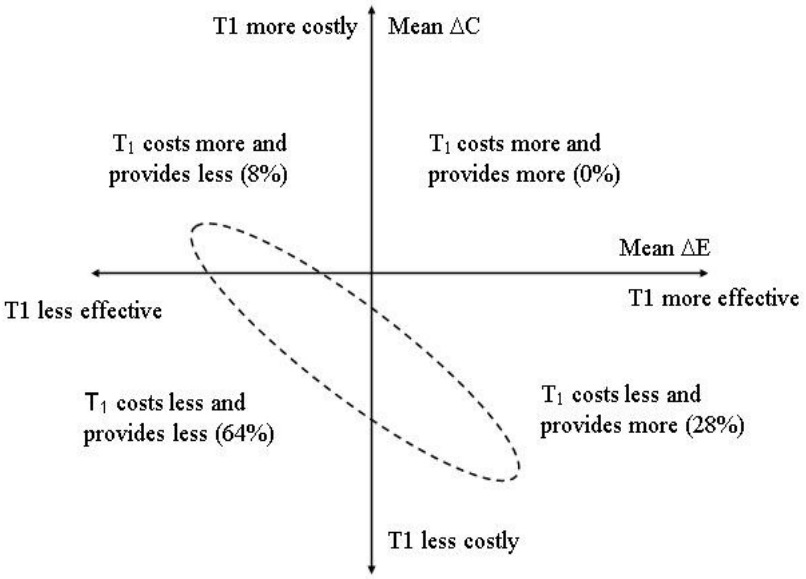

Figure 1-3. Bootstrapped confidence ellipse of ICERs on the cost-effectiveness plane.

CHAPTER 2
METHODOLOGICAL REVIEW

Net-Benefit Approach to Overcome the Ratio Statistic of Cost-Effectiveness

To quantify this sampling uncertainty in ICER measure, NMB was proposed by Stinnett and Mullaphy in 1998.[43] The *net benefit* (NB) was proposed as an alternative summary measure of value for money of health interventions. The NB approach employs a simple scale in order to overcome the problems with cost-effectiveness (CE) ratios. When the CE ratio comparing a new treatment (T_1) with an alternative intervention (T_0), the threshold value (R_T) in the analysis was defined in Equation 2-1.

$$R_T \equiv \frac{(\mu_{C1} - \mu_{C0})}{(\mu_{E1} - \mu_{E0})} = \frac{\mu_{\Delta C}}{\mu_{\Delta E}} \tag{2-1}$$

New treatment will be adopted if the net monetary benefit (NMB) is greater than 0 in Equation 2-2.

$$\frac{\mu_{\Delta C}}{\mu_{\Delta E}} < R_T \text{ or } R_T \times \mu_{\Delta E} - \mu_{\Delta C} > 0 \tag{2-2}$$

In the model, $\mu_{\Delta C}$ and $\mu_{\Delta E}$ are mean cost and mean health effect, respectively, of treatment T_i (i=1 or 0).

$R_T \times \mu_{\Delta E} - \mu_{\Delta C}$ is called net monetary benefit (NMB) of the health intervention. It is the increase in effectiveness ($\mu_{E1} - \mu_{E0}$) multiplied by the amount of money the decision maker is willing to pay per unit of increased effectiveness ($R_T=\lambda$), less the increase in cost ($\mu_{C1} - \mu_{C0}$). Therefore, the new health intervention is cost effective (Equation 2-3), if

$$NMB = \lambda \times \mu_{\Delta E} - \mu_{\Delta C} > 0 \tag{2-3}$$

Another form of NB is *net health benefit* (NHB), which defines the new health intervention as cost effective (Equation 2-4), if

$$NHB = \mu_{\Delta E} - \frac{\mu_{\Delta C}}{\lambda} > 0 \qquad (2\text{-}4)$$

Advantages of *net benefit* compared to the traditional ICER are summarized below. First, NB is better to manage uncertainty in CEA. Unlike the ICER, variance of net benefits can be estimated from sample mean costs and mean effects. Variance of NMB is determined by

$$\text{var}(\hat{NMB}) = \lambda^2 \text{ var}(\Delta\overline{E}) + \text{var}(\Delta\overline{C}) - 2\lambda \text{cov}(\Delta\overline{E}, \Delta\overline{C})$$

and the variance of NHB is determined by

$$\text{var}(\hat{NHB}) = \text{var}(\Delta\overline{E}) + \frac{1}{\lambda^2}\text{var}(\Delta\overline{C}) - \frac{2}{\lambda}\text{cov}(\Delta\overline{E}, \Delta\overline{C})$$

Based on the estimated variance and central limit theorem, a (1-α) % confidence interval (CI) can be constructed as:

$$CI = \hat{NB} \pm z_{\alpha/2}\sqrt{\sigma^2_{NB}}$$

Second, it avoids the ambiguity of traditional ICERs. As model 2 showed, NMB is a function of the threshold value of ICER. When λ or R_T is equal to zero, the negative ICER will be represented as an intercept on the y axis (α). Also, NMB is 0 when the ICER of health intervention (T_1) is equal to the threshold value (λ or R_T). See Figure 2.1.

Net-Benefit Regression Approach of Cost-effectiveness Analysis

Hoch et al. first published the net benefits statistic which can be used to estimate incremental cost-effectiveness within the regression framework.[46] They incorporated the net benefit in the standard linear regression framework to assess the impact of explanatory variables on the cost effectiveness.

In the net benefit approach, the difference in the mean net benefit of the new intervention (T_1) and mean net benefit of standard care treatment (T_0) can provide the overall incremental net benefit by

$$\begin{aligned}\overline{NMB}_1 - \overline{NMB}_0 &= \left(\lambda \times \overline{E}_1 - \overline{C}_1\right) - \left(\lambda \times \overline{E}_0 - \overline{C}_0\right) \\ &= \lambda(\overline{E}_1 - \overline{E}_0) - (\overline{C}_1 - \overline{C}_0) \\ &= \lambda \times \Delta\overline{E} - \overline{C} \\ &= \Delta\hat{NMB}\end{aligned}$$

Therefore, cost effectiveness is estimated by using the net-benefit framework to define a net-benefit value for individual subject,

$$NMB_i = \lambda \times E_i - C_i$$

Where Ei and Ci are the observed effect and cost for subject i. A linear model for subject i's net-monetary-benefit (NMB) is formed as in Equation 2-5:

$$NMB_i = \alpha + \sum_{j=1}^{p} \beta_j X_{ij} + \delta T_i + \varepsilon_i \qquad (2\text{-}5)$$

Where α is the intercept term, p covariates X, T is a treatment dummy variable (taking 1 for new treatment intervention under consideration, 0 for standard care or no treatment), and ε is a stochastic error term. Regression coefficient (δ) on the treatment dummy variable provides the estimate of the incremental net-benefit (cost effectiveness), $\overline{NMB}_1 - \overline{NMB}_0$. Significance of this net-benefit regression framework is to add additional explanatory variables in order to directly examine their impact on cost-effectiveness. In the model, δ gives the incremental net-benefit of implementing new treatment intervention controlling for confounding variables. In addition, the interaction terms can be added into the model for examining marginal effects influenced by the covariates:

$$NMB_i = \alpha + \sum_{j=1}^{p} \beta_j X_{ij} + \delta T_i + T_i \sum_{j=1}^{p} \gamma_j X_{ij} + \varepsilon_i \quad (2\text{-}6)$$

Where the magnitude and significance of the coefficient γj on the interaction between treatment and covariates indicate how the cost-effectiveness of T_1 is expected to vary at the margin. Advantages of a regression model 4 are the ability to examine the impacts of covariates on the incremental cost-effectiveness.

Current CEA results pay less attention to the impact of a patient's comorbid conditions and medication adherence on the effectiveness of treatment. Furthermore, most studies were conducted in the earlier years when many techniques were under development; therefore, decision making uncertainty was not undertaken in the estimation of cost effectiveness. There are two distinct advantages of the net-benefit regression model, which are the purpose of using this method of CEA. First, it is able to provide the ability to evaluate the importance of covariates on the marginal cost-effectiveness of antiviral therapy, thus allowing the identification of patient subgroups for HCV therapies that are more cost-effective. Second, it provides attractive statistical properties to summarize the uncertainty surrounding the outcome measure of ICER in the cost-effectiveness analysis.

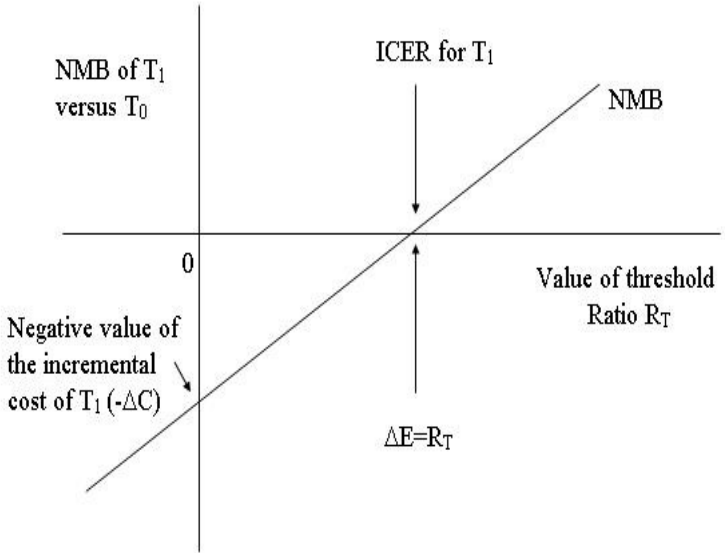

Figure 2-1. Net monetary benefit (NMB) as a function of the threshold cost-effectiveness ratio. (Source: Drummond MF, SM TG, O'Brien BJ. Methods for the Economic Evaluation of Health Care Programmes, Chaper 5: Cost Effectiveness Analysis. Third ed. New York: Oxford University Press; 2005).

CHAPTER 3
METHODOLOGY

Data Sources

Our study sample was constructed using the Integrated Health Care Information Services (IHCIS) National Managed Care Benchmark Database between January 1997 and June 2007. The IHCIS is a national managed care database that includes more than 80.1 million patients from a total of 46 health plans in September 2007. Data elements used in the study include eligibility records, patient demographics, inpatient and outpatient medical services, and pharmacy claims.

The IHCIS cost figures are standardized across health plans, reflecting health plan payments for all provider services. There are several different approaches (e.g., algorithms, multivariate models) for standardizing pricing for each of the following services categories: inpatient and outpatient facilities, professional services, pharmacy claims, and ancillary services. Adjustments performed by the IHCIS are designed to create standard process reflecting allowed payments. Therefore, price comparisons across patients and geographical areas can be made in a consistent manner. All expenditures for each study sample were collected and adjusted to 2007 US dollars using the Consumer Price Index for Medical Care Services. All data was linked by de-identified person identifiers.

According to personal contact, the IHCIS prescription drug information is reliable for the date of prescription and amount paid, but is not reliable for quantity or days of supply for an antiviral prescription dispensed. Patient's age is only available as year of birth in the dataset. Moreover, information on death and causes of death are not reliable in the IHCIS dataset. In place of such a dataset, operational definitions and assumptions to classify antiviral therapy exposure and effectiveness of antiviral treatment were derived based on clinical treatment

guidelines and the availability of dataset. This study was approved by the Institutional Review Board of the J. Hillis Miller Health Science Center at the University of Florida on 17 January 2008.

Study Population

Our study cohort consisted of patients with newly-diagnosed, hepatitis C virus (HCV) infection based on the presence of ICD-9 codes (70.44, 70.41, 70.54, 70.51) for HCV. To include patients with equal exposure to risk factor information for HCV progression between treated and non-treated patients, the newly-diagnosed HCV design allows for minimizing the difference in duration of HCV history and controlling co-existing comorbid conditions. For instance, one might expect patients who had a longer history of HCV infection may be more likely to receive treatment for HCV infection, and perhaps may have failed to respond to previous treatment. Moreover, duration of HCV infection is associated with probability of progression from mild disease to ESLD. While it is impossible to confirm the accurate time of HCV infection, an operationally defined "newly-diagnosed HCV-infected" cohort would provide the ability to adjust for the potential influence of these factors on treatment effect.

Inclusion criteria for the study cohort were as follows (Figure 3-1):

- **Step 1.** Patients with ≥1 ICD-9codes for a HCV infection in inpatients, or patients with ≥2 outpatient encounters ≥30 days apart with ≥1 ICD-9 codes for a HCV diagnosis, or patients with <2 outpatient encounters ≥30 days apart with ≥1 ICD-9 codes for a HCV diagnosis, but with ≥1 interferon claims between January 1997 and June 2007. Date of the first claim in which an ICD-9 code for HCV is observed was defined as the diagnosis date.
- **Step 2.** Patients must have continuous enrollment for 365 days before the diagnosis date with no gap in enrollment greater than 30 days. Newly-diagnosed HCV patients were defined as those who had no HCV claims during the 365 days in the pre-diagnosis period.
- **Step 3.** Exclusion criteria for patient selection included the following:
    - Patients with prior organ transplantation (except for liver) and alcoholism, identified by the presence of ICD-9 codes in the pre-index date period. (See Table 3-1)

- Patients re-infected with HCV after liver transplantation. These patients were identified by the first occurrence of ICD-9 codes for liver transplantation in the pre-index date period, and earlier than the first occurrence of HCV-related cirrhosis claim. Coding system for liver transplantation was described in "Effectiveness Outcome" section.

- Patients with co-existing HCC, identified by the presence of ICD codes for HCC in the pre-index date period. Coding system for liver transplantation was described in "Effectiveness Outcome" section.

- **Step 4.** Included patients must be aged between 18 to 64 years at the index date. Age at HCV diagnosis was calculated from the year of diagnosis date to the year of birth.

- **Step 5.** Additional study criteria for comparisons of study outcomes were described in the following sections.

Exposure to Combination Antiviral Therapy

Exposure to combination antiviral therapy was determined by the presence of National Drug Code (NDC) in pharmacy claims and Healthcare Common Procedure Coding System (HCPCS) codes (Table 3-1) in outpatient claims for all forms of interferon, including interferon alfa 2a, interferon 2b, Rebetron® (interferon alfa 2b combined with ribavirin), PEGINTERFERON® (interferon alfa 2a combined with ribavirin), pegylated interferon alfa 2a and pegylated interferon alfa 2b, and NDC for ribavirin available in the dataset.[32, 48]

Only newly-diagnosed HCV patients with initial antiviral combination therapy were included in the analysis. In other words, all treated patients in the study had received at least one claim of interferon in combination with ribavirin after the diagnosis date (i.e., post- diagnosis period). Patients were excluded if they were monotherapy users or had a prior antiviral prescription (including any form of interferon and ribavirin) in the pre-diagnosis period. Rationales of using new treatment users are (1) inclusion of prevalent treatment users can lead to a treatment group with difference duration of prior therapy, which can lead to over- or underestimating treatment effect; (2) inclusion of prevalent treatment users may lead to fail to

adjust for baseline confounders between treatment groups because these factors are plausibly affected by treatment.[49]

Definition of Treatment Exposure

Because the reliability of the pharmacy claims is restricted to date of service (prescription fill date) and amount paid, the date of the first interferon prescription was defined as the index date. Operational definitions of treatment exposure were defined by the numbers of continuous prescription refills in each month (30 days) after the index date.

Continuous refills were constructed based on the following findings in the pharmacy claims:

- Over 60% of interferons were dispensed every 24 to 32 days among treated patients; the days supply of antiviral medications was assumed 30 days;
- Medication interruption was defined by an allowable gap (i.e., 30 days) between 2 consecutive refills. Continuous refills, therefore, were defined as a ≤60-days period between 2 consecutive refills. If a patient had >60 days between 2 consecutive refills it indicated the presence of a medication gap (i.e., >30 days without treatment) before the subsequent refill. If the patients had a medication gap >60 days (i.e., ≥90 days between 2 consecutive refills), then the patient was considered to continue another new course of treatment on the subsequent refill.
- Ribavirin was assumed to be dispensed concurrently with interferon for a treated patient, because the majority of treated patients (>90%) had ribavirin total refills less than ±20% interferon total refills, and ribavirin and interferon had similar patterns on dispensing frequency among treated patients in Table3-3.

Therefore, information related to interferon refilling in each month was used to indicate exposure to antiviral combination therapy in the analyses. Ribavirin refilling and prescribing duration was assessed in the follow-up to examine the level of combination therapy persistency.

In the base case analysis, patients who ever received at least one refill of interferon combination with ribavirin were compared to those who never received treatment. To explore the influence of treatment duration on the cost-effectiveness of antiviral therapy, subgroup analysis was performed in the comparisons of net benefit of treatment among patients with “usual care”

or “extended care” relative to no treatment. We used “usual treatment” to indicate patients who ever received 11to14 continuous refills of antiviral therapy after the index date (referring to 12 months or 48 weeks of treatment duration within 15 months). Treated patients who received ≥15 continuous refills of antiviral therapy were classified as “extended care.” Based on the operational definition using continuous prescription refills, we assumed that patients in the subgroup analysis remained in the study cohort at least 12 months.

Establishment of Comparison Groups

Base case analysis

Study treatment (treated patients) and control (untreated patients) groups were generated by a pseudo-index date randomly assignment. Because there is no information on dates of interferon refills among untreated patients, a pseudo-index date was assigned to a subset of non-treated patients (controls) based on the distribution of length of time between the diagnosis date and the index date (i.e., date of first interferon prescription) among treated patients. Study controls were randomly selected with treated patients with a 3:1 ratio. For example, for a patient who initiated antiviral therapy 60 days after the HCV diagnosis date, one of the eligible untreated patients (control) was randomly selected and assigned a pseudo-index date, 60 days after this control patient’s diagnosis date, as shown in Figure 3-2.

Subgroup analysis

In the subgroup analysis, controls were individually selected from a set of untreated patients based on the distribution of length of time between the HCV diagnosis date and the end of treatment (i.e., date of last interferon prescription plus 30 days) in patients with usual care or extended care. Similarly, subgroup controls were randomly selected with treated patients with a 3:1 ratio. Similarly, decision on the index date in the subgroup analysis used the same approach in the base case analysis described above (based on the length in time between date of HCV

diagnosis to the date of first interferon prescription among patients with usual care or extended care and their matched controls).

Stratified analysis

According to the natural history of HCV infection, once an advanced liver disease (e.g., cirrhotic fibrosis) is established, the risk of hospital readmission for the initial or other decompensation, HCC development, and liver transplantation or death may vary across individual patients (Figure 1-1). Since treatment was initiated in patients with HCV-related cirrhotic symptoms in clinical practice (as compared to patients with asymptomatic chronic HCV in the clinical trial setting), a dimension of risk heterogeneity may also underlie treatment effect heterogeneity. For this reason, differences in treatment effectiveness and costs were analyzed between HCV-infected patients with and without compensated cirrhosis. Furthermore, considering low doses of interferon combined with ribavirin may be initiated to patients with mild degree of cirrhosis decompensation who have been a candidate of liver transplantation in practice. Treatment effect in the cirrhotic group could be confounded by the severity of HCV infection (e.g. portal hypertension, variceal bleeding, encephalopathy) are treated with antiviral therapy. To account for the impact of cirrhosis decompensation on the ESLD development, patients with severe decompensated cirrhosis were categorized and analyzed in the stratified cirrhotic group both in base case and subgroup analyses.

Uses of the ICD-9, CPT, and HCPCS codes for cirrhosis diagnoses and procedures are shown in Table 3-1. Operational definitions of cirrhosis diagnoses are shown in the "Effectiveness Outcomes" and "Confounders and Covariates" sections. In the analysis phase, an interaction term that evaluates the difference in treatment effectiveness and cost attributed to cirrhosis was examined by an interaction with treatment in the effectiveness and cost estimation model.

Study Outcomes and Follow-Up

Patients were followed from the index date up to when the outcomes of interest occurred, the date of the last data in the database, or they turned 65 years of age, whichever came first. Clinical outcomes were censored at the patient's last follow-up visit or when they turned 65 years of age after the index date. The clinical effectiveness and cost outcomes are defined in the following sections. (Figure 3-3. Study outcomes and follow-up)

Effectiveness Outcomes

Study primary effectiveness measure was defined as a delay in ESLD measured by survival time in months. ESLD was defined as the occurrence of severe decompensation, HCC, LT, or a proxy of death in the study follow-up period (i.e., the period of observation after the index date). Study secondary effectiveness measure was the Kaplan-Meier estimate of ESLD occurrence rate during the study follow-up.

Clinical end point of study interest (ESLD) was categorized over the study follow-up, including ≥1 ICD-9 codes of HCC, severe decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic coma), and LT in the first 3 diagnostic and procedure fields in outpatient claims, or ≥1 ICD-9/CPT codes of HCC, severe hepatic decompensation and LT in first 4 diagnostic and procedure fields in inpatient claims, using ICD-9, CPT, and HCPCS codes as shown in Table 3-1. To establish the validity of ICD-9 codes of severe hepatic decompensation status, patients were required to have ≥2 outpatient encounters ≥7 days apart with ≥1 ICD-9 codes for severe decompensated cirrhosis in the outpatient claims file. For patients with a diagnosis of severe decompensated cirrhosis in both pre-index and after the index date were excluded from the analysis. In addition, the status code V58.69 (in Table 3-1) is commonly coded for long-term use of medication monitoring in patients who received a liver transplant and with other medical conditions. Patients with V58.69 in the first 3 diagnostic and procedure fields

in outpatient claims file or the first 4 diagnostic and procedure fields in inpatient claims were required to have a concomitant diagnosis of liver transplant.

A proxy of death was defined by loss of health insurance eligibility within 32 days after receiving nursing home and hospice services. Information on the nursing home and hospice service was obtained from the provider type code and service type code in the IHCIS user manual in 2007.

Cost Outcomes

From the MCO perspective, direct medical costs among individual patients including inpatient, outpatient, and pharmacy services incurred in each follow-up month were examined. All costs were adjusted to 2007 dollars using the medical service component of the Consumer Price Index.

Confounders and Covariates

Baseline Characteristics of Study Cohort

To control for those patients at high risk for complications with either antiviral therapy or no treatment, baseline characteristics of cohort members and changes in some of these during the study follow-up were identified. The known risk factors for HCV-related complications could be obtained and allowed discrete categorizations operationalized from the database, as shown in Table 3-2. These are hypothetical potential confounders:

Patients' social demographic characteristics. Patient's age, gender, year of HCV diagnosis, and social economic status were identified for all study subjects. Studies of the natural history of chronic hepatitis C have shown male patients and those over age 40 at the time of infection were associated with more rapid HCV-induced fibrosis progression.[50] In this study, patient's age was retrieved in each month during study follow-up followed by the age at HCV diagnosis year, and was treated as a time-dependent covariate in the Cox regression model and in

the inverse probability weighting process for total cost estimation. It is important to note that gender is not only associated with disease progression but also tied to poor treatment response. A binary variable created for gender was analyzed; female patients were coded by 0 and male patients were coded by 1.

Social economic conditions, including type of insurance, type of health plan, and census region, are associated with patient access to antiviral therapy in clinical practice and the willingness to initiate and complete treatment.[34-36, 38] The social economic indicators were subtracted from the eligibility duration covering the HCV diagnosis date, including type of insurance, type of health plan, and geographic region. Two binary variables were created for the type of insurance (private/public). Patients with public insurance, including Medicare and Medicaid, were coded by 0, and those with private insurance were coded by 1. To further account for the differences among types of health plans, HMO (health maintenance organization) was categorized as plan1, PPO (preferred provider organization) as plan2, and POS (point of service) as plan3. Three binary variables were created for those patients with the type of health plan (i.e. 1/0=yes/no). As a general rule, POS and PPO offer more freedom and choices than an HMO. Even if patients go out-of-network for their medical needs, they are still covered to a certain degree. HMOs, for example, do not cover members if they go outside of the HMO network of providers. Unlike PPO, POS plans have no deductibles and limited co-payments for in-network coverage. With a PPO, patients are required to meet deductibles and pay co-payments.[51] In a chronic health condition, like HCV infection, PPO and POS offer a greater choice, yet a higher copayment on the access or referral to specialists or the doctor who patients trust may have impacts on the choice of antiviral therapy initiation. Although geographic area may not directly influence HCV care, the practice patterns and patient education levels vary in

different geographic regions. Census regions were categorized by 1=New England and Middle Atlantic, 2=East North Central and West North Central, 3=South Atlantic, East South Central, and West South Central, 4=Mountain and Pacific, and 5=National and Other in the IHCIS dataset. And, 5 binary variables were created for each category of census region was analyzed; patients resided in the census region were coded by 1 and outside the region were coded by 0.

Since the National Institute of Health (NIH) initiated their second consensus guideline regarding the management and treatment of HCV infection in 2002,[52] HCV identification and management have been disseminated among health professionals through updated clinical guidelines for the HCV-infected subpopulation (e.g., HIV and HBV con-infection, psychiatric/or drug disorders).[18, 19, 53, 54] To examine the potential impact of practice pattern variation on HCV care, the patient's year of HCV diagnosis was categorized as 1998=0, 1999=1, and on up to 2007=9 in this study, and 10 binary variables created for the individual year of HCV diagnosis was analyzed.

Patient comorbid conditions. Risks for more rapid HCV-induced fibrosis progression, such as individuals co-infected with HBV or HIV were identified in all study subjects.[55, 56] Even though HIV accelerates HCV-related liver disease, studies showed HCV antiviral therapy appear to be protective in most instances, including those with HIV co-infection and delay hepatic decompensation.[57-59] Patients with co-infection were identified by the presence of ≥1 claims of ICD-9 codes for HIV/HBV during the pre-index period. A binary variable was created in patients co-infected with/without HBV infection (1/0) and with/without HIV infection (1/0).

There is increasing information showing that obesity and type II diabetes are associated with liver fibrosis progression and poor response to hepatitis C treatment.[32 60, 61] Obesity and the

metabolic syndrome, including insulin resistance and hyperlipidemia are associated with steatosis (fatty liver), which is linked with a greater risk of cirrhosis and HCC.[60]

To account for the fact that current ICD-9 codes may not be sufficient to capture patient's diabetic and/or obese condition, Food and Drug Administration (FDA)-approved hypoglycemic agents and anti-obesity drugs were used. Patients with obesity and diabetes were identified by the presence of ≥1 claims of ICD-9 codes for diabetes or obesity in inpatient or outpatient claims file, or ≥1 claims of NDC for FDA-approved prescriptions for obesity and diabetes therapy in pharmacy file during the pre-index period. FDA-approved prescriptions for diabetes included in this study were insulin; metformin and Metaglip® (glipizide and metformin), Janumet® (sitagliptin and metformin) , Glucovance® (glyburide and metformin), Actoplus Met® (pioglitazone and metformin), Avandamet®(rosiglitazone and metformin); sulfonylurea (i.e., glipizide, glyburide, glimepiride), thiazolidinediones (i.e., rosiglitazone, pioglitazone) and Avandaryl® (rosiglitazone and glimepiride), Duetact® (glimepiride and pioglitazone); alpha-glucosidase inhibitors (i.e., acarbose, miglitol), Prandimet® (repaglinide and metformin); and meglitinides (i.e., repaglinide, nateglinide). FDA-approved prescriptions for obesity used in this study were sibutramine and orlistat. A binary variable was created in patients with/without obesity (1/0) and with/without diabetes (1/0).

Patients with mental illness (including depression) and drugs disorders (injection drug users) have a greater risk of HCV infection. However, active psychiatric/ drug disorders once were considered as relative contraindications for combination antiviral therapy because of HCV treatment-related psychiatric side effects and lack of successful collaborating care between experts in HCV and healthcare providers specializing in substance-abuse. [33, 52] Research has shown it is feasible and effective to treat patients with HCV and comorbid psychiatric and

substance use disorders through a multidisciplinary team.[62] In addition, the depression side effects may lead to dose reduction and treatment discontinuation affecting the efficacy of antiviral therapy. The FDA-approved selective serotonin reuptake inhibitors (SSRIs) have been concomitantly prescribed with interferon-based antiviral therapy to reduce the risk of unwanted effect and complete treatment.[63]

Patients with psychiatric/drugs disorders were identified by the presence of ≥1 claims of ICD-9 codes for psychiatric/drugs disorders in inpatient or outpatient claims file during the pre-index period. Patients with depression were identified by the presence of ≥1 claims of ICD-9 codes for depression in inpatient or outpatient claims file or ≥1 claims of NDC for FDA approved SSRIs during the pre-index period. A hepatologist suggested the common SSRIs used in HCV-infected patients with depression were fluoxetine, paroxetine, sertraline, citalopram, escitalopram, fluvoxamine, venlafaxine, and duloxetine. Additionally, to explore the association between antidepressant use and treatment outcome, patients prescribed with antidepressants (SSRIs) were identified by the presence of ≥1 claims of NDC for FDA-approved SSRIs in the follow-up period. Three binary variables were created for patients with/without psychiatric disorder (1/0), with/without drug dependence (1/0), and use/no-use antidepressants (1/0).

Other comorbid conditions, end-stage renal disease (ESRD) or dialysis, heart diseases, chronic obstructive pulmonary disease (COPD), cerebral vascular disease (CVD), and hyperthyroidism, were reported to possibly impact treatment decisions.[52] Some of the important factors that need to be taken into consideration of appropriate timing for antiviral therapy in patients with the comorbid conditions above include severity of liver disease, comorbid conditions, and motivation. Patients with comorbid conditions were identified by the presence of ≥1 claims of ICD-9, CPT, and HCPCS codes for ESRD/dialysis, COPD, CVD, heart disease, and

hyperthyroidism either in inpatient or outpatient claims filed during the pre-index period. Binary variables were created for patients with/without ESRD (1/0), with/without COPD (1/0), with/without CVD (1/0), with/without heart disease (1/0), and with/without hyperthyroidism (1/0). All comorbid conditions were identified using ICD-9, CPT, and HCPCS codes, shown in Table 3-1.

Prior medical services uses. Annual medical expenditure, hospitalization, outpatient visits, and emergency room visits within the same pre-index period were used as proxies of patient health status. Patients with higher levels of medical service utilization can be expected to have many health issues and greater severity of co-morbidities might adversely affect the initiation of antiviral therapy and thereby increase the possibility of poor outcome.

Patients' prior annual medical expenditure was calculated by the total amount of payment per year, including outpatient, inpatient, and pharmacy services. Total healthcare expenditure was adjusted to 2007 dollars using the medical service component of the Consumer Price Index. To be comparable to the general population, "National Health Care Expenses in the U.S. Civilian Noninstitutionalized Population, 2003" data available at the time this study conducted ,[64] were used in this study. On average, the annual medical expenditure per patients aged <65 years was approximately $5,670 in 2003 ($6,634 adjusted to 2007 dollars). A binary variable therefore, was created for patients having an annual medical expenditure $6700 higher than the national adult population and patients having an annual medical expenditure $6700 lower than the national adult population (1/0).

Liver biopsy once was recommended to be routinely performed prior to treatment initiation for unsuspected cirrhosis diagnosis, which may change the prognosis and considerations regarding therapy or follow-up.[52] There are increasing arguments related with the effectiveness

of biopsy on unsuspected cirrhosis,[65-67] and social costs of biopsy for treatment decision among patients with cirrhosis.[65] Some clinicians are tending to reserve biopsy for circumstances in which the biopsy would influence the decision regarding either initiation or continuation of therapy.[68] Therefore, it is importance to examine the influence of pre-treatment biopsy on treatment initiation and treatment outcome among patients without cirrhosis. A binary variable was used for patients having a liver biopsy during the pre-index period and patients without a liver biopsy during the pre-index period (1/0).

Characteristics of certain health professional visits in patients with HCV infection were used as proxies for the need in comorbid and HCV infection. Patients with more visits of certain professionals were considered to have a greater need for their comorbid or HCV infection. Numbers of health professional visits were documented during the pre-index period, including family practice, gastroenterology, internal medicine, and infectious disease specialties, identified to examine their impacts on treatment initiation and outcome.

Instrument of HCV symptomatic conditions. Although patients with chronic HCV are potential candidates for treatment, each patient's unique characteristics, HCV-related symptoms, and motivation may affect the timing of treatment initiation. Time to treatment initiation was calculated based on the duration between index date and HCV diagnosis date, and empirically categorized by ≥6 months and <6 months (0/1). In the absence of controlled study data, no definitive recommendations can be made about the timing of treatment initiation; however, it seems reasonable to delay treatment for 2 to 4 months after acute onset to allow for spontaneous resolution. It is suggested to repeat viral check 6 months to 1 year after spontaneous clearance due to the possibility of replication restart. [18] Therefore, a cut-point of 6 month was considered as

a proxy to indicate that patients with a shorter time to initiation had a greater level of severity of HCV-related cirrhotic symptoms compared to patients who deferred treatment.

Treatment Initiation-Related Covariates

To identify and account for potential bias introduced by treatment initiation-related covariates on outcome measure, multivariate logistic regressions were used to development adjusted odds ratio (OR) to determine the statistically significant covariates to be included in the effectiveness and costs estimation models. A stepwise selection method was used to create a final model with statistically significant effects of exploratory variables on receiving antiviral therapy. There were 32 identified baseline characteristics included into a stepwise, multivariate logistic selection model with a 5% significant level. Table 3-2 shows the specifications and descriptions of these baseline characteristics.

Analysis Plan and Study Hypothesis

Descriptive Data Analysis

Data were expressed as frequencies, mean (standard deviation), and percent. The associations between treatment initiation and an individual patient's baseline characteristics were examined using adjusted logistic regression model. The *a priori* level of significance was set at 0.05 (α). All data management was performed using SAS version 9.2 (SAS Institute, Cary, NC). Statistical analyses were done with the STATA IC10.0 (Stata Corp., College Station, TX).

Effectiveness Estimation

One inevitable limitation to the study is that some patients were not followed until the last date of dataset (6/30/2007), so their clinical outcomes and costs are were not fully observed (censoring). For example, the estimation of the difference in mean cost tends to be biased due to the fact that the distribution of healthcare costs is typically right skewed.[69-71] Moreover, healthcare costs may be related to effects of covariates changing over time. One of the suggested

statistical methods for handling both issues is to use inverse probability censoring weighting (ICPW).[72, 73] Our study uses weighted ordinary least squares (OLS) regression to estimate total costs and clinical effectiveness.[74, 75]

Furthermore, the ICPW statistical technique also has been used to estimate mean time to ESLD with censored data (Equation 3-1), where the weights are derived from survival model estimates from a Cox regression model conditionally on baseline characteristics and treatment indicator, as in Equation 3-2. Patient's age at HCV diagnosis in this model was set up as a time-dependent variable. Complete observations are weighted by their inversed probability of not being censored at the time of complication for patients with a complication within the study observation interval. For patients who are free of ESLD until the end of time interval, the observations are weighted by their inversed probability of not being censored at the end of the interval.[75] As with the ICPW method, the censoring indicator is reversed so that the event of interest is denoted as 0 and the censored event as 1.

$$E(E_i) = \beta_E Z_{Ei} \tag{3-1}$$

In Equation 3-1, i = 1,2,3,..,n (number of patients), Z_{Ei} is a set of covariates whose effects on time to a complication occurrence and β_E is a set of regression parameters. When $Z_{Ei} = 1$ indicates the i^{th} patient received treatment, then β_E is the impact of treatment on time of complication occurrence relative to no treatment, adjusted for the other covariates. Therefore, the β_E in Equation 3-1 can be estimated by Equation 3-2.

$$\hat{\beta}_E = \left(\sum_{i=1}^{n} \frac{\delta_i^*}{\hat{G}(X_i^*)} Z_{Ei} Z'_{Ei}\right)^{-1} \sum_{i=1}^{n} \frac{\delta_i^* X_i^*}{\hat{G}(X_i^*)} Z_E \tag{3-2}$$

Where;
n = number of patients
δ_i^* = 0 if i^{th} patient is censored during entire duration of follow-up, otherwise = 1

X_i^* = min (time of event, censoring time), X_i = time to event, τ = censoring time = end of follow-up
$\hat{G}(X_i^*)$ = Kaplan-Meier estimator of probability of not being censored at X_i^*
Z_{Ei} = a set of covariates whose effects in effectiveness

Costs Estimation

Using a similar approach as described above,[74, 75] the estimated costs for an individual patient within the study period were the sum of the product of the Kaplan-Meier probability of costs incurred in each time interval and the mean total costs from observed event in that interval in Equation 3-3. The weights used in the linear regression model are based on survival model estimates from the inverse of probability estimates in the time-dependent Cox regression model (Equation 3-4).[74, 75] Accrual intervals for the cost estimation in the follow-up were defined by month. Time intervals correspond to the intervals between data collection visits.

$$E(C_{ki}) = \beta_{Ck} Z_{Ci} \quad (3\text{-}3)$$

Where;
$C_{k\,I}$ = observed cost for i^{th} patient during interval k. k = 1,2,3…K, which is K intervals in the entire study follow-up $(0,\tau\rangle$ and $0 = a_1 < a_2 < \ldots < a_{k+1} = \tau$ (censoring time = length of follow-up).
Z_{Ci} = a set of covariates whose effects on costs of complication (or all causes) and β_C is a set of regression parameters.

Probability of being censored was estimated in the second step by the Kaplan-Meier estimator of $\hat{G}(X_{ki}^*)$ in a time-dependent Cox regression model, adjusted for the other covariates. Therefore, the β_C in the Equation 3-3 can be estimated by Equation 3-4.

$$\hat{\beta}_{CK} = \left(\sum_{i=1}^{n} \frac{\delta^* ki}{\hat{G}(X^* ki)} Z_{Ci} Z'_{Ci}\right)^{-1} \sum_{i=1}^{n} \frac{\delta^* ki CK_i}{\hat{G}(X^* ki)} Z_C \quad (3\text{-}4)$$

Where;
n = number of patients
k = time-period (i.e., month)
δ_{ki}^* = 0 if i^{th} patient is censored during month k, otherwise = 1
X_{ki}^* = min(*Xi*, k+1)

$\hat{G}(X_{ki}^{*})$ = Kaplan-Meier estimator of probability of not being censored at X_{ki}^{*}
Cki = observed costs for i^{th} patient during time period k

Cost-Effectiveness of Initial Combination Antiviral Therapy (Net Benefit Regression Model)

We performed the main analysis to estimate the cost-effectiveness of combination antiviral therapy relative to no treatment among newly-diagnosed HCV-infected patients. The primary effectiveness measure, time to occurrence of ESLD, was applied in the net benefit regression model. Because the treatment effectiveness analyses in the base case and subgroup cohorts was confirmed with primary and secondary effectiveness measures in patients with cirrhosis, the incremental net benefit was analyzed within two distinct cirrhotic patients cohorts with and without ≥12months antiviral therapy (i.e. base case and usual care groups of patients). Moreover, the net benefit regression model was performed for patients without cirrhosis in base case analysis to compare the magnitude of net benefit difference in patients with and without cirrhosis.

Individual patient's NMB was estimated in the Equation 3-5. The maximum willingness-to-pay (WTP, λ), as recommended by Stinnett and Mullhay, estimated net benefit is a function of a range of values for λ.[43] A value of λ of, for example, $0; $10,000; $25,000; $50,000; $75,000; and $100,000 was employed in Equation 3-5.

$$NMB_i = \lambda \times \hat{E}_i - \hat{C}_i \qquad (3\text{-}5)$$

Where;
$\widehat{E_i}$ = expected effectiveness with censoring adjustment for i^{th} patient obtained in Equation 3-1
$\widehat{C_i}$ = expected costs with censoring adjustment for i^{th} patient obtained in Equation 3-3

Primary study hypothesis

"Is antiviral therapy cost effective for HCV-infected patients with cirrhosis in a national MCO, controlling for confounders?" was explored in the construction of Equation 3-6.

$$NMB_i = \alpha + \sum_{j=1}^{p} \beta_j X_{ij} + \delta T_i + \varepsilon_i \quad (3\text{-}6)$$

Where;
T_i=1 indicates i^{th} patient receiving antiviral combination therapy, otherwise =0.
δ=estimated cost-effectiveness of antiviral therapy (i.e., incremental net-benefit) compared to no treatment (Ti=0) by controlling for covariates (Xij), including either statistically significant effectiveness-related or total costs-related covariates.

Null hypothesis (Ho): $\delta \leq 0$. It indicates that the mean NMB of combination antiviral therapy was not statistically significant higher than no treatment among newly diagnosed HCV-infected patients.

Rejection of the null hypothesis would suggest that the HCV-infected patients having antiviral therapy have higher NMB than those who went without treatment (if $\delta > 0$).

Secondary study hypothesis

"Which subgroup of patients with potential factors makes antiviral therapy more cost effective?" The individual impact of a variety of covariates on the estimated incremental net-benefit was assessed including the interactions of the treatment with covariates which were found to have a statistically significant risk of complication in Equation 3-7.

$$NMB_i = \alpha + \sum_{j=1}^{p} \beta_j X_{ij} + \delta T_i + T_i \sum_{j=1}^{p} \gamma_j X_{ij} + \varepsilon_i \quad (3\text{-}7)$$

In this equation, γ_j indicates if the cost effectiveness of antiviral therapy statistically differs among subgroups.

Null hypothesis (Ho): $\gamma_j = 0$. It indicates that there is no significant effect on the interaction between individual covariate and treatment.

Rejection of the null hypothesis would suggest that the cost effectiveness of antiviral therapy (mean NMB differences) differed significantly between patients with specific covariates

and their counterparts (if $\gamma j \neq 0$). Covariates (Xij) included in the interaction terms with treatment were from model 3-6 when their p-values for the NMB coefficient estimate were statistically significant (<0.05).

Regression diagnostics

To ensure the regression coefficient (δ) in the primary analysis is an unbiased, consistent, and efficient OLS estimator, the assumptions of OLS were examined by the following diagnostic analyses.[76]

Heteroskedasticity. The assumption of homoskedasticity is the variance of error term (εi), given Xi is constant. If the variances of error terms vary with Xi there is heteroskedasticity. Heteroskedasticity could lead to an invalid estimation of the standard error of the coefficient (δ). Although it does not bias the actual coefficient estimates, it can cause an incorrect conclusion due to invalid statistical inferences of coefficient significance. The Breusch-Pagan-Godfrey and White tests were used to detect heteroskedasticity. White's heteroskedasticity-consistent covariance matrix (1980) was used to correct heteroskedasticity.

Normality of error term. The use of normality of error term is to ensure the distribution of the dependent variable (NMBi) conditional on the independent variables (Xj) was normally distributed. If there are skewed, the OLS estimates would be inefficient. A Jarque-Bera test and standardized normal probability plot was used to examine the normality of the residuals.

Omitted variable bias. Omitted variable biases were used to examine if a relevant variable correlated with treatment (Ti) is omitted in the included variables (Xj). If an omitted variable (un-measured variable) is correlated with the independent variables, the regression coefficient will be biased. The instrumental variable approach was investigated to control potential unmeasured treatment selection bias. The instrumental variable approach involves the

assumption that an instrument is related to the treatment (Ti), but not related to the outcome of the interest (NMBi).

First, two variables, overall outpatient medication copayment rate and having a PPO health plan, were examined to ensure that they could serve as an effective instrumental variable. This factor was a valid instrument if (a) the overall medication copayment rate varies in the likelihood of treatment initiation (unadjusted F test ≥10), (b) the overall medication copayment rate is independent with measured confounders for treatment initiation (i.e., patient-level characteristics), and (c) the overall medication copayment rate is not related with the study outcome (NMB). Outpatient medication copayment rates were measured by the proportion of total amount of the copayment divided by the total medication expenditures incurred during the study period (>20% =1 implied the patient has high medication copayment; ≤20% = 0 indicated the patient has low copayment). A binary variable, PPO/non-PPO for patients with and without PPO, was examined. The relationship between treatment initiation and instrument measures was explored using multivariate logistic regression model, individually.

Because not every study patient had pharmacy claims, overall medication copayment rate was not able to be an instrument in this study. Type of health plan (PPO vs. non-PPO) was a strong predictor of treatment initiation. When PPO was not included in the effectiveness and costs estimation model, it was not associated with the net benefit difference controlling for patient baseline characteristics. However, the incremental net benefit was not significantly different between patients with PPO and those who without PPO in the instrumental variable regression model. One of possible causes was the association between PPO and treatment initiation is not unique. PPO was not only highly correlated with treatment initiation, but also correlated with other baseline characteristics in the multivariable logistic regression model.

Therefore, type of health plan was taken as one of the patient-level characteristic variables and included in the effectiveness, cost estimation, and net benefit regression models.

Plot of Incremental Net Benefits

At each λ value, the model containing the patient's baseline characteristics and the treatment indicator (multivariable-adjusted model) was performed for hypothesis 1. Included baseline characteristics in the multivariate adjusted model was either significant relevant with primary effectiveness or total costs. At each level of λ value, net benefit regression models were respectively performed in the patient subgroups, patients with and without cirrhosis.

Plots of incremental net benefit (INB), can provide visual results for the mean net benefit difference between treatment and no treatment as a function of WTP (λ) values ranging from $0 to $100,000 (e.g., $0; $10,000; $20,000; $30,000; $40,000; and $80,000). Figure 3-4 demonstrates the incremental net benefit (INB) plots. INB is expressed as a function of WTP and mean change in NMB. Along the x-axis are estimates of the WTP to achieve an additional treatment success (positive NMB). The slope of each line is positive, indicating that treatment increases effectiveness (i.e., INB), and the curved lines represent the upper and lower 95% confidence limits of the INB plot. If the WTP is equal to zero, INB is equal to minus the cost difference. Any negative intercept indicates that the treatment increases the cost. INBs will change in a linear fashion as the WTP amounts are varied. Health policy makers can then make resource allocation decisions based on various WTP values. For any value of λ, a net benefit regression produces a value of INB (i.e., cost-effectiveness); the 95% CI band of each NMB plot is allowed to demonstrate the strength of evidence that indicate treatment is cost-effective.

Table 3-1. The ICD-9, CPT, and HCPCS codes used for disease diagnoses and procedures

HCV-related disease conditions
HCV infection
70.41 Acute hepatitis C with coma
70.51 Acute hepatitis C without coma
70.44 Chronic hepatitis C with coma
70.54 Chronic hepatitis C without coma
Compensated cirrhosis (non-alcoholic cirrhosis)
571.4x Chronic liver disease
571.5 Cirrhosis of liver without mention of alcohol
571.6 Biliary cirrhosis
571.8 Other chronic nonalcoholic liver disease
571.9 Unspecified chronic liver disease without mention of alcohol
273.2 Paraproteinemia (Mixed cryoglobulinemia)
446.29 Leukocytoclastic vasculitis associated with chronic Hepatitis
573.0 Chronic passive congestion of liver
573.8 Hepatoptosis
573.9 Unspecified disorder of liver
Severe decompensated cirrhosis
456.0x Esophageal varices with bleeding
456.1x Esophageal varices without mention of bleeding
456.2x Esophageal varices in diseases classified elsewhere
456.8x Varices of other sites
572.2x Hepatic coma
572.3x Portal hypertension
572.4x Hepatorenal syndrome
572.8x Other sequelae of chronic liver disease
782.4 Jaundice
789.5x Ascites
HCV-related disorders in other system
286.7 Acquired coagulation factor deficiency
286.9 Other and unspecified coagulation defects
289.4 Hypersplenism
416.8 Pulmonary hypertension, secondary
511.8 Other specified forms of effusion, except tuberculous
Hepatocellular carcinoma (HCC)/ malignant neoplasm
155.0 Liver, primary
155.1 Intrahepatic bile ducts
155.2 Liver, not specified as primary or secondary

Table 3-1. Continued

HCV-related disease conditions
Liver transplantation
ICD-9 status codes
V42.7 Liver transplant
V58.69 Long-term (current) use of other medications (patients with V58.69 have to be associated with ≧1 claims ICD/CPT codes of liver transplant in inpatient or outpatient claims files)
ICD procedure codes:
50.51,50.59 Liver transplant
CPT: 47135, 47136
Comorbid conditions
HIV co-infection
079.53 Human immunodeficiency virus, type 2 [HIV-2]
042 Human immunodeficiency virus [HIV] disease
V08 Asymptomatic human immunodeficiency virus [HIV] infection status
HBV co-infection
070.2 Viral hepatitis B with hepatic coma
070.3 Viral hepatitis B without mention of hepatic coma
V02.61 Hepatitis B carrier
Alcoholism
291.xx Alcoholic psychoses
303.0x Acute alcoholic intoxication
303.9x Other and unspecified alcohol dependence
305.0x Alcohol abuse
357.5 Alcoholic polyneuropathy
425.5 Alcoholic cardiomyopathy
535.3x Alcoholic gastritis
571.0 Alcoholic fatty liver
571.1 Acute alcoholic hepatitis
571.2 Alcoholic cirrhosis of liver
571.3 Alcoholic liver damage, unspecified
Obesity
278.x, 278.xx
Diabetes
250.x, 250.xx
Cerebral vascular diseases
433.xx, 434.xx Occlusion or stenosis of cerebral arteries
435.x Transient ischemic attack
430.x-432.x, 436.x Stroke

Table 3-1. Continued

Comorbid conditions
Drugs dependence
304.0x Opioid-type dependence
304.2x Cocaine dependence
304.4x Amphetamine and other pscychostimulant dependence
304.7x Combinations of opioid-type drug with any other
305.5x Opioid abuse
305.6x Cocaine abuse
305.7x Amphetamine or related acting sympathomimetic abuse
Depression
293.83 Transient organic psychotic condition, depressive type
296.2x Major depressive disorder, single episode
296.3x Major depressive disorder, recurrent episode
296.5x Bipolar affective disorder, depressed
298.0 Depressive type psychosis
300.4 Neurotic depression
307.44 Hypersomnia associated with depression
309.0x Brief depressive reaction
309.1x Prolonged depressive reaction
309.28 Adjustment reaction with anxiety and depression
311 Depressive disorder, not elsewhere classified
Chronic mental or mood disorders (Psychiatric diseases)
290.xx Senile and presenile organic psychotic conditions
293.xx Transient organic psychotic conditions
294.xx Other organic psychotic conditions (chronic)
295.xx Schizophrenic disorders
296.xx Affective psychoses
298.9 Unspecified psychosis
300.xx Neurotic disorders excluding 300.4
Heart diseases[77, 78]
411.xx, 414.xx Ischemic heart disease
413.x Angina
428.0, 428.1, 428.9, 428.2x, 428.3x, 428.4x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91 Congestive heart failure
410.x, 412.x Myocardial infarction
785.9 Carotid bruit
Organ transplantation
V42.x (excluding V42.7)

Table 3-1. Continued

Comorbid conditions
Dialysis or End-stage renal disease, (ESRD)[77]
ICD- 9 codes:
V42.0 Kidney transplant
V45.1 Renal dialysis status
V56.0 Extracorporeal dialysis
V56.8 Other dialysis
ICD procedure codes: 39.27, 39.42, 39.43,39.49, 39.50, 39.53, 39.93, 39.94.
CPT-4: 90921, 90925, 90935, 90937, 90945, 90947, 90940, 90989, 90993, 90997, 90999, 93990, 50340, 50360, 50365,
Chronic obstructive pulmonary disease (COPD)
490.x-491.x Chronic bronchitis
492.x Emphysema
494.x Bronchiectasis
496.x Chronic airway obstruction
Hyperthyroidism
242.xx
Liver biopsy
CTP codes: 47000, 47100
Interferon injections
ICD procedure codes: 50.11, 50.12
HCPCS codes: J3590, J9219, J9212, J9213, J9214, J9215, J9216, S0145, S0146

Table 3-2. Study variable list

Variables	Coding of covariates	Data
Patient demographics		
Age at HCV diagnosis year	17 to 64 years	Continuous
	Age in the month[th]	Dichotomous
Gender	Female=0	Dichotomous
	Male=1	
Census region[1]		
Northeast=1	Yes/No (1/0)	Dichotomous
Midwest=2	Yes/No (1/0)	Dichotomous
Southeast=3	Yes/No (1/0)	Dichotomous
West=4	Yes/No (1/0)	Dichotomous
Other=5	Yes/No (1/0)	Dichotomous
Year of HCV diagnosis		
1998=0	Yes/No (1/0)	Dichotomous
1999=1	Yes/No (1/0)	Dichotomous
2000=2	Yes/No (1/0)	Dichotomous
2001=3	Yes/No (1/0)	Dichotomous
2002=4	Yes/No (1/0)	Dichotomous
2003=5	Yes/No (1/0)	Dichotomous
2004=6	Yes/No (1/0)	Dichotomous
2005=7	Yes/No (1/0)	Dichotomous
2006=8	Yes/No (1/0)	Dichotomous
2007=9	Yes/No (1/0)	Dichotomous
Insurance coverage	Public=0	Dichotomous
	Private=1	
Types of health plans[2]		
POS=plan1	Yes/No (1/0)	Dichotomous
PPO=plan2	Yes/No (1/0)	Dichotomous
HMO=plan3	Yes/No (1/0)	Dichotomous
Time to treatment initiation	<6 months=1	Dichotomous
	≥6 months=0	
Comorbid conditions		
Severe decompensated cirrhosis	Yes/ No (1/0)	Dichotomous
Compensated cirrhosis	Yes/ No (1/0)	Dichotomous
Chronic obstructive pulmonary diseases, COPD	Yes/ No (1/0)	Dichotomous
Cerebral vascular disease, CVD	Yes/ No (1/0)	Dichotomous
Drugs dependence	Yes/ No (1/0)	Dichotomous
Diabetes	Yes/ No (1/0)	Dichotomous
Depression	Yes/ No (1/0)	Dichotomous
Heart diseases	Yes/ No (1/0)	Dichotomous
Hyperthyroidism	Yes/ No (1/0)	Dichotomous
Obesity	Yes/ No (1/0)	Dichotomous
Psychiatric disorders	Yes/ No (1/0)	Dichotomous

Table 3-2. Continued

Variables	Coding of covariates	Data
Comorbid conditions		
HIV co-infection	Yes/ No (1/0)	Dichotomous
HBV co-infection	Yes/ No (1/0)	Dichotomous
Use of health services		
Annual medical expenditure[3]	≥$6700=1 <$6700=0	Dichotomous
Hospitalization	Yes/ No (1/0)	Dichotomous
Number of outpatient visits	0, 1, 2, 3, ….	Continuous
Number of Emergency visits	0, 1, 2, 3, ….	Continuous
Liver biopsy	Yes/ No (1/0)	Dichotomous
Provider-level factor		
Number of Family/General practice visits	0, 1, 2, 3, ….	Continuous
Number of Gastroenterological visits	0, 1, 2, 3, ….	Continuous
Number of Internal Medicine visits	0, 1, 2, 3, ….	Continuous
Number of Infectious Disease visits	0, 1, 2, 3, ….	Continuous
Effectiveness outcome[4]		
Time to first event of ESLD in months	0, 1, 2, 3, …	Continuous
Costs outcome		
Direct health care costs in dollar amount	0, 1, 2, 3, …	Continuous

1. Census Region: 1=New England and Middle Atlantic; 2=East North Central and West North Central; 3=South Atlantic, East South Central, and West South Central; 4=Mountain and Pacific; 5=National and Other in the dataset. 2. Health plan: Preferred Provider Organization (PPO), Health Maintenance Organization (HMO) and Point of Service (POS). 3. Health care costs and expenditure, including inpatient, outpatient, diagnostic, procedure costs, and prescriptions, were adjusted to 2007 U.S. dollars using the medical service component of the Consumer Price Index. The cut-off point was based on the "National Health Care Expenses in the U.S. Civilian Noninstitutionalized Population, 2003" results,[64] the annual medical expenditure per patients aged <65 years was approximately $5,670 in 2003 ($6,634 adjusted to 2007 dollars). 4. End-stage liver disease (ESLD), including occurrences of severe decompensated cirrhosis, HCC and liver transplantation, and a proxy of death defined as loss of health insurance eligibility ≤32 days after receiving hospice services.

Table 3-3. Patterns of antiviral therapy

	Total treated[1] (n=3,896)	Usual care[1] (n=882)	Extended care[1] (n=119)
Duration of treatment[2], mean (±SD) month			
INF use	8.3 (7.9)	13.3 (6.0)	25.2 (17.8)
RBV use	7.5 (6.2)	12.2 (5.1)	17.7 (11.9)
RBV/INF duration ratio, %	98.0 (38.6)	94.2 (17.5)	79.7 (30.1)
Number of prescription refills, mean (±SD)			
INF refills,	7.4 (5.6)	12.7 (2.3)	24.3 (11.7)
RBV refills,	6.5 (4.4)	11.1 (3.0)	15.3 (7.8)
RBV/INF refills ratio, %	94.5 (41.5)	88.2 (20.0)	68.6 (30.8)

Abbreviations: INF=interferon alpha, RBV=Ribavirin. 1. Total treated (treatment group) includes those patients who ever received ≥1 INF and ≥RBV claims. Using INF claims as treatment exposure indicator, usual care is defined as those patients receiving 11 to 14 continuous INF refills (indicating at least 12 months or 48 weeks of treatment within a 15-month period). Extended care is defined as those patients receiving ≥15 continuous INF refills. 2. Total treatment duration was defined as the number of days between the last and first prescription claims plus 30 days.

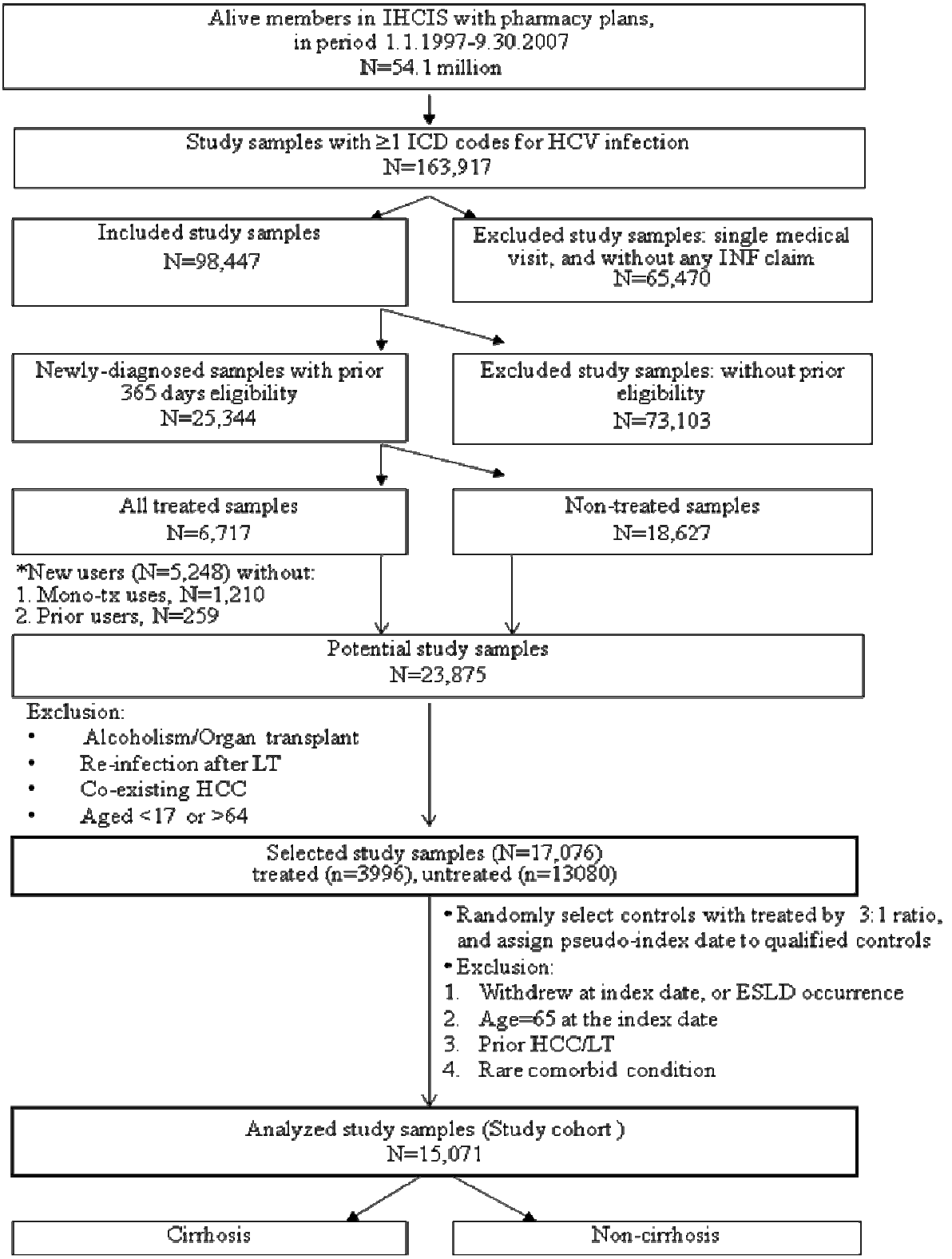

Figure 3-1. Sample selection process.

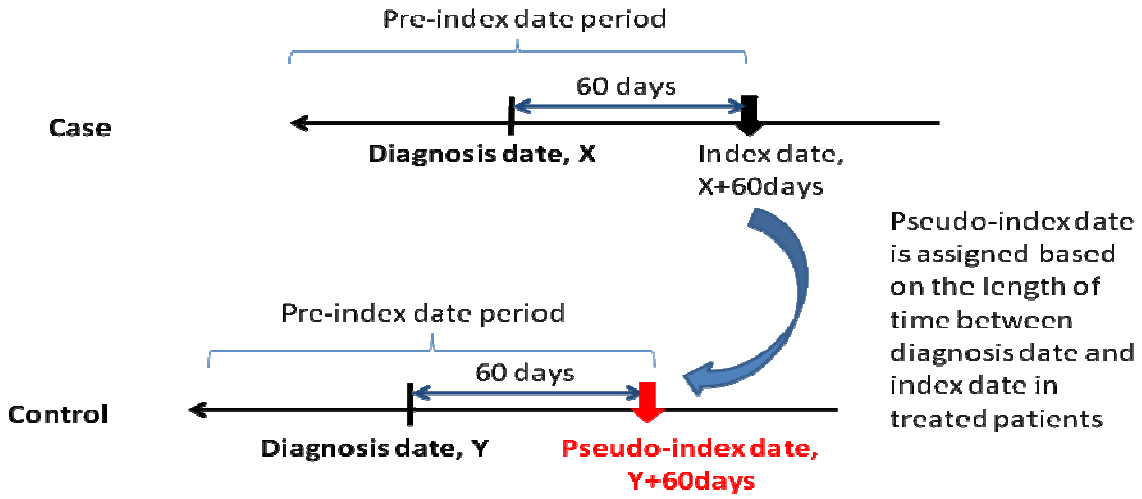

Figure 3-2. Establishment of comparisons groups. Note: Diagnosis date = first date of HCV diagnosis, Index date = first date of interferon prescription.

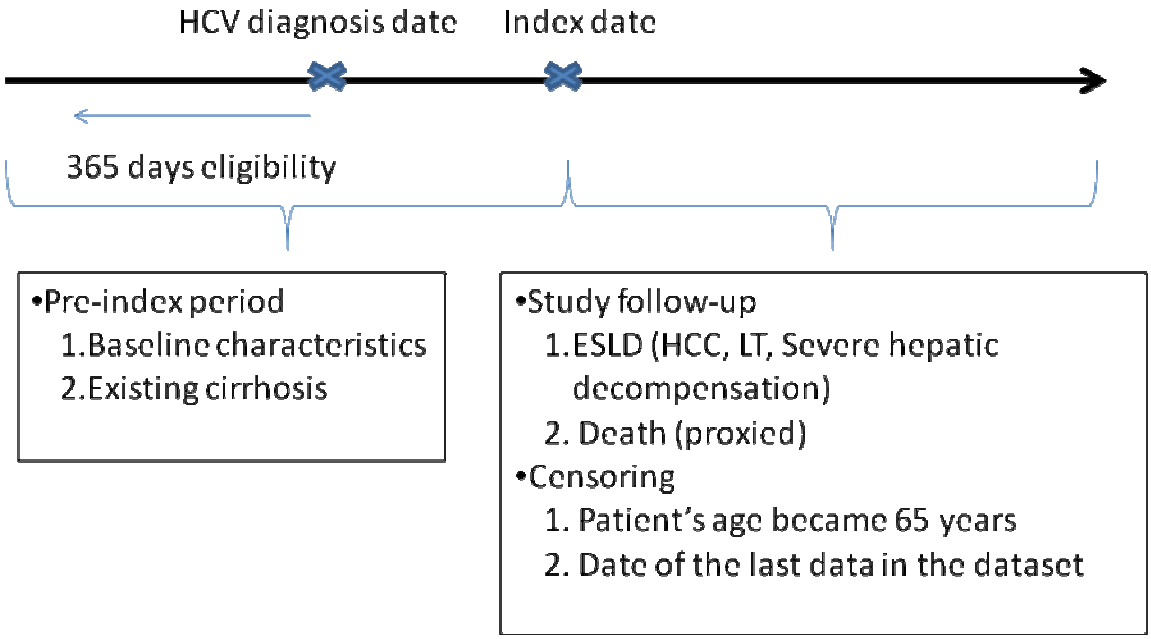

Figure 3-3. Study outcomes and follow-up. Note: Diagnosis date = first date of HCV diagnosis, Index date = first date of interferon prescription, ESLD (end-stage liver disease), HCC (hepatocellular carcinoma), LT (liver transplantation), severe hepatic decompensation, including variceal bleeding, hepatic coma, etc.

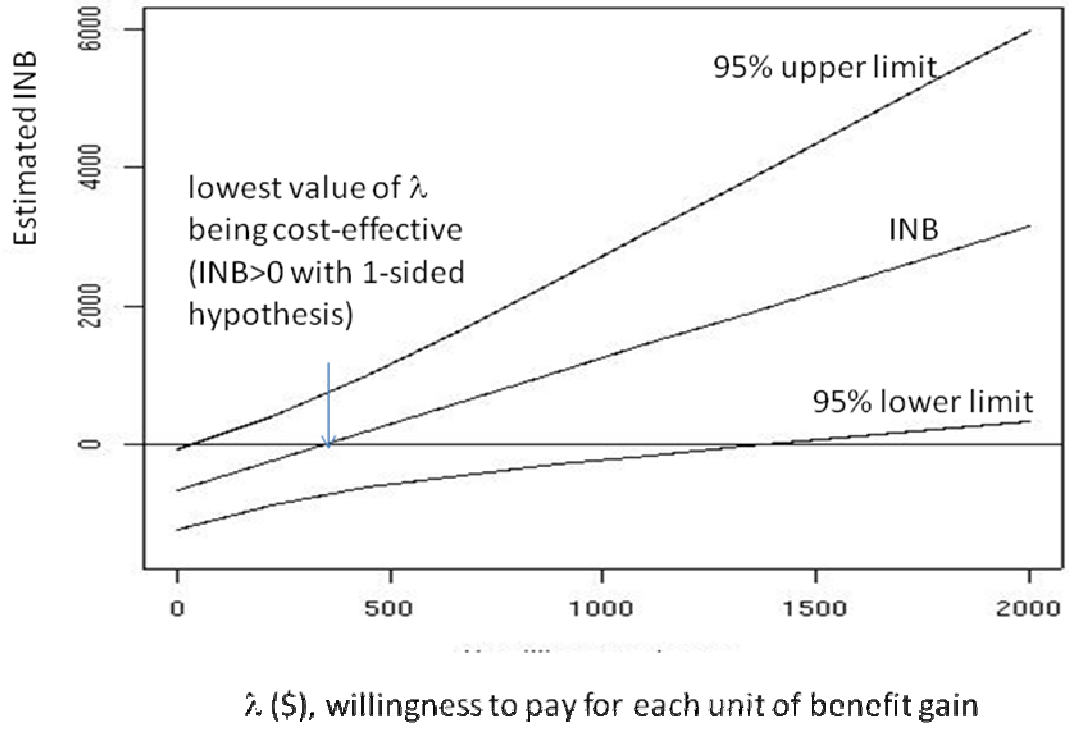

Figure 3-4. Plot of incremental net benefit (INB).

CHAPTER 4
RESULTS

Descriptive Characteristics

Study Cohort

A total of 163,917 MCO members were diagnosed with HCV infection between 1997 and 2007. Eliminations of individuals without ≥2 medical claims of HCV infection and without an INF claim, individuals without continuous eligibility, individuals receiving monotherapy, individuals receiving antiviral therapy prior to the HCV diagnosis date, and those with alcoholism, organ transplantation, HCV re-infection after liver transplantation, HCC, or ages <18 or >64 years old reduced the study sample to 17,076 individuals (treated 3996, untreated 13,080). Among those selected in the study samples, non-treated patients were randomly selected with a 3:1 ratio to treated patients and assigned the pseudo-index date. Untreated patients were randomly selected based on 3996 treated patients, and those who became 65 years old by the pseudo-index date (n=52), had either HCC or LT before the assigned index date (n=352), withdrew at the same date with index date (n=63), and had rare comorbid conditions (<1%) in either the treatment or control group [i.e., end-stage renal disease/hemodialysis (n=72), and hyperthyroidism (n=317)] were excluded from the analysis.

A total of 15,071 patients satisfied all requirements for inclusion into the study analysis. (Figure 3-1) The base case study cohort consisted of 3,896 patients (treatment group) who ever received combination antiviral therapy and 11,175 patients (control group) who never received treatment in the study period.

Baseline Characteristics of All Study Patients in Base Case Analysis

Table 4-1 reports baseline characteristics of study patients. Briefly, the newly-diagnosed HCV-infected patient cohort had a mean age of 47.5 (±8.3) years and included more male than

female patients (61.4%% vs. 38.6%, respectively). More than half the cohort resided in the New England and Middle Atlantic regions of the US. Most patients (97.7%) had private insurance coverage at the time of HCV diagnosis. Among all patients, 37.0% enrolled in a HMO, following by 36.2% closed a PPO plan and 26.9% in POS plan. Considerable proportions of patients had existing cirrhosis, including 1.5% of patients with severe decompensated cirrhosis and 18% with compensated cirrhosis. Patients had mental health–related conditions, including depression incurred after HCV diagnosis (4.8%), and psychiatric disorders (17.5%).

Of the observed baseline characteristics of the study cohort, variables statistically associated with initiation of antiviral therapy in base case cohort were shown in Table 4-2. Treated patients (treatment group) were more likely than untreated patients (control group) to be male (OR=1.25, 95% CI=1.15–1.36), and enrolled in a PPO plan (OR=1.14, CI=1.04–1.25). Having a condition associated with compensated cirrhosis (OR=1.68, 95% CI=1.52–1.86), depression (OR=1.85, 95% CI=1.57-2.1), receiving a higher annual medical expenditure (OR=1.94, 95% CI=1.76-2.15), having a biopsy procedure (OR=3.30, 95% CI=2.90–3.75), and often visiting a gastroenterologist (OR=1.12, 95% CI=1.10-1.14) were associated with an increased likelihood of initiating antiviral therapy (Table 4-2).

Factors associated with patients receiving antiviral therapy initiation varied by the presence of cirrhosis in the base case cohort. Table 4-3 shows patients' baseline characteristics of two groups of patients with and without cirrhosis at baseline. Patients without cirrhosis were more likely to have comorbid conditions than patients with cirrhosis, including diabetes (OR=0.83, 95% CI=0.71–0.96), drugs dependence (OR=0.40, 95% CI=0.29–0.56, and HIV co-infection (OR=0.47, 95% CI=0.34–0.65).

Baseline Characteristics of Patients in Subgroup Analysis

Table 4-4 shows the distribution baseline characteristics of qualified patients in subgroup analysis. Among patients with usual care (n=1001) in subgroup analysis, 882 patients received a 48-weeks treatment course (indicating 12to15 continuous months of antiviral treatment). Among patients with extend care (n=472), 119 patients had a longer than 48-weeks therapy (indicating greater than 15 continuous months of antiviral therapy). Among those randomly selected untreated patients (n=2958), 2605 patients were matched to usual care patients and 353 untreated patients to extended care patients.

Compared to the patients in the base case analysis, the year of HCV diagnosis was more likely to incur during 2000to2006 among patients receiving either usual care or extended care. In the following analyses, therefore, were performed for those patients firstly diagnosed with HCV infection during the period. Of subgroup patients, approximately 20% were diagnosed with cirrhosis, which was more than those cirrhotic patients (18%) involved in the base case analysis.

Of the observed baseline characteristics of the subgroup patients, variables statistically associated with initiation of antiviral therapy among patients with usual care and extended care were shown in Table 4-5. A broader spectrum of comorbid conditions were negatively associated with treatment initiation among patients with usual care, including COPD, depression, HBV and HIV co-infection than those who received extended care (diabetes and psychiatric disorders).

Estimated Effectiveness and Costs

Study Follow-Up and Clinical Outcome Events

On average, the observed follow-up period from the index date to first ESLD occurrence or censoring was 18.2±17.0 months, ranging from less than 1 month to a maximum of 88.3 months. ESLD developed in a 1.7% (n=67) of treated patients and 1.5% (n=166) of untreated patients. Cumulative incidences of outcome events between treated and untreated patients with or without

cirrhosis during the follow-up period are shown in Table 4-11. Most common event of ESLD was decompensated cirrhosis (n=127), following by HCC (n=91) and LT (n=45). The rate of ESLD development among patients with cirrhosis was lower in treatment groups than control groups (3.7% vs. 5.4%, respectively). Among patients without cirrhosis, the rate of ESLD development was higher in treatment than control (1.0% vs. 0.8%, respectively).

In those patients with usual care, the average observed follow-up period from the index date to first ESLD or censoring was 30.4±16.7 months (95% of subgroup patients remained at least 12 months in the study cohort). ESLD developed in a 2.1% (n=21) of treated patients and 1.4% (n=42) of untreated patients during observed follow-up in the Table 4-13. Patients with cirrhosis in usual care analysis had 1.4% of ESLD development rate in treatment group and 1.3% in control group. Among patients with extended care, the average observed follow-up period from the index date to first ESLD or censoring was 40.5±16.7 months. The rate of ESLD development was higher in treatment than control (7.6% vs. 2.6%, respectively). Figure 4-1 to 4-3 depicts the ESLD event rates between patients with and without cirrhosis in base case, usual care and extended care analysis. Note that a lower rate of ESLD progression in treatment than in untreated group among patients with cirrhosis existed in base case and usual care analyses. Unfortunately, among patients without cirrhosis, a higher ESLD event rate in treatment than in untreated group was in base case, usual care and extended care analyses.

Primary Effectiveness Measure: Time to ESLD Development

Base case analysis. Study results of estimated time to first ESLD occurrence are shown in Table 4-6. The adjusted regression coefficient comparing the treatment to the control in the base case analysis was 3.32 (se=0.06, p<.0001) months, indicating that on the average time to ESLD occurred in treated patients delayed 3.32 months as compared with untreated patients, while controlling for treatment initiation-related covariates and instruments related with symptomatic

conditions and maintenance. The effect of cirrhosis on the time to ESLD occurrence of treatment intervention was determined by examining the coefficient of interaction with treatment in the multivariate adjusted regression model, which was a difference of -0.33 (se=0.13, p= 0.01). There was a significant difference in the mean time to ESLD occurrence in patients with cirrhosis [coefficient=3.01 (se=0.15, p<.0001)] and without cirrhosis [coefficient=3.44 (se=0.06, p<.0001)] in the stratified analyses.

Table 4-7 shows the various baseline characteristic influences on the heterogeneity of treatment effect according to the time to ESLD occurrence. In patients with and without cirrhosis, a significant increase in the mean time to ESLD occurrence was related with the year of HCV diagnosis, the performance of liver biopsy, time to treatment initiation greater than 6 months. The average time to ESLD occurrence was shorter in male than female in patients with and without cirrhosis patients [coefficient=-1.16 (se=0.14), p<.0001, coefficient=-0.36 (se=0.05), p<.0001, respectively]. Patients with depression after HCV diagnosed was significantly related with a shorten time of ESLD occurrence in cirrhotic and non-cirrhotic groups [coefficient=-1.41 (se=0.28), p<.0001 vs. coefficient= -1.19 (se=0.08), p<.0001]. Surprisingly, HIV co-infection was related with a significant increase in the time to ESLD occurrence in patients without cirrhosis [coefficient=1.31 (se=0.14), p<.0001]. A possible explanation is that patients receiving antiviral therapy were more likely to be those who at well HIV disease conditions (e.g. CD4 counts≥350 cells/mm^3) comparing to HIV-co-infected patients without suppressed HIV and the pre-existing risk of rapid progression of liver fibrosis were not high as expected among treated patients. Interpretations and discussions for this study finding were shown in the discussions section.

In addition, in patients with and without cirrhosis, a significant reduction in mean time to ESLD occurrence was related with prior health service utilization, including prior annual medical expenditure ≥$6700 [coefficient=-1.75 (se=0.16), p<.0001 vs. coefficient= -1.08 (se=0.07), p<.0001], and hospitalization [coefficient= -2.01 (se=0.18), p<.0001 vs. coefficient= -1.45 (se=0.07), p<.0001], and gastroenterology visits [coefficient= -0.07 (se=0.01), p<.0001 vs. coefficient= -0.12 (se=0.01), p<.0001].

Subgroup analysis. The significant increase in the average time to ESLD between treatment and control was 1.33 months (se=0.09, p<.0001) in usual care analysis. The average time to ESLD event estimated no difference between treatment and control in the extended care analysis [coefficient=1.27 (se=1.20), p=0.29] in Table 4-8.

Various baseline characteristic influences on the heterogeneity of treatment effect according to the time to ESLD occurrence in subgroup analysis as shown in Table 4-9. In patients with usual care and extended care, a significant mean reduction in time to ESLD event was associated with cirrhosis [coefficient= -3.32 (se=0.10), p<.0001 vs. coefficient= -3.15 (se=1.186), p=<.01]. In patients with usual care, other comorbid conditions led to a reduction in the time to ESLD occurrence included depression [coefficient= -2.74 (se=0.10), p<.001], HBV co-infection [coefficient= -1.93 (se=0.20), p<.0001]. Comorbid condition significantly reduced the time to ESLD occurrence in patients with extended care was diabetes [coefficient= -5.44 (se=1.43), p<.0001]. HIV co-infection was related with a significant increase in the time to ESLD occurrence in patients with usual care [coefficient=3.95 (se=0.22), p<.0001]. In patients with usual care, prior health service utilization led to a significant reduction in the time to ESLD occurrence included prior annual medical expenditure ≥$6700 [coefficient= -1.94 (se=0.10), p<.0001], biopsy [coefficient= -1.28 (se=0.14), p<.0001], hospitalization [coefficient= -0.59

(se=0.11), p<.0001], outpatient visits [coefficient= -0.02 (se=0.00), p<.0001], gastroenterology visits [coefficient= -0.20 (se=0.01), p<.0001] and infectious disease visits [coefficient=0.03 (se=0.01), p<0.01]. In patients with extended care, biopsy and antiviral therapy initiation ≥6 months after the diagnosed date led to a significant reduction in the time to ESLD development [coefficient= -5.90 (se=2.00), p<0.01, and coefficient= -3.05 (se=1.02), p<0.01, respectively].

Similarly, the effect of cirrhosis on the time to ESLD occurrence of treatment intervention was determined by examining the coefficient of interaction with treatment in the multivariate adjusted regression model, a significant difference of -0.59 (se=0.20, p< 0.01) was seen in patients with usual care and a difference of 3.12 (se=2.48, p=0.21) in patients with extended care. Among patients with usual care, there was a significant increase, with 0.92 months (se=0.32, p<0.001) in patients with cirrhosis and 1.56 months (se=0.07, p<.0001) in patients without cirrhosis in Table 4-10. Results of stratified analyses among patients with usual care, a similar, significantly delayed the ESLD progression in treated patients as comparing to untreated patients, were consistent with patients in the base case analysis.

Table 4-11 shows the influence of various patients' characteristics on the treatment effect among patients with and without cirrhosis in usual care analysis. Among patients with cirrhosis, patients' characteristics related with a significant reduction in the time to ESLD occurrence in base case analysis were similar with the factors among patients with usual care. Table 4-7 and Table 4-11 show that age, time to treatment initiation and antidepressant use among cirrhotic patients were related with the time to ESLD development in the base case analysis, but not significantly relevant with patients in the usual care analysis. Among patients without cirrhosis, a broader spectrum of comorbid conditions was associated with a similar, significant decrease in the time to ESLD development as compared with patients without cirrhosis. Patients'

characteristics associated with heterogeneous treatment effect in non-cirrhotic patients in the base case analysis were most likely to be seen in the patients with non-cirrhosis in the usual care analysis; despite the drugs dependences and antidepressant use were associated with non-cirrhotic patients in the base case analysis and COPD was associated with those patients in the usual care analysis. ,

Secondary Effectiveness Measure: Rate of ESLD Development

Base case analysis. Another effectiveness measure, the Kaplan-Meier survival estimate for ESLD-related events (HCC, liver transplantation, severe decompensated cirrhosis, or proxied death) after a start of treatment initiation was shown in Table 4-12. The KM estimate of ESLD progression rate (hazard ratio) comparing treated patients to untreated was 0.28 (95% CI, 0.20–0.40), controlling for treatment initiation related covariates, instruments related with symptomatic condition and treatment maintenance. The adjusted hazard ratio comparing treatment to no treatment revealed the beneficial effect among patients who received combination antiviral therapy were approximately 30% as likely to have an ESLD as patients without treatment at any point in time after a start of treatment (at 80.3 months).

The adjusted hazard ratio among patients with cirrhosis was 0.32 (95% CI, 0.21–0.50) for treated patients relative to untreated patients, and among patients without cirrhosis was 0.23 (95% CI, 0.13–0.40) for treated patients relative to untreated patients controlling for the potential confounders. Table 4-13 shows the various baseline characteristics influences on the heterogeneous treatment effect according to the adjusted hazard ratio in the Cox regression model. Among patients with and without cirrhosis, older and male patients were associated with a risk of ESLD progression, despite that the greater risk for male patients was not significant (hazard ratio=1.42, 95% CI, 0.93–2.15) in patients without cirrhosis. Additionally, patients with HBV co-infection had a higher risk of ESLD progression than patients without HBV co-infection;

the hazard ratio was 2.91 (95% CI, 1.57–5.41) in patients with cirrhosis and hazard ratio was 2.55 (95% CI, 1.02–6.40) in patients without cirrhosis. In patients without cirrhosis, diabetes was related with a high risk of ESLD progression (hazard ratio=4.71, 95% CI, 2.93–7.55). Patients had undergone liver biopsy and initiated therapy <6 months had a lower risk of ESLD progression, although the lower risk for treatment initiation within 6 months was not significant (hazard ratio=0.67 (95% CI, 0.41–1.09) among non-cirrhotic patients.

Subgroup analysis. Table 4-14 shows the results of secondary effectiveness in subgroup patient cohort. Among patients with usual care, the ESLD developed in 1.4% (n=12) of treated patients and 1.3% (n=33) of untreated patients. The KM estimate of ESLD progression (hazard ratio) revealed no difference between treated patients and untreated patients (hazard ratio=0.61, 95% CI, 0.28–1.35) controlling for treatment initiation related covariates and instruments related with symptomatic condition. Among patients with extended care, the ESLD developed in 7.6% (n=9) of treated patients and 2.6% (n=9) of untreated patients. The adjusted hazard ratio estimate showed no difference in ESLD development between treated and untreated patients (hazard ratio=1.79, 95% CI, 0.58–5.54).

Table 4-15 shows the various baseline characteristic influences on the heterogeneity of treatment effect according to the Kaplan-Meier estimate in the Cox regression model. In patients with usual care, a higher risk of ESLD progression was associated with male (hazard ratio=2.80, 95% CI,1.38–5.70), cirrhosis (hazard ratio=10.72, 95% CI, 5.23–21.91) and decompensated cirrhosis (hazard ratio=5.54, 95% CI, 1.80–17.08), HBV co-infection (hazard ratio=3.95, 95% CI, 1.14–13.60) and initiating treatment within 6 months (hazard ratio=2.19, 95% CI, 1.07–4.49). Among patients receiving extended care, the presence of cirrhosis (hazard ratio=18.24, 95% CI,

4.25–78.25), decompensated cirrhosis (hazard ratio=13.88, 95% CI, 3.05–63.08), and diabetes (hazard ratio=7.58 (95CI, 2.01–28.59) were associated with a risk of ESLD development.

Additionally, the stratification on the presence of cirrhosis was performed in patients with usual care and extended care as shown in Table 4-14. Hazard ratios for the interaction term between treatment and prior cirrhosis revealed a significant reduction among patients in usual care analysis (hazard ratio=0.17, 95% CI, 0.04–0.81), and no difference of 1.92 (95% CI, 0.62–5.96) in patients with extended care. As shown in Table 4-16, cirrhotic patients with usual care having a significant estimated 24% (hazard ratio=0.24, 95% CI, 0.06-0.94) reduction in the hazard for ESLD development, while no significant reduction on the risk of ESLD development among non-cirrhotic patients with usual care (hazard ratio=0,88, 95% CI, 0.27–2.87).

Summary of Effectiveness Results

In the prior sections presents the effectiveness results individually obtained in the base case, usual care and extended care analyses. Table 4-10 shows a summary of results obtained by using the primary effectiveness estimate (mean time to ESLD event) for the effect of antiviral therapy in base case and usual care analyses. Likewise, Table 4-16 summarizes the secondary effectiveness estimate, hazard ratios for the treatment effect in base case and usual care analyses. Both estimates of treatment effect revealed a significant beneficial effect on the prevention of ESLD event among patients with cirrhosis. Although, among patients without cirrhosis in the usual care analysis did not reach statistical difference in hazard of ESLD event between treated and untreated patients (hazard ratio=0.88, 95% CI, 0.27-2.87), the trend for the beneficial effect using primary effectiveness estimate versus hazard ratios were consistent (coefficient=1.56, se=0.07, p <.0001). Effectiveness results among patients with extended care, the two estimates in Table 4-8 and Table 4-14 for the treatment effect revealed consistent no difference in ESLD

progression between treatment and control among a number of different fitted models with various important baseline characteristics.

Data from randomized, controlled trials and current treatment recommendations on HCV management suggested that the cost-effectiveness of initial antiviral therapy for patients with cirrhosis has important interpretations to the decision makers in a MCO health delivery system. First, although individuals with advanced fibrosis typically responded less well to antiviral therapy in terms of SVR rate, [23, 24] additional benefits of antiviral therapy were seen among patients with advanced fibrosis and cirrhosis on more prolonged and potent viral suppression activity. [23, 79, 80] The histological response may lead to a reduction in the rate of ESLD progression. In practice, this group of patients had a greatest need for effective therapy in order to avoid HCC development and liver transplant. Second, several recent studies involving in responses rates have established that the low likelihood of achieving SVR with further antiviral therapy for HCV genotype 1 infected patients who lack of virological response after 24 weeks of combination therapy. More recently, discontinuation of antiviral therapy for patients remaining viral positive with qualitative PCR testing after 12-weeks of initial therapy has been suggested as a means of reducing antiviral treatment related adverse effects and costs.[23, 81]

As the treatment was more likely initiated to HCV-infected patients with cirrhosis in this patient cohort, the question is raised as to whether the continuous 12 months (48 weeks) antiviral therapy is more cost-effective than a shorter duration of treatment in cirrhotic patients, assuming that treatment discontinuation was mainly caused by the lack of early virological response at the end of 6- months therapy. Of note, the average duration of antiviral therapy was 7.5-8.3 months in all treated patients receiving at least one claim of combination therapy in Table 3-3. To determine the net benefit of initial antiviral therapy for patients with cirrhosis from a MCO

perspective, the following total cost and cost-effectiveness analysis were shown for patients with cirrhosis in the base case and usual care analyses.

Total Cost

Total direct medical costs during the study period were assessed for patients with cirrhosis in base case and subgroup analyses. As described in chapter 3.6, the total costs were obtained by the sum of weighted monthly costs in the follow-up by inverse probability of censoring. All baseline characteristics in the primary effectiveness estimation model were included in the inverse probability of censoring weighting procedure. Table 4-18 summarizes the estimated total cost comparisons of patients with cirrhosis in base case and usual care analyses. As expected, the mean difference in total costs between the treatment and control group was higher for patients with cirrhosis in the usual care (coefficient=$32,953, se=5642.31, p<.0001) than those patients in base case analysis (coefficient= $25,722, se=2365.28, p<.0001).

All measured baseline characteristics and created instruments were adjusted in the multivariate regression model to examine its influence on total cost difference between treatment and control, except for the variable of prior annual medical expenditure. The various baseline characteristics impact on the mean total costs difference among patients with cirrhosis is shown in Table 4-19. Social-demographic characteristics, including census regions, POS versus HMO health plan played a statistically significant role in the mean total cost difference between treatment and control in the base case analysis, despite POS versus HMO was insignificantly associated with total cost in the usual care analysis. The role of patient's co-morbidity conditions and prior health care services utilization in the total cost were varied between base case and usual care analyses. For example, patients with drug dependence emergency room visits were associated with a reduction in total cost during the initial treatment period in the usual care analysis [coefficient=$86,435, se=19783, p<.0001, and coefficient=$5796, se=19783, p<.0001,

respectively], yet diabetes and psychiatric disorders were significantly associated with the difference in the mean total cost in the base case analysis [coefficient=$7025, se=2969, p=0.02, and coefficient=-$6670, se=2924, p=0.02, respectively].

Cost-Effectiveness of Initial Combination Antiviral Therapy

Net Benefit Regression Model

Results of the net benefit regression were shown at selected values of WTP (λ=$0; $10,000; $20,000; and up to $80,000). Table 4-20 shows the mean net benefit difference (i.e., INB) between treatment and control for patients with cirrhosis in base case and usual care analyses. On average, the net benefit of treatment was higher among patients involving in the base case analysis compared to patients with the usual care at the same value of WTP (Table 4-20). In the base case analysis, the hypothesis that antiviral therapy is cost-effective was found in the multivariate adjusted regression model where minimum value of WTP at $15,000 (INB=11471, 95% CI=16822-22173, one-sided test with $p<0.001$). In patients with usual care, however, the hypothesis that antiviral therapy is cost-effective was found in the multivariate adjusted regression model where minimum value of WTP at $60,000 (INB=24553, 95% CI= -3819-52925, one-sided test with p=0.04). Given the values of WTP, the strength of statistical evidence about treatment efficiency (i.e., INB estimate) supported by 95% CI are shown in regression models in Figure 4-2.

Plots for the adjusted estimates of INB and its 95% CI by WTP depict the evidence that the antiviral therapy has a larger effect of net benefit for patients in the base case analysis than those who with usual care in Figure 4-2. The 95% lower limit of INB for patients with cirrhosis in the usual care analysis crosses the x-axis at WTP≥$60,000 , indicating that only a WTP as high as $60,000 would lead us to reject the null hypothesis ($\delta \leq 0$) in favor of treatment, INB (λ)>0 at

the 5% level significance. In addition, the greater variance of INB also increased as WTP became higher in patients with usual care compared to those patients in the base case cohort. Appendix A and B show the adjusted net benefit difference for patients in base case and usual care at selected WTP values.

Significance and Effect of Covariates

Significances and effects of risk factors and/or covariates on the INB estimate for the antiviral therapy intervention including factors that were either significantly relevant with primary effectiveness estimate or difference in average total costs are summarized in Table 4-21 and Table 4-22. The covariates effect on the INB between treatment and control were examined by the interaction terms with treatment in a multivariate adjusted model at various selected values of WTP (Appendix C and D).

As Table 4-21 and Appendix C show, among patients in base case analysis, year of HCV diagnosis during 2002 and 2006, severe decompensated cirrhosis, diabetes, HIV co-infection, and antidepressant use were potential important covariates on incremental cost-effectiveness of treatment, although not all of interaction terms across the regression model at WTP=$15,000; $20,000; and $30,000 were consistently significant at the 5% level. Among patients with usual care, year of HCV diagnosis at 2001 and 2002 relative to 2006 were potential important on a decrease in the cost-effectiveness of treatment, although not all of the interaction terms across the regression model at WTP=$60,000; $70,000; and $8,000 were consistently significant at the 5% level, as in Table 4-22 and Appendix D.

Lower treatment efficiency in base case cohort was associated with decompensated cirrhosis, diabetes and HIV co-infection among cirrhotic patients. The primary effectiveness estimate for the initial antiviral therapy was lower in cirrhotic patients having decompensated cirrhosis and diabetes compared to their counterparts (coefficient=-7.86, se=0.24, p<.0001, and

coefficient=-2.66, se=0.18, p<.0001, respectively). On the other hand, although the presence of HIV co-infection did not have a significant influence on the treatment effectiveness, total costs was substantially higher than those patients without HCV-HIV co-infection (coefficient=$40,509, se=7386.52, p<.0001).

Visual inspection for the assumptions of error term normality confirmed the heterogeneity of treatment effect in the group of patients with cirrhosis between base case and usual care analyses. Figure 4-3 depicts an example of standardized normal probability (P-P) plot of net benefit at the value of WTP=$15,000 for patients in base case analysis. The P-P plots showed that patients in the base case analysis were less sensitive to deviation from normality in the middle range of data than those patients in the usual care analysis as shown in Figure 4-4 at the value of WTP=$60,000. Possible explanations could be related with greater diversity of study samples in the usual care analysis than those in the base case analysis that didn't receive antiviral therapy but had good outcomes and relatively low costs.

Table 4- 1. Baseline characteristics of all patients between treatment and control groups in base case analysis

Variable	All patients (15071)	Treatment (3896)	Control (11175)
Social demographics			
Age at HCV diagnosis, years			
Mean (±SD)	47.5 (8.3)	47.5 (7.5)	47.5 (8.5)
Gender, %			
Female	38.6	35.5	39.7
Male	61.4	64.6	60.3
Census region,[1] %			
1	52.5	54.3	51.9
2	8.3	8.7	8.2
3	26.1	26.0	26.1
4	9.3	7.7	9.9
5	3.8	3.4	3.9
Insurance, %			
Public	2.3	1.5	2.5
Private	97.7	98.5	97.5
Health Plan,[2] %			
HMO	37.0	35.8	37.4
PPO	36.2	38.7	35.3
POS	26.9	25.6	27.3
Year of HCV diagnosis, %			
1998	1.3	0	1.7
1999	1.3	0	1.7
2000	7.0	4.9	7.8
2001	8.8	9.8	8.5
2002	14.2	17.2	13.2
2003	10.0	11.9	9.4
2004	12.4	13.6	11.9
2005	24.4	24.8	24.3
2006	16.7	14.9	17.3
2007	3.9	3.0	4.3

1. Census Region: 1=New England and Middle Atlantic; 2=East North Central and West North Central; 3=South Atlantic, East South Central, and West South Central; 4=Mountain and Pacific; 5=National and Other in the dataset. 2. Health plan: Preferred Provider Organization (PPO), Health Maintenance Organization (HMO) and Point of Service (POS).

Table 4-1. Continued

Variable	All patients (n=15071)	Treatment (n=3896)	Control (n=11175)
Prior comorbid conditions,%			
Severe decompensated cirrhosis	1.5	1.1	1.6
Cirrhosis	18.0	25.4	15.4
Chronic obstructive pulmonary diseases (COPD)	12.7	11.5	13.2
Cerebral vascular disease (CVD)	2.8	2.4	2.9
Depression after HCV diagnosis	4.8	7.4	13.8
Diabetes	12.3	11.2	12.7
Drug dependence	3.7	1.8	4.4
HBV co-infection	3.6	2.7	3.9
Heart diseases	9.5	8.9	9.8
HIV co-infection	3.2	1.9	3.6
Obesity	5.0	4.9	5.0
Psychiatric disorders	17.5	16.2	18.0
Prior medical services use			
Annual medical expenditure, %			
$<$\$6700	66.6	63.1	67.8
$\geqq$ \$6700	33.4	36.9	32.2
Liver biopsy, %	8.1	17.5	4.9
Hospitalization, %	20.9	13.8	23.4
Emergency room, visits Mean ±(SD)	1.2 (3.3)	1.1 (3.2)	1.3 (3.3)
Outpatient, visits Mean ± (SD)	21.6 (26.0)	21.9 (23.6)	21.6 (26.8)
Family/general practice, visits Mean ± (SD)	3.5 (6.4)	3.4 (6.1)	3.5 (6.6)
Gastroenterology, visits Mean ± (SD)	2.1 (3.6)	3.0 (3.2)	1.8 (3.6)
Infectious disease, visits Mean ± (SD)	0.3 (2.9)	0.2 (1.0)	0.4 (3.3)
Internal Medicine, visits Mean ± (SD)	5.3 (9.1)	5.2 (8.0)	5.3 (9.5)
Instruments related with symptomatic conditions and maintenance			
Time to treatment,%			
$<$6 months	64.2	64.3	63.7
$\geqq$6 months	35.8	35.7	36.3
Antidepressant use,%	15.9	29.3	11.3

Table 4-2. Factors associated with initiation of combination antiviral therapy among patients in base case analysis

Variable	Adjusted OR[1] (95% CI)
Social demographics	
Age at HCV diagnosis	0.99 (0.99–1.00)
Gender	
Male vs. Female	1.25(1.15–1.36)
Health Plan[2]	
POS vs. HMO	1.00 (0.90-1.11)
PPO vs. HMO	1.14 (1.04–1.25)
Year of HCV diagnosis	
1998 vs. 2007	0
1999 vs. 2007	0
2000 vs. 2007	0.68 (0.52–0.89)
2001 vs. 2007	1.45 (1.13–1.86)
2002 vs. 2007	1.65 (1.31–2.10)
2003 vs. 2007	1.35 (1.06–1.73)
2004 vs. 2007	1.41 (1.11–1.79)
2005 vs. 2007	1.25 (1.00–1.57)
2006 vs. 2007	1.14 (0.90–1.44)
Prior comorbid conditions	
Severe decompensated cirrhosis	0.32 (0.22–0.48)
Cirrhosis	1.68 (1.52–1.86)
Chronic obstructive pulmonary diseases (COPD)	0.88 (0.78–0.99)
Depression	1.85 (1.57–2.19)
Diabetes	0.81 (0.72–0.92)
Drug dependence	0.50 (0.38–0.65)
HBV co-infection	0.53 (0.42–0.67)
HIV co-infection	0.53 (0.40–0.70)
Prior medical services use	
Annual medical expenditure	
≥$6700 vs. <$6700	1.94 (1.76–2.15)
Liver biopsy	3.30 (2.90–3.75)
Hospitalization	0.38 (0.34–0.43)
Outpatient visits	0.996 (0.994–0.998)
Emergency room visits	0.985 (0.971–0.999)
Gastroenterologist visits	1.12 (1.10–1.14)
Infectious disease visits	0.95 (0.92–0.98)

1. Adjusted OR was obtained by multivariate logistic regression analysis with stepwise selection procedure, including 27 baseline characteristics. 2. Heath plan: PPO=Preferred Provider Organization, non-PPO= Health Maintenance Organization (HMO), Point of Service (POS), and Other labeled in the dataset

Table 4-3. Factors associated with initiation of combination antiviral therapy among patients with or without cirrhosis involving in base case analysis

Variable[1]	Cirrhosis	Non-cirrhosis
Social demographics		
Age at HCV diagnosis	NS[3]	0.99 (0.98–0.99)
Gender		
Male vs. Female	1.28 (1.07–1.52)	1.23 (1.12–1.35)
Health Plan[2]		
POS vs. HMO	1.15 (0.92–1.44)	NS
PPO vs. HMO	1.32 (1.09–1.61)	NS
Year of HCV diagnosis		
1998 vs. 2007	0	0
1999 vs. 2007	0	0
2000 vs. 2007	1.55 (0.76–3.15)	0.56 (0.41–0.77)
2001 vs. 2007	2.44 (1.21–4.91)	1.36 (1.04–1.78)
2002 vs. 2007	2.89 (1.46-5.72)	1.60 (1.25–2.06)
2003 vs. 2007	2.93 (1.46–5.88)	1.20 (0.92–1.56)
2004 vs. 2007	2.35 (1.17–4.69)	1.34 (1.04–1.74)
2005 vs. 2007	2.12 (1.08–4.13)	1.17 (0.92–1.50)
2006 vs. 2007	2.11 (1.07–4.18)	1.02 (0.79–1.31)
Prior comorbid conditions		
Severe decompensated cirrhosis	0.46 (0.31–0.67)	--
Depression	2.23 (1.60–3.12)	1.71 (1.41-2.08)
Diabetes	NS	0.83 (0.71–0.96)
Drugs dependence	NS	0.40 (0.29–0.56)
HBV co-infection	0.36 (0.24–0.55)	0.62 (0.47–0.82)
HIV co-infection	NS	0.47 (0.34–0.65)
Prior medical services use		
Annual medical expenditure		
≥$6700 vs. <$6700	1.58 (1.29–1.93)	2.04 (1.82–2.89)
Liver biopsy	2.61 (2.03–3.36)	3.37 (2.90–3.91)
Hospitalization	0.38 (0.30–0.48)	0.39 (0.34–0.45)
Outpatient visits	0.994 (0.991–0.998)	0.996 (0.993–0.998)
Emergency room visits	NS	0.97 (0.96–0.99)
Gastroenterologist visits	1.04 (1.02–1.06)	1.20 (1.18–1.23)
Infectious disease visits	0.94 (0.89–1.00)	0.94 (0.92–0.96)

1. Adjusted OR (odds ratio) was obtained by multivariate logistic regression analysis with stepwise selection procedure, including 26 baseline characteristics in patients with cirrhosis, and 25 baseline characteristics in patients without cirrhosis. 2. Health plan: Preferred Provider Organization (PPO), non-PPO=Health Maintenance Organization (HMO) and Point of Service (POS). 3. NS (not selected), indicating the variable failed to reach statistical significance in the multivariate logistic regression analysis with stepwise selection.

Table 4-4. Baseline characteristics of subgroup patients with usual care or extended care

Variable[1]	Usual care		Extended care	
	Treatment (n=882)	Control (n=2605)	Treatment (n=119)	Control (n=353)
Social demographics				
Age at HCV diagnosis, years	47.2	47.8	48.5	47.6
Mean (±SD)	(7.3)	(8.2)	(6.5)	(8.1)
Gender , %				
Female	33.8	42.2	27.7	40.8
Male	66.2	57.8	72.3	59.2
Census region[1], %				
1	64.9	62.7	69.8	64.9
2	6.8	7.1	3.4	4.0
3	20.0	19.3	17.7	17.3
4	4.7	7.2	4.2	6.0
5	3.7	3.8	5.0	7.9
Insurance, %				
Public	0.7	2.7	1.7	0.9
Private	99.3	97.3	98.3	99.1
Health Plan[2], %				
HMO	37.3	39.5	31.9	37.1
PPO	40.8	37.1	47.1	41.1
POS	21.9	23.4	21.0	21.8
Year of HCV diagnosis,%				
1998	0.0	0.8	0.0	0.9
1999	0.0	0.0	0.0	0.0
2000	6.5	10.2	21.0	17.6
2001	14.5	11.1	21.0	18.4
2002	17.5	15.8	14.3	20.7
2003	14.5	13.7	12.6	11.3
2004	14.7	16.0	7.6	12.8
2005	25.7	27.1	21.0	16.2
2006	6.6	5.2	2.5	2.3
2007	0.0	0.0	0.0	0.0

1. Census Region: 1=New England and Middle Atlantic; 2=East North Central and West North Central; 3=South Atlantic, East South Central, and West South Central; 4=Mountain and Pacific; 5=National and Other in the dataset. 2. Health plan: Preferred Provider Organization (PPO), Health Maintenance Organization (HMO) and Point of Service (POS).

Table 4-4. Continued

Variable[1]	Usual care		Extended care	
	Treatment (n=882)	Control (n=2605)	Treatment (n=119)	Control (n=353)
Prior comorbid conditions,%				
Severe decompensated cirrhosis	0.3	0.7	2.5	2.0
Cirrhosis	29.0	16.7	37.0	21.0
Chronic obstructive pulmonary diseases (COPD)	10.2	13.9	16.0	11.6
Cerebral vascular disease (CVD)	1.6	3.0	3.4	1.4
Depression after HCV diagnosis	8.1	3.4	5.0	2.6
Diabetes	10.3	13.1	9.2	15.9
Drug dependence	1.7	3.5	0.8	1.7
HBV co-infection	2.5	4.0	0.8	3.1
Heart diseases	9.0	10.5	10.1	8.2
HIV co-infection	2.0	3.6	3.4	2.8
Obesity	5.0	5.2	1.7	3.4
Psychiatric disorders	15.1	17.9	7.6	15.6
Prior medical services use				
Annual medical expenditure, %				
<$6700	66.7	67.3	56.3	71.7
≧$6700	33.3	32.7	43.7	28.3
Liver biopsy, %	18.3	5.2	13.5	4.0
Hospitalization, %	11.7	22.4	13.5	17.3
Emergency room, visits Mean ±(SD)	1.1 (2.3)	0.8 (1.9)	0.9 (2.1)	0.9 (1.9)
Outpatient, visits Mean ± (SD)	22.7 (26.4)	22.5 (22.5)	19.9 (13.4)	21.3 (28.8)
Family/general practice, visits Mean ± (SD)	3.3 (6.2)	3.4 (5.8)	3.6 (6.1)	2.8 (6.2)
Gastroenterology, visits Mean ± (SD)	2.1 (3.6)	3.2 (3.7)	3.0 (2.5)	1.8 (3.5)
Infectious disease, visits Mean ± (SD)	0.3 (3.4)	0.2 (1.1)	0.2 (1.2)	0.2 (0.9)
Internal Medicine, visits Mean ± (SD)	5.6 (9.1)	5.5 (8.0)	5.1 (6.2)	5.3 (7.4)
Instruments related with symptomatic conditions and maintenance				
Time to treatment,%				
＜6 months	60.7	61.1	67.2	67.7
≥6 months	39.3	38.9	32.8	32.3
Antidepressant use	33.5	14.7	40.3	17.3

Table 4-5. Factors associated with initiation of combination antiviral therapy among patients with usual care or extended care

Variable[1]	Usual care	Extended care
Social demographics		
Age at HCV diagnosis	0. 98 (0.97–0.99)	NS
Gender		
Male vs. Female	1.52 (1.27–1.82)	1.80 (1.11–2.92)
Private insurance	3.05 (1.19–7.82)	NS
Health Plan[2]		
POS vs. HMO	0.87 (0.69–1.10)	NS
PPO vs. HMO	1.21 (1.00–1.46)	NS
Year of HCV diagnosis		
2000 vs. 2006	0.33 (0.21–0.53)	NS
2001 vs. 2006	0.87 (0.58–1.30)	NS
2002 vs. 2006	0.69 (0.47–1.03)	NS
2003 vs. 2006	0.55 (0.37–0.83)	NS
2004 vs. 2006	0.56 (0.37–0.83)	NS
2005 vs. 2006	0.68 (0.47–0.98)	NS
Prior comorbid conditions		
Severe decompensated cirrhosis	0.12 (0.02–0.58)	NS
Depression	1.65 (1.60–2.01)	2.03 (1.25-3.30)
Chronic obstructive pulmonary diseases (COPD)	0.71 (0.55–0.94)	NS
Depression	2.39 (1.67–3.42)	NS
Diabetes	NS	0.42 (0.20–0.87)
HBV co-infection	0.37 (0.22–0.63)	NS
HIV co-infection	0.46 (0.26–0.83)	NS
Psychiatric disorders	NS	0.40 (0.18–0.87)
Prior medical services use		
Annual medical expenditure		
≥$6700 vs. <$6700	1.78 (1.43–2.20)	2.47 (1.46–4.16)
Liver biopsy	3.50 (2.66–4.60)	3.40 (1.54–7.54)
Hospitalization	0.34 (0.26–0.46)	0.45 (0.22–0.92)
Outpatient visits	0.996 (0.992–0.999)	NS
Emergency room visits	0.92 (0.88–0.97)	NS
Gastroenterologist visits	1.17 (1.31–1.20)	NS
Infectious disease visits	0.96 (0.93–0.99)	NS

1. Adjusted OR (odds ratio) was obtained by multivariate logistic regression analysis with stepwise selection procedure, including 26 baseline characteristics in patients with cirrhosis, and 25 baseline characteristics in patients without cirrhosis. 2. Health plan: Preferred Provider Organization (PPO), non-PPO=Health Maintenance Organization (HMO) and Point of Service (POS). 3. NS (not selected), indicating the variable failed to reach statistical significance in the multivariate logistic regression analysis with stepwise selection.

Table 4-6. Primary effectiveness results in base case analysis: Time to ESLD development in patients with and without cirrhosis at baseline

Time to ESLD outcome	All patients		Cirrhosis		Non-cirrhosis	
	Treatment (n=3896)	Control (n=11175)	Treatment (n=991)	Control (n=1721)	Treatment (n=2905)	Control (n=9454)
Mean (±SD) months	20.1 (8.1)	15.7 (9.0)	19.4 (8.0)	14.3 (8.8)	20.3 (8.2)	16.0 (9.0)
Adjusted mean difference (se) [p value][1]	3.32 (0.06) [<.0001][2]		3.01 (0.15) [<.0001]		3.44 (0.06) [<.0001]	

1. Various baseline characteristics included in the multivariate adjusted regression models to examine the heterogeneity of treatment on time to ESLD were listed in Table 4-5. 2. The coefficient of interaction term between cirrhosis and treatment intervention was -0.33 (se=0.13, p=0.01).

Table 4-7. Factors associated with primary effectiveness of antiviral therapy among patients with and without cirrhosis in base case analysis

Variable[1]	All patients	Cirrhosis	Non-cirrhosis
Social demographics			
Age at HCV diagnosis	0.04 (0.00) [<.0001]	-0.01 (0.01) [0.30]	0.05 (0.00) [<.0001]
Gender	-0.49 (0.05) [<.0001]	-1.16 (0.14) [<.0001]	-0.36 (0.05) [<.0001]
PPO health Plan			
POS vs. HMO	-0.06 (0.06) [0.32]	0.22 (0.16) [0.16]	--
PPO vs. HMO	1.08 (0.06) [<.0001]	0.16 (0.18) [0.36]	--
Year of HCV diagnosis			
1998 vs. 2007	8.28 (0.24) [<.0001]	7.82 (0.67) [<.0001]	8.05 (0.26) [<.0001]
1999 vs. 2007	2.79 (0.24) [<.0001]	2.27 (0.77) [<0.01]	2.84 (0.25) [<.0001]
2000 vs. 2007	29.86 (0.15) [<.0001]	25.17 (0.49) [<.0001]	30.45 (0.16) [<.0001]
2001 vs. 2007	27.01 (0.14) [<.0001]	23.42 (0.49) [<.0001]	27.22 (0.15) [<.0001]
2002 vs. 2007	22.16 (0.14) [<.0001]	19.01 (0.47) [<.0001]	22.42 (0.14) [<.0001]
2003 vs. 2007	22.07 (0.14) [<.0001]	19.48 (0.48) [<.0001]	23.27 (0.15) [<.0001]
2004 vs. 2007	17.80 (0.13) [<.0001]	14.21 (0.47) [<.0001]	17.96 (0.13) [<.0001]
2005 vs. 2007	12.37 (0.13) [<.0001]	9.98 (0.45) [<.0001]	12.58 (0.13) [<.0001]
2006 vs. 2007	5.57 (0.13) [<.0001]	4.31 (0.46) [<.0001]	5.68 (0.13) [<.0001]
Prior comorbid conditions			
Severe decompensated cirrhosis	-7.93 (0.20) [<.0001]	-8.00 (0.26) [<.0001]	--
Cirrhosis	-1.26 (0.06) [<.0001]	--	--
Depression	-1.52 (0.11) [<.0001]	-1.41 (0.28) [<.0001]	-1.19 (0.08) [<.0001]
Drugs dependence	-1.32 (0.13) [<.0001]	--	-1.31 (0.13) [<.0001]

Table 4-7. Continued

Variable[1]	All patients	Cirrhosis	Non-cirrhosis
Prior comorbid conditions			
Diabetes	-1.54 (0.07) [<.0001]	--	-1.19 (0.08) [<.0001]
HBV co-infection	-0.94 (0.13) [<.0001]	-1.79 (0.79) [<.0001]	-0.51 (0.14) [<.0001]
HIV co-infection	1.41(0.14) [<.0001]	--	1.31 (0.14) [<.0001]
Prior medical services use			
Annual medical expenditure	-1.24 (0.06) [<.0001]	-1.75 (0.16) [<.0001]	-1.08 (0.07) [<.0001]
Liver biopsy	1.46 (0.09) [<.0001]	2.19 (0.21) [<.0001]	1.29 (1.00) [<.0001]
Hospitalization	-1.46 (0.07) [<.0001]	-2.01 (0.18) [<.0001]	-1.45 (0.07) [<.0001]
Outpatients visits	0.01 (0.00) [<.0001]	0.01 (0.00) [<.0001]	0.02 (0.00) [<.0001]
Emergency room visits	-0.12 (0.01) [<.0001]	--	-0.01 (0.01) [<.0001]
Gastroenterology visits	-0.09 (0.01) [<.0001]	-0.07 (0.01) [<.0001]	-0.12 (0.01) [<.0001]
Infectious disease	0.01(0.01) [0.35]	0.02 (0.02) [0.42]	-0.01 (0.01) [0.54]
Instruments related with symptomatic conditions and maintenance			
Time to treatment ≧6 vs. <6 months	2.82 (0.05) [<.0001]	2.74 (0.14) [<.0001]	2.77 (0.05) [<.0001]
Antidepressants use	0.20 (0.07) [<0.01]	0.71 (0.18) [<.001]	0.09 (0.07) [0.23]

1. Values shown in the tables are coefficients (mean (se), [p-value]) associated with treatment initiation relevant covariates and instruments related with symptomatic conditions and maintenance in the multivariate adjusted regression models. Treatment initiation related covariates in base case analysis were shown in Table 4-2, Table 4-3 for patients with or without cirrhosis in base case analysis.

Table 4-8. Primary effectiveness results in subgroup analysis: Time to ESLD development in patients with usual care and extended care

Time to ESLD Outcome	Usual care		Extended care	
	Treatment (n=882)	Control (n=2605)	Treatment (n=119)	Control (n=353)
Mean (±SD) months	29.8 (10.6)	29.4 (11.0)	33.6 (11.3)	33.1 (11.2)
Adjusted mean difference (se) [p value][1]	1.33 (0.09) [<.0001][2]		1.27 (1.20) [0.29][3]	

1. Various baseline characteristics included in the multivariate adjusted regression models to examine the heterogeneity of treatment on time to ESLD are listed in Table 4-9. 2. The interaction between treatment and prior cirrhosis was -0.59 (0.20) [p<0.01]. 3. The interaction between treatment and prior cirrhosis was 3.12 (2.48) [p=0.21].

Table 4-9. Factors associated with primary effectiveness among patients with usual care and extended care

Variable[1]	Usual care	Extended care
Social demographics		
Age at HCV diagnosis	0.05 (0.00) [<.0001]	-0.00 (0.06) [0.98]
Gender (Male vs. Female)	-0.68 (0.08) [<.0001]	0.27 (1.00) [0.78]
Private insurance	1.64(0.26) [<.0001]	--
Type of health Plan		
POS vs. HMO	0.06 (0.10) [0.52]	--
PPO vs. HMO	0.00 (0.08) [0.95]	--
Year of HCV diagnosis		
2000 vs. 2006	34.15 (0.20) [<.0001]	--
2001 vs. 2006	28.20(0.19) [<.0001]	--
2002 vs. 2006	25.46 (0.19) [<.0001]	--
2003 vs. 2006	21.58 (0.19) [<.0001]	--
2004 vs. 2006	13.16 (0.18) [<.0001]	--
2005 vs. 2006	5.74 (0.17) [<.0001]	--
Prior comorbid conditions		
Severe decompensated cirrhosis	-0.69 (0.48) [0.15]	-8.02 (3.48) [0.02]
Cirrhosis	-3.32 (0.10) [<.0001]	-3.15 (1.18) [<0.01]
Chronic obstructive pulmonary diseases (COPD)	0.02 (0.11) [0.85]	--
Depression	-2.74 (0.18) [<.001]	--
Diabetes	--	-5.44 (1.43) [<0.001]
HBV co-infection	-1.93 (0.20) [<.0001]	--
HIV co-infection	3.95 (0.22) [<.0001]	--
Psychiatric disorders	--	-2.37 (1.44) [0.10]

Table 4-9. Continued

Variable[1]	Usual care	Extended care
Prior medical services use		
Annual medical expenditure	-1.94 (0.10) [<.0001]	-2.28 (1.21) [0.06]
Biopsy	-1.28 (0.14) [<.0001]	-5.90 (2.00) [<0.01]
Hospitalization	-0.59 (0.11) [<.0001]	-2.57 (1.50) [0.09]
Outpatient visits	-0.02 (0.00) [<.0001]	--
Emergency visits	-0.01 (0.01) [0.44]	--
Gastroenterology visits	-0.20 (0.01) [<.0001]	--
Infectious disease visits	0.03 (0.01) [<0.01]	--
Instruments related with symptomatic conditions and maintenance		
Time to treatment ≥6 vs. <6 months	0.00 (0.08) [1.00]	-3.05 (1.02) [<0.01]
Antidepressants use	0.06 (0.10) [0.54]	-0.88 (1.22) [0.47]

1. Values shown in the tables are coefficients (mean (se), [p-value]) associated with treatment initiation relevant covariates and instruments related with symptomatic conditions and maintenance (as shown in Table 4-5) in the multivariate adjusted regression models.

Table 4-10. Summary of primary effectiveness results in base case and usual care analyses among patients with or without cirrhosis at baseline

Time to ESLD outcome	Cirrhosis		Non-cirrhosis	
	Treatment	Control	Treatment	Control
Base case cohort (n)	991	1721	2905	9454
Mean (±SD) months	19.4 (8.0)	14.3 (8.8)	20.3 (8.2)	16.0 (9.0)
Adjusted mean difference (se) [p value]	3.01 (0.15) [<.0001]		3.45 (0.06) [<.0001]	
Usual care (n)	256	462	626	2169
Mean (±SD) months	27.8 (10.4)	27.2 (10.9)	30.6 (10.6)	29.9 (10.9)
Adjusted mean difference (se) [p value][1]	0.92 (0.32) [<.001]		1.56 (0.07) [<.0001]	

1. Various baseline characteristics related to the heterogeneity of treatment on time to ESLD for patients with or without cirrhosis in usual care analysis are listed in Table 4-11.

Table 4-11. Factors associated with primary effectiveness among patients with or without cirrhosis in usual care analysis

Variable[1]	Cirrhosis	Non-cirrhosis
Social demographics		
Age at HCV diagnosis	0.10 (0.02) [<.0001]	0.04 (0.00) [<.0001]
Gender (Male vs. Female)	-1.56 (0.29) [<.0001]	-0.20 (0.06) [<0.001]
Type of health Plan		
POS vs. HMO	-1.14 (0.39) [<0.01]	0.44 (0.07) [<.0001]
PPO vs. HMO	-0.14 (0.32) [0.65]	0.01 (0.06) [0.85]
Year of HCV diagnosis		
2000 vs. 2006	31.52 (0.78) [<.0001]	34.84 (0.15) [<.0001]
2001 vs. 2006	25.34 (0.75) [<.0001]	28.94 (0.14) [<.0001]
2002 vs. 2006	21.60 (0.72) [<.0001]	26.45 (0.14) [<.0001]
2003 vs. 2006	20.00 (0.75) [<.0001]	21.94 (0.14) [<.0001]
2004 vs. 2006	11.58 (0.73) [<.0001]	13.49 (0.14) [<.0001]
2005 vs. 2006	4.69 (0.69) [<.0001]	6.13 (0.13) [<.0001]
Prior comorbid conditions		
Severe decompensated cirrhosis	0.33 (0.84) [0.69]	--
Chronic obstructive pulmonary diseases (COPD)	0.00 (0.43) [0.99]	-0.24 (0.08) [<0.01]
Depression	-1.37 (0.57) [0.02]	-3.41 (0.14) [<.0001]
HBV co-infection	-4.22 (0.63) [<.0001]	-0.74 (0.16) [<.0001]
HIV co-infection	6.45 (0.98) [<.0001]	3.46 (0.16) [<.0001]

Table 4-11. Continued

Variable[1]	Cirrhosis	Non-cirrhosis
Prior medical services use		
Annual medical expenditure	-4.00 (0.33) [<.0001]	-1.86 (0.07) [<.0001]
Biopsy	-1.70 (0.43) [<.0001]	-1.20 (0.11) [<.0001]
Hospitalization	-1.14 (0.42) [<0.01]	-0.46 (0.08) [<.0001]
Emergency visits	0.39 (0.08) [<0.01]	-0.08 (0.01) [<.0001]
Gastroenterology visits	-0.23 (0.03) [<.0001]	-0.25 (0.01) [<.0001]
Infectious disease visits	0.11 (0.05) [0.02]	0.02 (0.01) [0.01]
Instruments related with symptomatic conditions and maintenance		
Time to treatment	-0.30 (0.30)	0.24 (0.06)
≥6 vs. <6 months	[0.32]	[<.0001]
Antidepressants use	0.24 (0.35)	-0.19 (0.07)
	[0.49]	[0.01]

1. Values shown in the tables are coefficients (mean (se), [p-value]) associated with treatment initiation relevant covariates and important baseline included in the multivariate adjusted regression models.

Table 4-12. Secondary effectiveness results in base case analysis: Rate of ESLD development in patients with or without cirrhosis

Outcome	All patients		Cirrhosis		Non-cirrhosis	
	Treatment (n=3896)	Control (11175)	Treatment (n=991)	Control (n=1721)	Treatment (n=2905)	Control (n=9454)
Overall, n (%)	67(1.7)	166 (1.5)	37 (3.7)	92 (5.4)	30 (1.0)	74 (0.8)
ESLD						
HCC	31	60	18	37	13	23
LT	11	34	6	28	5	6
Decompensated cirrhosis[1]	38	89	20	42	18	47
Proxy	2	10	2	1	0	9
Adjusted HR[2] (95% CI)	0.28 (0.20–0.40)[3]		0.32 (0.21–0.50)		0.23 (0.13–0.40)	

Abbreviations: ESLD=end stage liver disease, HCC=hepatocellular carcinoma, LT=liver transplantation, HR=Hazard Ratio. 1. Decompensated cirrhosis=variceal bleeding, hepatic coma and other decompensated conditions in Table 3-1. 2. Various baseline characteristics, including treatment initiation relevant covariates and important baseline characteristics included in Cox regression models to examine the heterogeneity of treatment effect are shown in Table 4-13. 3. The interaction between treatment and prior cirrhosis was 0.61 (0.34–1.10).

Table 4-13. Factors associated with secondary effectiveness among patients with or without cirrhosis in base case analysis

Variable[1]	All patients	Cirrhosis	Non-cirrhosis
Social demographics			
Age at HCV diagnosis	1.03 (1.01–1.04)	1.03 (1.00–1.05)	1.02 (0.99–1.05)
Gender (Male vs. Female)	1.81 (1.35–2.43)	2.30 (1.52–3.49)	1.42 (0.93–2.15)
PPO health Plan			
POS vs. HMO	0.92 (0.66–1.26)	0.97 (0.64–1.49)	0.99 (0.65–1.50)
PPO vs. HMO	1.05 (0.74–1.47)	1.12 (0.70–1.79)	0.97 (0.64–1.49)
Year of HCV diagnosis			
1998 vs. 2007	0.00 (0.00–0.04)	0.01 (0.00–0.09)	0.00 (0.00–∞)
1999 vs. 2007	0.20 (0.04–1.05)	0.40 (0.05–2.92)	0.00 (0.00–∞)
2000 vs. 2007	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
2001 vs. 2007	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
2002 vs. 2007	0.00 (0.00–0.00)	0.00 (0.00–0.01)	0.00 (0.00–0.00)
2003 vs. 2007	0.00 (0.00–0.00)	0.00 (0.00–0.03)	0.00 (0.00–0.00)
2004 vs. 2007	0.00 (0.00–0.01)	0.01 (0.00–0.05)	0.00 (0.00–0.00)
2005 vs. 2007	0.02 (0.00–0.02)	0.05 (0.01–0.23)	0.00 (0.00–0.02)
2006 vs. 2007	0.04 (0.01–0.10)	0.10 (0.02–0.49)	0.03 (0.01–0.18)
Prior comorbid conditions			
Decompensated cirrhosis	59.22 (33.82–103.69)	31.48 (17.72–55.91)	–
Cirrhosis	8.69 (6.11–11.73)	–	–
COPD	0.57 (0.38–0.87)	–	–
Depression	1.24 (0.66–2.31)	1.44 (0.71–2.94)	0.68 (0.16–2.81)
Diabetes	4.24 (3.07–5.86)	–	4.71 (2.93–7.55)
Drug dependence	1.62 (0.78–3.36)	–	0.90 (0.22–3.77)
HBV co-infection	3.28 (1.97–5.46)	2.91 (1.57–5.41)	2.55 (1.02–6.40)
HIV co-infection	0.58 (0.27–1.23)	–	0.25 (0.06–1.07)
Prior medical services use			
Annual medical expenditure	2.45 (1.69–3.26)	2.49 (1.62–3.82)	2.44 (1.45–4.08)
Biopsy	0.30 (0.17–0.53)	0.39 (0.20–0.75)	0.18 (0.06–0.52)
Hospitalization	1.83 (1.27–2.62)	1.52 (0.96–2.41)	2.96 (1.69–5.17)
Outpatient visits	0.99 (0.99–1.00)	1.00 (0.99–1.00)	0.99 (0.98–1.00)
Emergency room visits	1.05 (1.02–1.08)	–	1.01 (0.90–1.12)
Gastroenterology visits	1.00 (0.98–1.03)	1.03 (1.00–1.06)	1.02 (0.95–1.10)
Infectious disease visits	1.01 (0.99–1.04)	0.92 (0.81–1.05)	1.03 (1.00–1.05)
Instruments related with symptomatic conditions and maintenance			
Time to treatment			
<6 vs. ≥6months	0.67 (0.50-0.91)	0.65 (0.44–0.96)	0.67 (0.41–1.09)
Antidepressants use	1.44 (1.02–2.02)	1.26 (0.78–2.02)	1.66 (1.01–2.71)

1. Values shown in the tables are adjusted hazard ratios, HR (95% CI) associated with treatment initiation relevant covariates and important baseline characteristics included in the Cox regression models

Table 4-14 Second effectiveness results in subgroup analysis: Rate of ESLD development in patients with usual care or extended care

Outcome	Usual care		Extended care	
	Treatment (n=882)	Control (n=2605)	Treatment (n=119)	Control (n=353)
Overall , n (%)	12 (1.4)	33 (1.3)	9 (7.6)	9 (2.6)
ESLD				
HCC	8	11	4	3
LT	1	10	2	5
Decompensated cirrhosis	5	14	5	2
Proxy	0	3	0	1
Adjusted HR (95% CI)[1]	0.61 (0.28–1.35)[2]		1.79 (0.58–5.54)[3]	

Abbreviations: ESLD=end stage liver disease, HCC=hepatocellular carcinoma, LT=liver transplantation, HR=Hazard Ratio. 1. Various baseline characteristics, including treatment initiation relevant covariates and instruments related with symptomatic conditions and maintenance included in the Cox regression models to examine the heterogeneity of treatment effect are shown in Table 4-15. 2. The interaction between treatment and prior cirrhosis was 0.17 (0.04–0.81). 3. The interaction between treatment and prior cirrhosis was 1.92 (0.62–5.96)

Table 4-15. Factors associated with secondary effectiveness among patients with usual care or extended care

Variable[1]	Usual care	Extended care[3]
Social demographics		
Age at HCV diagnosis	0.97 (0.93–1.01)	0.89 (0.82–0.95)
Gender (Male vs. Female)	2.80 (1.38–5.70)	1.52 (0.44–5.27)
Private insurance	∞ (0.00–∞)	--
PPO health Plan		
POS vs. HMO	2.14 (0.98–4.66)	--
PPO vs. HMO	0.86 (0.41–1.82)	--
Year of HCV diagnosis[2]		
2000 vs. 2006	0.00 (0.00–0.01)	--
2001 vs. 2006	0.01 (0.00–0.12)	--
2002 vs. 2006	0.02 (0.00–0.25)	--
2003 vs. 2006	0.01 (0.00–0.17)	--
2004 vs. 2006	0.07 (0.01–0.96)	--
2005 vs. 2006	0.47 (0.05–4.43)	--
Prior comorbid conditions		
Decompensated cirrhosis	5.54 (1.80–17.08)	13.88 (3.05–63.08)
Cirrhosis	10.72 (5.23–21.91)	18.24 (4.25–78.25)
Chronic obstructive pulmonary diseases (COPD)	1.22 (0.46–3.20)	1.33 (0.39–4.61)
Depression	0.59 (0.08–4.55)	0.75 (0.18–3.10)
Diabetes	--	7.58 (2.01–28.59)
HBV co-infection	3.95 (1.14–13.60)	--
HIV co-infection	0.00 (0.00–∞)	--
Psychiatric disorders	--	1.25 (0.27–5.81)
Prior medical services use		
Annual medical expenditure	4.87 (2.25–10.56)	1.47 (0.44–4.89)
Biopsy	1.90 (0.60–6.06)	3.66 (0.60–22.29)
Hospitalization	1.21 (0.53–2.77)	1.00 (0.26–3.95)
Outpatient visits	1.01 (0.99–1.02)	--
Emergency visits	0.86 (0.67–1.09)	--
Gastroenterology visits	1.01 (0.92–1.11)	--
Infectious disease visits	0.66 (0.34–1.26)	--
Instrument related with symptomatic condition and treatment maintenance		
Time to treatment		
<6 vs. ≥6 months	2.19 (1.07–4.49)	1.44 (0.49–4.26)
Antidepressants use	1.53 (0.73–3.23)	0.86 (0.27–2.75)

1. Values shown in the tables are adjusted hazard ratios, HR (95% CI) associated with treatment initiation relevant covariates and important baseline characteristics (as shown in Table 4-5) included in the Cox regression models. 2. Due to the majority of patients in subgroup analysis were firstly diagnosed with HCV infection during 2000 and 2006, all analyses were performed within the period. 3. Additional baseline covariates added into the Cox regression model (same covariates in the usual care analysis), the HR= 2.34 (0.58–9.41) for patients with extended care.

Table 4-16. Summary of secondary effectiveness results in base case and usual care analyses among patients with or without cirrhosis at baseline

Rate of ESLD development	Cirrhosis		Non-cirrhosis	
	Treatment	Control	Treatment	Control
Base case cohort, n	991	1721	2905	9454
ESLD event, n (%)	37 (3.7)	92 (5.4)	30 (1.0)	74 (0.8)
Adjusted HR(95% CI)	0.32 (0.21-0.50)		0.23 (0.13-0.40)	
Usual care, n	256	436	626	2169
ESLD event, n (%)	3 (1.2)	22 (5.1)	9 (1.4)	11 (0.5)
Adjusted HR (95% CI)[1]	0.24 (0.06-0.94)		0.88 (0.27-2.87)	

1. Various baseline characteristics included in the Cox regression models to examine the heterogeneity of treatment effect are shown in Table 4-17 for patients involving in usual care analysis.

Table 4-17. Factors associated with secondary effectiveness among patients with or without cirrhosis in usual care analysis

Variable[1]	Cirrhosis	Non-cirrhosis
Social demographics		
Age at HCV diagnosis	0.94 (0.90–0.99)	1.00 (0.93–1.06)
Gender	3.72 (1.38–10.05)	1.95 (0.69–5.52)
PPO health Plan		
POS vs. HMO	2.51 (0.83–7.58)	1.69 (0.54–5.26)
PPO vs. HMO	0.93 (0.33–2.60)	0.87 (0.29–2.65)
Year of HCV diagnosis[2]		
2000 vs. 2006	0.00 (0.00–0.08)	0.00 (0.00–∞)
2001 vs. 2006	0.01 (0.00–0.16)	0.00 (0.00–∞)
2002 vs. 2006	0.02 (0.00–0.47)	0.00 (0.00–∞)
2003 vs. 2006	0.00 (0.00–∞)	0.00 (0.00–∞)
2004 vs. 2006	0.05 (0.00–0.94)	2.06 (0.00–∞)
2005 vs. 2006	0.22 (0.02–2.54)	∞ (0.00–∞)
Prior comorbid conditions		
Decompensated cirrhosis	3.87 (1.16–12.89)	13.88 (3.05–63.08)
Chronic obstructive pulmonary diseases (COPD)	0.92 (0.19–4.47)	1.33 (0.39–4.61)
Depression	1.06 (0.12–8.77)	0.75 (0.18–3.10)
HBV co-infection	6.53 (1.61–26.40)	--
HIV co-infection	0.00 (0.00–∞)	--
Prior medical services use		
Annual medical expenditure	5.31 (1.75–16.11)	5.18 (1.57–17.02)
Biopsy	2.25 (0.43–11.91)	2.93 (0.56–15.50)
Hospitalization	0.88 (0.27–2.90)	1.51 (0.43–5.32)
Emergency visits	0.81 (0.54–1.21)	0.93 (0.68–1.27)
Gastroenterology visits	1.01 (0.91–1.12)	1.00 (0.75–1.35)
Infectious disease visits	1.00 (0–∞)	0.85 (0.48–1.53)
Instrument related with symptomatic condition and treatment maintenance		
Time to treatment		
<6 vs. ≥6 months	2.19 (0.81–5.91)	2.46 (0.78–7.78)
Antidepressants use	1.21 (0.36–4.05)	1.81 (0.66–4.93)

1. Values shown in the tables are adjusted hazard ratios, HR (95% CI) associated with treatment initiation relevant covariates and important baseline characteristics included in the Cox regression models

Table 4-18. Total cost among patients with cirrhosis in base case and usual care analyses

	Patients n	Total costs per patient Mean ± (SD) dollar	Adjusted mean difference (se) [1]	P value
Base case cohort				
Control	1721	$25,092.91 (56,000.58)	0	
Treatment	991	$54,907.83 (62,656.31)	25,722(2365.28)	<.0001
Usual care				
Control	436	$42,714.59 (81,376.59)	0	
Treatment	256	$76341.62 (62,464.60)	32,953 (5642.31)	<.0001

1. The statistical relevant covariates on mean total cost difference are shown in Table 4-19.

Table 4-19. Factors associated with mean total cost difference between treatment and control among patients with cirrhosis in base case and usual care analyses

Variables[1]	Base case	Usual care
Social demographics		
Age at HCV diagnosis	58 (139.11) [0.68]	43 (345.37) [0.90]
Gender	231 (2257.23) [0.92]	2621 (5375.24) [0.63]
Census region[2]		
1 vs. 5	-42859 (4655.73) [<.0001]	-109370 (12538) [<.0001]
2 vs. 5	-51017 (6074.78) [<.0001]	-116435 (16092) [<.0001]
3 vs. 5	-51289 (5313.53) [<.0001]	-115558 (14627) [<.0001]
4 vs. 5	-49004 (6090.18) [<.0001]	-116623 (17145) [<.0001]
Insurance (Private vs. Public)	5659 (7778.04) [0.47]	-36391 (23827) [0.13]
Types of Health Plans		
POS vs. HMO	6486 (2863.74) [0.02]	-7315 (7069.79) [0.30]
PPO vs. HMO	47 (2532.88) [0.99]	-1612 (5666.40) [0.78]
Year of HCV diagnosis[3]		
1998 vs. 2007 (2006)	15421(10611) [0.15]	--
1999 vs. 2007 (2006)	-558 (12180) [0.96]	--
2000 vs. 2007 (2006)	38928 (7841.05) [<.0001]	20608 (14495) [0.16]
2001 vs. 2007 (2006)	39718 (7721.35) [<.0001]	32861 (13874) [0.02]
2002 vs. 2007 (2006)	28228 (7474.19) [<0.001]	30128 (13272) [0.02]
2003 vs. 2007 (2006)	31800 (7631.29) [<.0001]	27133 (13568) [0.05]
2004 vs. 2007 (2006)	24501 (7452.65) [0.001]	18479 (13220) [0.16]
2005 vs. 2007 (2006)	18267 (7056.34) [0.01]	2185 (12434) [0.86]
2006 vs. 2007	9949 (7181.14) [0.17]	--

Table 4-19. Continued

Variables[1]	Base case	Usual care
Prior comorbid conditions		
Severe decompensated cirrhosis	-2126 (4080.52) [0.60]	5430 (15051) [0.72]
Chronic obstructive pulmonary diseases (COPD)	-2072 (3196.42) [0.52]	-11565 (7874.15) [0.14]
Cerebral vascular disease (CVD)	20552 (5680.32) [<.0001]	51728 (14214) [<0.001]
Depression	-2336 (4471.02) [0.60]	2837 (10232.00) [0.78]
Diabetes	7025 (2968.87) [0.02]	9638 (7462.10) [0.20]
Drug dependence	-3483 (6311.27) [0.58]	86435 (19783) [<.0001]
HBV co-infection	-4560 (4540.02) [0.32]	5033 (11187) [0.65]
Heart diseases	11723 (3388.20) [<0.001]	19820 (7911.23) [0.01]
HIV co-infection	40509 (7386.52) [<.0001]	87912 (17353) [<.0001]
Obesity	-4031 (4489.65) [0.37]	-6306 (11674) [0.59]
Psychiatric disorders	-6670 (2923.69) [0.02]	-4452 (6882.19) [0.52]
Prior medical services use		
Biopsy	-1196 (3344.17) [0.72]	5030 (7702.84) [0.51]
Hospitalization	3469 (2717.14) [0.20]	2717 (7127.38) [0.70]
Outpatient visits	-179 (43.07) [<.0001]	-114 (108.08) [0.29]
Emergency room visits	510 (263.35) [0.05]	5796 (1460.05) [<.0001]
Family practice visits	624 (148.07) [<.0001]	118 (403.68) [0.77]
Gastroenterology visits	-17 (193.90) [0.93]	250 (520.36) [0.59]
Infectious disease visits	-176 (361.44) [0.63]	-1352 (899.60) [0.14]
Internal medicine visits	281 (117.59) [0.02]	-428 (280.02) [0.13]

Table 4-19 Continued

Variables[1]	Base case	Usual care
Instrument related with symptomatic condition and treatment maintenance		
Time to treatment initiation	8858 (2262.50) [<.0001]	13985 (5483) [0.01]
Antidepressants use	19784 (2898.35) [<.0001]	21558 (6272.09) [<.001]

1. Values shown in the tables are coefficients (mean (se), [p-value]) associated with all baseline characteristics into the multivariate adjusted regression models. 2. Reference group= 5 (National and Other in the dataset); =New England and Middle Atlantic; 2=East North Central and West North Central; 3=South Atlantic, East South Central, and West South Central; 4=Mountain and Pacific. 3. In usual care analysis, because no patient was diagnosed HCV in the year of 2007, the reference year was analyzed with 2006.

Table 4-20. Adjusted mean net benefit difference between treatment and control among cirrhotic patients in base case and usual care analyses

	Base case[1]			Usual care[2]		
WTP	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit
λ=0	-25254	-29815	-20692	-33052	-42635	-23469
λ=10K	2797	-2076	7669	-23451	-33132	-13771
λ=20K[3]	30847	24862	36831	-13850	-25782	-1918
λ=30K	58897	51346	66448	-4250	-19671	11172
λ=40K	86947	77600	96294	5351	-14145	24847
λ=50K	114997	103734	126260	14952	-8904	38809
λ=60K[4]	143047	129801	156294	24553	-3819	52925
λ=70K	171098	155826	186370	34154	1175	67133
λ=80K	199148	181823	216472	43755	6111	81399

1-2. The value of lower and upper limit indicate 95% CI limit were varied at selected WTP (λ) in the multivariate adjusted model. Both base case and usual care visual results in INB estimate for antiviral therapy are shown in Figure 4-2. 3. In base case analysis, the hypothetical assumption that treatment is cost-effective was found at WTP≥$15,000 in the multivariate adjusted regression model (mean net benefit difference= 11471, 95% CI=16822 to 22173, one-sided test with $p<0.001$). 4. In usual care analysis, the hypothetical assumption that treatment is cost-effective was found at WTP≥$60,000 in the multivariate adjusted regression model (mean net benefit difference=24553, 95% CI= -3819 to 52925, one-sided test with $p=0.04$)

Table 4-21. Covariates effects on the INB of antiviral therapy for patients with cirrhosis in base case analysis

Covariate	INB (λ=15,000) (se) [p value]	INB (λ=20,000) (se) [p value]	INB (λ=30,000) (se) [p value]
Constant term	-36469 (12438.11) [0.003]	-36460 (13946.66) [0.01]	-36440 (17622.49) [0.04]
Treatment	9204 (25610.39) [0.72]	14211 (28716.54) [0.62]	24225 (36285.17) [0.50]
Year of HCV diagnosis			
2002 vs. 2007	45944 (22364.45) [0.04]	65096 (25076.92) [0.01]	103400 (31686.29) [0.006]
2003 vs. 2007	36245 (22588.63) [0.11]	55034 (25328.29) [0.03]	92613 (32003.91) [0.004]
2004 vs. 2007	40262 (22296.52) [0.07]	57884 (25000.75) [0.02]	93128 (31590.04) [0.003]
2005 vs. 2007	31253 (21442.88) [0.15]	45360 (24043.58) [0.06]	73573 (30380.59) [0.02]
2006 vs. 2007	35264 (21706.19) [0.10]	47596 (24338.83) [0.05]	72259 (30753.66) [0.02]
Severe decompensated cirrhosis	-30947 (11959.51) [0.01]	-40045 (13410.02) [0.003]	-58240 (16944.41) [0.001]
Diabetes	-7888 (7450.70) [0.29]	-13237 (8354.36) [0.11]	-23934 (10556.27) [0.02]
HIV co-infection	-37300 (18270.06) [0.04]	-34539 (20485.94) [0.09]	-29019 (25885.29) [0.26]
Antidepressant use	-12951 (6967.70) [0.06]	-15809 (7812.78) [0.04]	-21527 (9871.95) [0.03]
R-squared (adjusted)	0.77	0. 83	0.88
Prob>F	<.0001	<.0001	<.0001

Note: The full model of covariate adjusted incremental net benefit estimate with treatment interactions in base case analysis is shown in the Appendix C.

Table 4-22. Covariates effects on the INB of antiviral therapy for patients with cirrhosis in usual care analysis

Covariate	INB (λ=60,000) (se) [p value]	INB (λ=70,000) (se) [p value]	INB (λ=80,000) (se) [p value]
Constant term	-259712 (80461.09) [<001]	-284491 (92924.82) [<0.01]	-309271 (105605.51) [<.01]
Treatment	203740 (138586.38) [0.14]	240612 (160053.94) [0.13]	277483 (181895.20) [0.12]
Year of HCV diagnosis			
2001 vs. 2006	-146771 (68895.53) [0.04]	-166747 (79567.72) [0.04]	-186723 (90425.68) [0.04]
2002 vs. 2006	-155104 (67504.53) [0.02]	-186277 (77961.24) [0.02]	-217450 (88599.98) [0.01]
HBV	130600 (79808.36) [0.10]	156443 (92170.98) [0.09]	182286 (104748.81) [0.08]
Emergency room visits	16448 (9118.66) [0.07]	18692 (10531.17) [0.08]	20936 (1968.28) [0.08]
R-squared (adjusted)	0.94	0. 94	0.94
Prob>F	<.0001	<.0001	<.0001

Note: The full model of covariate adjusted incremental net benefit estimate with treatment interactions in usual care analysis is shown in the Appendix D.

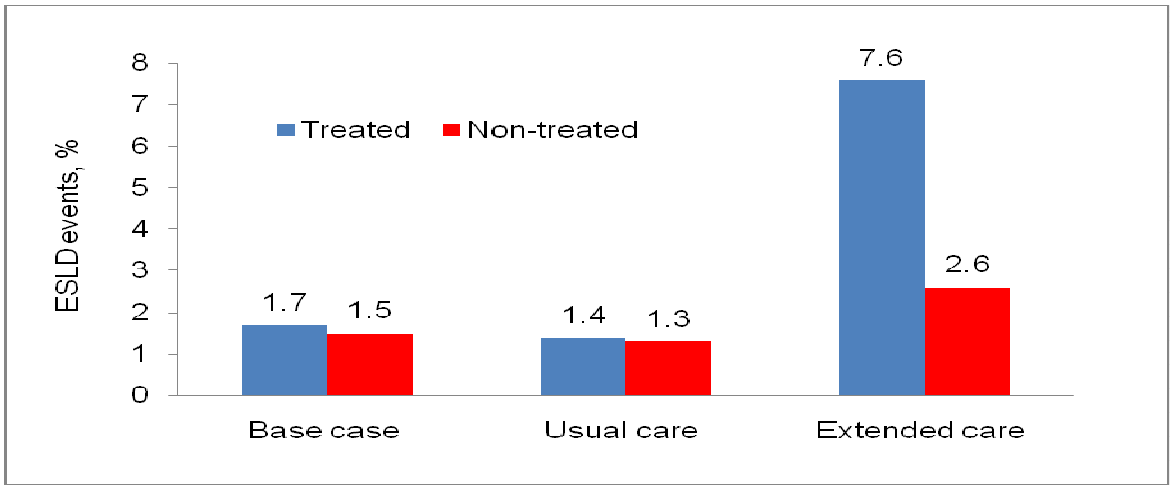

Figure 4-1. Cumulative ESLD events in the study follow-up.

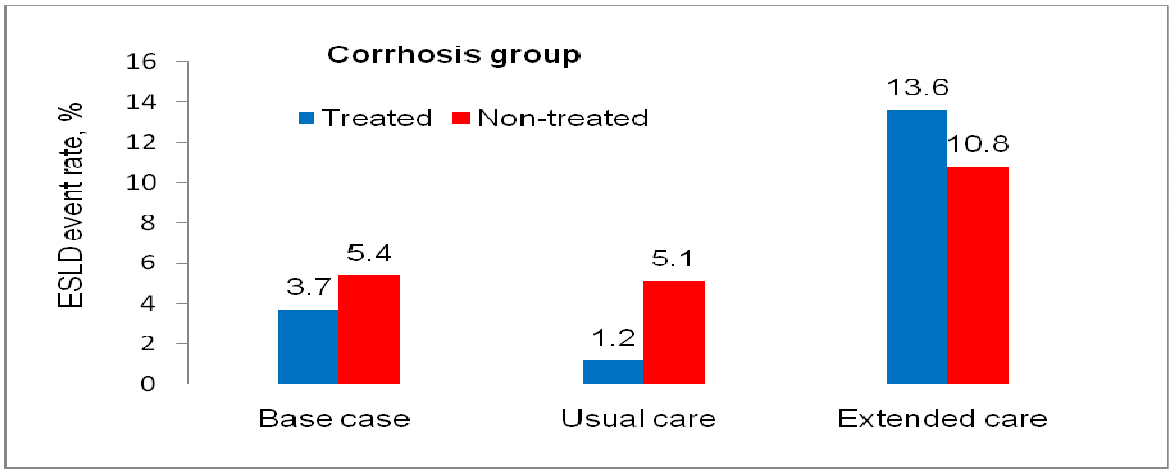

Figure 4-2. Cumulative ESLD events in the study follow-up (cirrhotic patients).

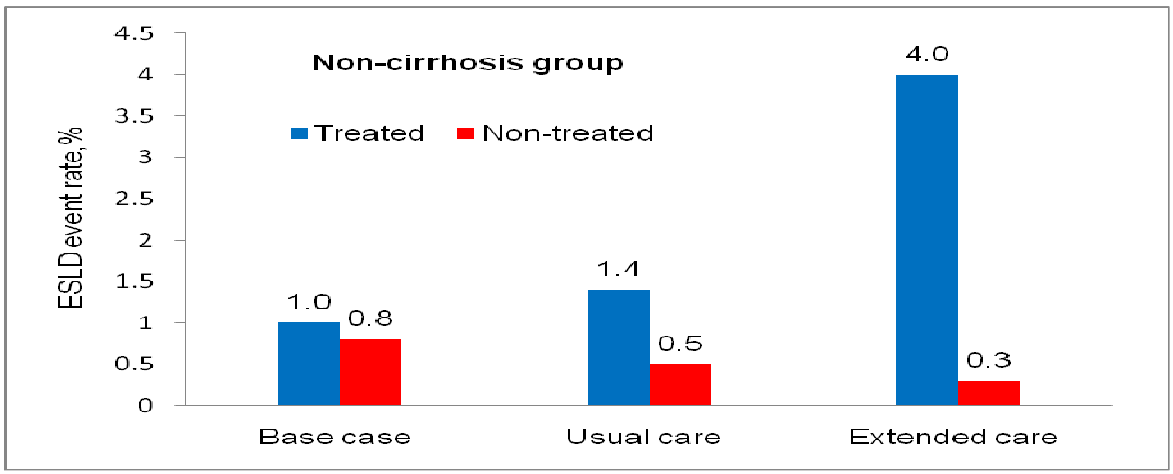

Figure 4-3. Cumulative ESLD events in the study follow-up (non-cirrhotic patients).

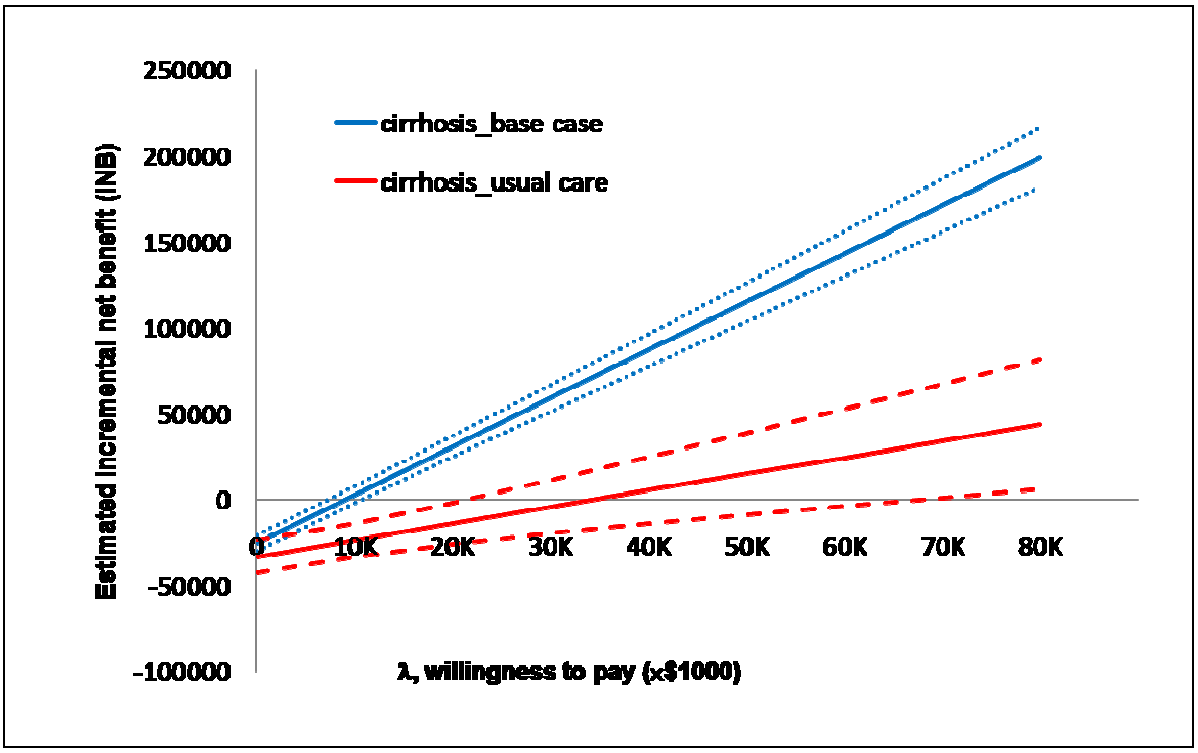

Figure 4-4. Plot of INB (95% CI) between treatment and control among patients with cirrhosis in base case and usual care analyses. The values are shown in Table 4-20. Among patients with cirrhosis in base case analysis, treatment is cost-effective was found at WTP≥$15,000 (δ= 11471, 95% CI=16822 to 22173, one-sided test with p<0.001). Among patients with cirrhosis in usual care analysis, treatment is cost-effective was found at WTP≥$60,000 (δ=24553, 95% CI= -3819 to 52925, one-sided test with p=0.04).

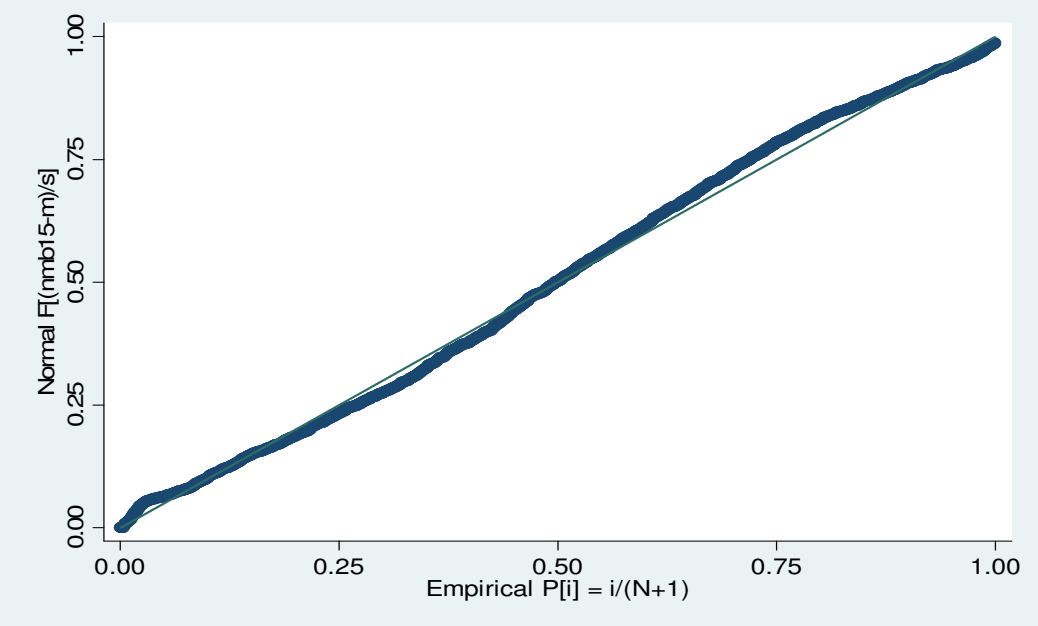

Figure 4-5. P-P plot of the net benefit (λ=$15,000) for cirrhotic patients in base case analysis.

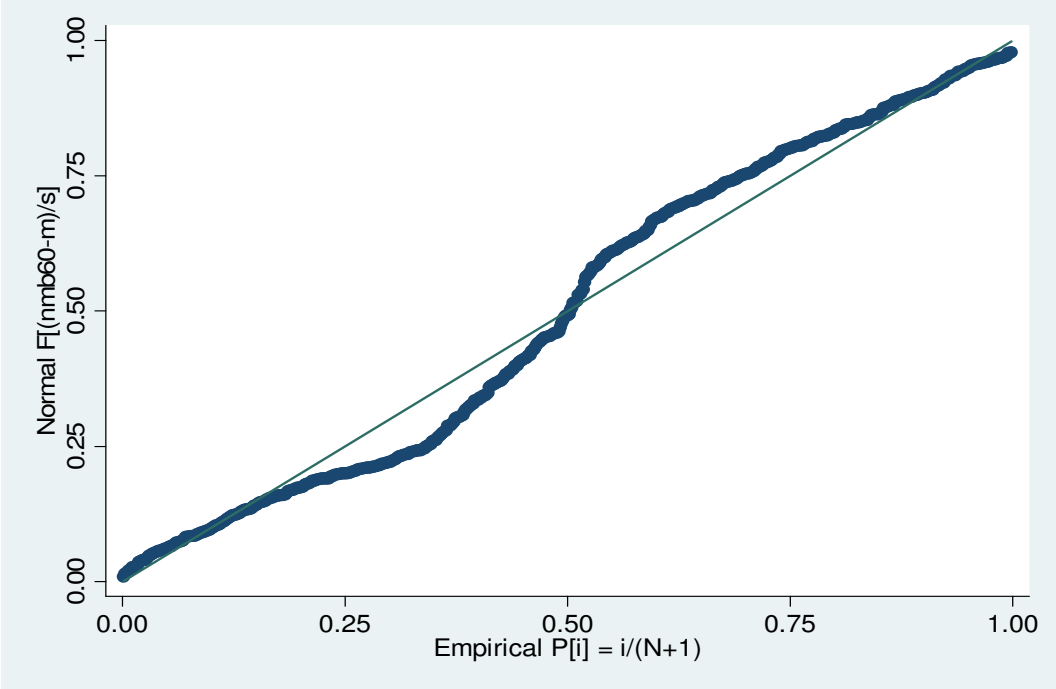

Figure 4-6. P-P plot of the net benefit (λ=$60,000) for cirrhotic patients in usual care analysis.

CHAPTER 5
DISCUSSION

Our study shows that, the INB estimate for the cost-effectiveness of initial combination antiviral therapy varies depending on the duration of antiviral therapy and the presence of cirrhosis among patients infected with HCV in the managed care setting. Patients with extended care of antiviral therapy suggest no evidence in prevention of ESLD progression between treatment and control without considering the presence of cirrhosis. Among patients without cirrhosis, KM estimate of treatment effect suggests the potential beneficial trend of initial combination therapy, although the evidence was lack of statistical power in patients with usual care. It further demonstrates that using the net benefit regression framework estimates the efficiency of antiviral therapy varies depending on the cirrhosis status and comorbid conditions. Lastly, this study provides empirical evidence on the efficiency of initial antiviral therapy in practice, which facilitate better understanding and implementation of HCV care in the managed care setting.

Effectiveness of Antiviral Therapy

Descriptions of Patients Characteristics

Descriptive analyses in the Table 4-1 and Table 4-4 of Chapter 4 present the extent of imbalance in patients' baseline characteristics between base case and subgroup analyses. First, risks associated with ESLD progression at baseline vary across patients involving in different sample groups. For examples, treated patients with extended care compared to all treated patients were more likely to be older and male patients, having compensated and decompensated cirrhosis at the time of antiviral therapy initiated. Consequently, the magnitude of pre-existing differences between treatment and control vary across three sampled groups. As shown in Table 4-3 and Table 4-5,

potential confounders with respect to baseline characteristics associated with the initiation of antiviral therapy vary in different analysis groups.

Second, the rationale of using sample groups for analysis based on the duration of treatment in this study was to estimate difference in treatment effects between patients who were non-responders or slow-responders with an extended care after a full course of antiviral therapy and those who have a SVR after a standard of care while controlling for potential confounders in the sample group. Thus, as usual care and extended care analyses were performed in this study will allow providing complementary evidence to the treatment effect obtained in the original base case analysis. The summary of effectiveness results in Table 4-10 and Table 4-16 display the trend for a beneficial treatment effect of antiviral therapy in base case analysis was consistent with usual care analysis. Additionally, as shown in Table 4- 8 and Table 4-14 there is no difference in treatment effect between treatment and control among patients with extended care.

Estimates of Treatment Effectiveness

Study results revealed that two metrics of treatment effectiveness measures agreed on a reduction in the risk of ESLD progression among cirrhotic patients in base case analysis and those with usual care (Table 4-10 and Table 4-16). However, among non-cirrhotic patients in usual care analysis, both estimates (average time to ESLD event in months and hazard ratio) had a same trend for a beneficial effect of antiviral therapy, despite the KM estimate in a time-dependent Cox regression model failed to achieve a statistically significant difference between treatment and control (coefficient=1.56, se=0.07, $p<.0001$ and hazard ratio=0.88, 95% CI=0.27-2.87, respectively).

Assuming correct model specification and no violation of assumptions necessary for the ordinary least squares (OLS) linear regression model and the Cox regression model, two estimates for treatment effect vary by their structural assumptions and applications. First, the

dependent variable is commonly to be a continuous variable in OLS regression model, while it is a binary variable in Cox regression. Cox regression is more likely to use at predicting the probability of a binary outcome incurring at any given time during the follow-up, and the time is measured as a "median" statistic in the model.[82] It is possible that the observed follow-up periods in the study samples are skewed and estimated magnitude of treatment effect distorts when the mean differs from the median estimate. Second, model specification for covariates included in the model may influence tests of significance for the treatment dummy variable. For example, age at HCV diagnosis was treated as time-dependent variable in Cox regression analyses, which may provide more robust estimation for its relationship with treatment effect than OLS does. Also, the number of ESLD event was small in the control group of patients without cirrhosis due to a relatively short follow-up to observe the development of advanced liver disease (average observation period, months =32.2/31.0 (treatment/control)), which leads to an insufficient power of statistical analysis in the Cox regression model.

It has remained unclear whether the extended antiviral therapy reduces the risk of ESLD. In the present study, we also found that of no difference in treatment effect between treat and untreated patients with extended care. Alternative low-dose peginterferon maintenance therapy (90 mcg/wk) combination with ribavirin has been investigated prospectively in the HALT-C trial for patients with advanced fibrosis who had failed initial therapy. [83] After a 3.5-year follow-up, there was no statistical difference in outcomes between the treatment group and the controls, indicating that their data do not support the use of maintenance therapy in treatment of non-responders. However, in recent data, Kaiser et al [84] showed that in a subgroup of patients with at least a one-log drop in HCV RNA levels, long-term low-dose maintenance therapy decreased fibrosis scores in non-responders with fibrosis and cirrhosis. Further

subgroup of patient analyses may identify patients who are more likely to respond to extended duration of therapy.

Incremental Net Benefit of Initial Combination Antiviral Therapy

Cirrhotic Patients

Examining treatment dummy coefficients in comparison to the control group coefficient reveals that the INB for cirrhotic patients in the base case analysis were more efficient than those patients with usual care. Although, all analyses were assumed by the assumptions of treatment discontinuation incurred by the lack of early virological response or treatment-related adverse effects for patients in the base case analysis. It is imperative to MCO decision makers in health plan design that enhancing patient identification, such as patients with developing cirrhosis or characteristics related to likelihood of rapid treatment response will allow for optimizing therapy to ensure that the intended goals of therapy are met.

For patients with developing cirrhosis, although they have a lower likelihood of virological response,[52, 85] the present study results support the cumulative evidences suggest that antiviral therapy can reduce the need of liver transplant, risk of cirrhosis decompensation and HCC development, even if it does not eradicate the hepatitis C virus.[58 86-89] Considering approximately 20% of study samples already had cirrhosis, further treatment goal will be focus on the health-related quality improvement, and the prolongation on HCC development and the need for liver transplants. As not all patients respond to antiviral therapy or necessarily develop progressive liver disease, using patient's infected HCV genotype and early virological response rate to guide duration of treatment have been shown to increase cost-effectiveness of combination antiviral therapy.[26, 81] Emerging recent clinical opinions on initial treatment for HCV-infected patients, patients with cirrhosis should be assessed for virological response at the

end of week 12 or 24 treatment depending on genotype (24 weeks for genotypes 1/4 and 12 weeks for genotypes 2/3) and treatment continued in those who are viral negative at the time. MCO decision makers should support the reassessment of virological response during treatment to reduce substantial drug costs and minimize adverse treatment effects, thereby improving efficiency of initial combination antiviral therapy.

Significance and effect of covariates. The differences on the costs, benefits and cost-effectiveness of treatment intervention varied widely across the range of different levels of patient's co-morbid conditions between base case and usual care were noteworthy. Among cirrhotic patients received approximately 7.5 months of antiviral therapy, cirrhosis status and comorbid conditions have more impact on the marginal cost-effectiveness compared with patients receiving 12 months of antiviral therapy under the statistical significance in Table 4-21 and Table 4-22.

Although treatment of patients with decompensated cirrhosis (e.g., variceal bleeding and hepatic coma) is feasible,[90] the observed decreased benefits or total cost increase is noteworthy in the present study. Theoretically, patients with cirrhosis decompensation are candidates on the waiting list of liver transplant. Treatment of patients with advanced liver cirrhosis waiting for liver transplant is costly and the likelihood of preventing recurrence is not clear.[91] [92, 93] Optimum timing of treatment initiation for patients at different stage of disease severity for the prevention of HCC, liver transplant and death must be studied further.

Diabetes is not just a risk factor of developing HCC in chronic hepatitis C patients.[61] Recent studies suggest that increasing level of insulin resistance are associated with impaired initial virological response and SVR.[94, 95] The results of less cost-effectiveness in the presence of diabetes compared to non-diabetic patients with cirrhosis, was mainly associated with less

effectiveness in base case analysis. The prevalence of diabetes and impaired fasting glucose is high; thus, further interventions aimed at reducing insulin resistance in chronic hepatitis C through a multidisciplinary approach are warranted, including the administration of hypoglycemic agents and lifestyle changes should probably be included in the clinical management of patients with chronic hepatitis C and insulin resistance, although the potential beneficial effects on liver fibrosis progression and response to therapy remain to be assessed.

Patients co-infected with HIV/HCV infection are difficult-to-treat. Although HIV co-infected patients, in particular, when CD4 count appears less than 200cells/mm^2 might accelerate HCV-related disease progression,[18] treatment efficacy of pegylated interferon combination with ribavirin in recent randomized, controlled trial showed 40% of SVR in patients with HCV/HIV co-infection [57, 59] and it was cost-effective in terms of increase in life-expectancy.[96, 97] We assumed that combination antiviral therapy was more likely to be prescribed to those who with well control HIV co-infected patients, as HIV-infected patients with low CD4 cell count would suffer a higher risk of opportunistic infection and worsen quality of life in practice. The results of base case analysis showed that treatment of cirrhotic patients with HCV/HIV co-infection was effective; while the cost of treatment was substantial and outweigh the benefits was seen among patients co-infected with HCV/HIV, even though its effect on the marginal cost-effectiveness was not consistent across any value of WTP. The results are limited with sufficient data to characterize the stage and severity of HIV infection.

Year of HCV diagnosis was another important factor associated with the cost-effectiveness of treatment in the group of cirrhotic patients with usual care. In Table 4-22, the results of marginal cost-effectiveness in patients diagnosed with HCV in the year of 2001 and 2002 was less efficient than those who were diagnosed with HCV in year of 2006. The

difference in cost and primary effectiveness measure in the year of 2001 and 2002 could be related with varied patterns of initial combination therapy in HCV-infected patients across the MCO health care system. It is also possible that pegylated interferons combination with ribavirin was approved and recommended as a standard of treatment from 2000 to 2002; consequently, the number of patients newly diagnosed with HCV around the period increased and patients were likely to introduce with this relatively expensive combination regiments.

Non-Cirrhotic Patients

Decision to treat or not with combination antiviral therapy should take several important factors into consideration, including histological findings, symptoms, patient's co-morbid conditions, age, and motivation. Management of patients with mild histological fibrosis remains controversial because not all patients with HCV infection progress to cirrhosis and some may delay initiation of treatment to avoid its potential side effects. [55] The cost-effectiveness of treating patients with no cirrhosis or mild fibrosis has been questioned, since the prognosis even without therapy is excellent, further underscoring the importance of accurately staging the severity of liver disease.[29, 98] On the other hand, with delayed treatment, HCV-infected patients become older, develop risk for cirrhosis progression, impaired quality of life, and comprise cost-effectiveness of treatment intervention. For patients with no or only mild fibrosis, in those whose treatment is deferred, liver biopsy can be used to monitor liver disease progression. The immediate treatment initiation for a group of patients with only mild cirrhosis has been suggested to be cost effective compared to a watchful waiting strategy with liver biopsy every 3 years and combination therapy in patients found to have cirrhosis on liver biopsy.[27]

After weighting the risks, benefits and costs of existing HCV treatment, periodical liver biopsy and biochemical markers monitoring could be used to guide recommendation for treatment with optimal timing. However, considering the bias of liver biopsy performance, [99]

patient's perceptions on the severity of disease manifestation [100], a efficient regular monitoring strategy involving a good referral mechanism to the gastroenterology specialty could be costly and lack of an appropriate screening rate in the MCO setting .

In the present study, combination therapy was also favor for a group of asymptomatic patients in base case analysis. It implicitly suggests that treatment might be cost-effective when the discontinuation of therapy was associated with lack of virological response after 7 months therapy. From the MCO perspective, it further highlights the value of confirmatory tests for early virological response at end of 24 weeks therapy (genotype 1/4 infection); thereby increases marginal cost-effectiveness of antiviral therapy. The comparisons of INB between patients with and without cirrhosis in base case cohort shown in Figure 5-1. From the perspective of the society, further research for asymptomatic HCV-infected patients is required on the cost-effectiveness of combination therapy compared to a periodical watchful waiting strategy; in particular the intervention's long-term impact on HRQoL and health service costs requires further evaluation.

Limitations

Our study has several noteworthy limitations. As previously discussed, the primary limitation and threat to the internal validity of this study was the possible presence of selection bias in treatment. In this study, the concern is whether patients who received combination antiviral therapy were at a greater risk of ESLD compared to those in the control group. Although benefit, costs, and cost-effectiveness of treatment intervention were stratified analyzed with an adjustment for those baseline characteristics relevant to treatment initiation and several created instruments, the treatment and control groups may not have equal unmeasured confounding, and that selection bias may present in the stratified level. It has been suggested that a low baseline serum viral load is associated with a significantly higher probability of achieving

SVR following initial combination therapy. For example, treatment effect in cirrhotic individuals with a higher baseline serum viral load (>800,000 IU/mL) appeared less effective than in non-cirrhotic patients with a low baseline serum viral load. [85] The amount of bias in effectiveness measure between patients with and without cirrhosis was not clear due to the unmeasured confounding.

A limitation includes a disadvantage of the IHCIS dataset. The information related with prescription dosage and duration of prescription provided was not reliable in the dataset. Although the operational definitions of continuous refilling were employed to categorize patients with usual or extended care in subgroup cohort, it would loss information in a group of treated patients who reduce doses of prescription due to treatment-related side effects. This un-measured confounder is a strong predictor of achieving SVR, which may affect the precision of provided results. If patients receiving extended care were more likely to decrease doses of either interferon alpha or ribavirin because of side effects, then that observed treatment variability in extended care analyses would lead to a smaller extent of difference in treatment effect. No laboratory and histological evidence is available to confirm treatment outcome and HCV-related cirrhosis progression.

Study results obtained in the MCO population may not be generalizable to HCV-infected patients in different health care systems. Specifically, patients with fewer barriers to access to HCV care than patients with public health insurance may have better medication adherence to achieve a successful treatment outcome. Also more than half the study sample resided in the Northeast and Middle Atlantic regions, and the patterns of antiviral therapy use in this study population may differ from HCV-infected persons outside the UnitedHealth managed care program. However, this MCO program with more than 80 million members alive represents a

large and important high risk population that has not been well evaluated for HCV care and therefore warrants comprehensive investigation.

Future Research

Managed care organizations are sharing a large proportion of economic burden related with HCV infection.[14] MCOs appear to have more incentives than fee-for-service environment to slow the growth of health care expenditures. Applications of the net benefit regression framework in this study presented the valuable information about current initial antiviral therapy efficiency among newly-diagnosed, HCV-infected patients to decision makers involved in the MCO program. It demonstrates the statistical merits to decide whether antiviral therapy is cost-effective based on the predicated value (i.e., INB) in the linear regression model. Although this study was not able to answer with which patient outcome that policymakers would adopt what value of willingness to pay for treatment cost, future research will have to extend the investigation, such as a cost-benefit analysis. Analysis of WTP by HCV-infected patients for initial therapy, or the optimal timing of treatment initiation by progressive disease stages, will allow valuing all aspects of outcome improvement by antiviral therapy

Another important area of research is the application of the net benefit regression framework using observational data. In order to account for the incomplete data (censoring) issue in effectiveness and costs measure, a method of inverse probability censoring weighting (ICPW) was employed in this study to adjust for potential bias introduced by censoring patients who dropout in the study follow up. One of limitation of using ICPW in the linear regression models for both measures of cost and effectiveness was assumed the pattern of censoring has to be random. With respect to the primary effectiveness estimate in this study, survival time data are often right skewed with a small proportion of patients surviving much longer than the rest of patients. Although the reported median survival time is commonly in the KM estimate of

survival function, some consider it is not an efficient estimator of the expected survival time. For instance, median survival time is estimated as a single point in time on the survival curves, and it does not take the exact magnitude of most observations into account. Furthermore, median survival time is difficult to give a meaningful interpretation.[101] There are several approaches have been discussed in the literature, including restricted mean method[101] and ICPW[75, 102] have been investigated using randomized controlled trial data. Likewise, costs data are concerned with censoring and a highly right-skewed distribution in a small proportion of patients. The comparisons of advantages and disadvantages among different approaches have not been performed and well discussed in both survival time and cost estimation. Further research focus on ways to overcome incomplete data and methodological limitations in real-world observation data and comparisons of patterns of censorings in expected survival time and costs would increase the utility of the net benefit regression framework for maximizing value of heath resources.

Summary and Conclusions

Estimating the cost-effectiveness of treatment interventions using real-world data is challenging. The present study shows that the net benefit estimation of initial combination antiviral therapy within a regression framework is dependent on the richness of available patient-level data. This study is the first empirical investigation of HCV treatment to apply inverse probability of censoring weights to censored effectiveness data. The results support that initial combination antiviral therapy during compensated cirrhosis is cost-effective. The results of total cost estimation during the follow-up revealed the mean difference in total costs between the treatment and control group was higher for patients with cirrhosis in usual care analysis than those patients in base case analysis. A limitation is that median Kaplan-Meier estimate for the risk of end stage liver disease progression suffered from the lack of sufficient statistical power to

demonstrate beneficial effect of treatment among non-cirrhotic patients with usual care. Moreover, the presence of potential selection bias cannot be ignored.

Initial combination antiviral therapy during compensated cirrhosis is cost-effective compared with no therapy at a minimum willingness to pay threshold of $15,000 for patients receiving an average of approximately 7.5 months therapy, and has a minimum willingness to pay threshold of $60,000 for patients with an average of 12 months therapy. Treatment initiation for non-cirrhotic patients is also cost-effective at a minimum willingness to pay threshold of $15,000, and yielded greater net benefit only when therapy discontinued in those who are viral positive after approximately 7.5 months treatment. Additional work is needed to better understand whether these thresholds would be considered cost-effective from the MCO perspective. Future examinations of the best cost-effectiveness strategy for initial combination antiviral therapy should consider duration of therapy, early virological response, and genotype into account.

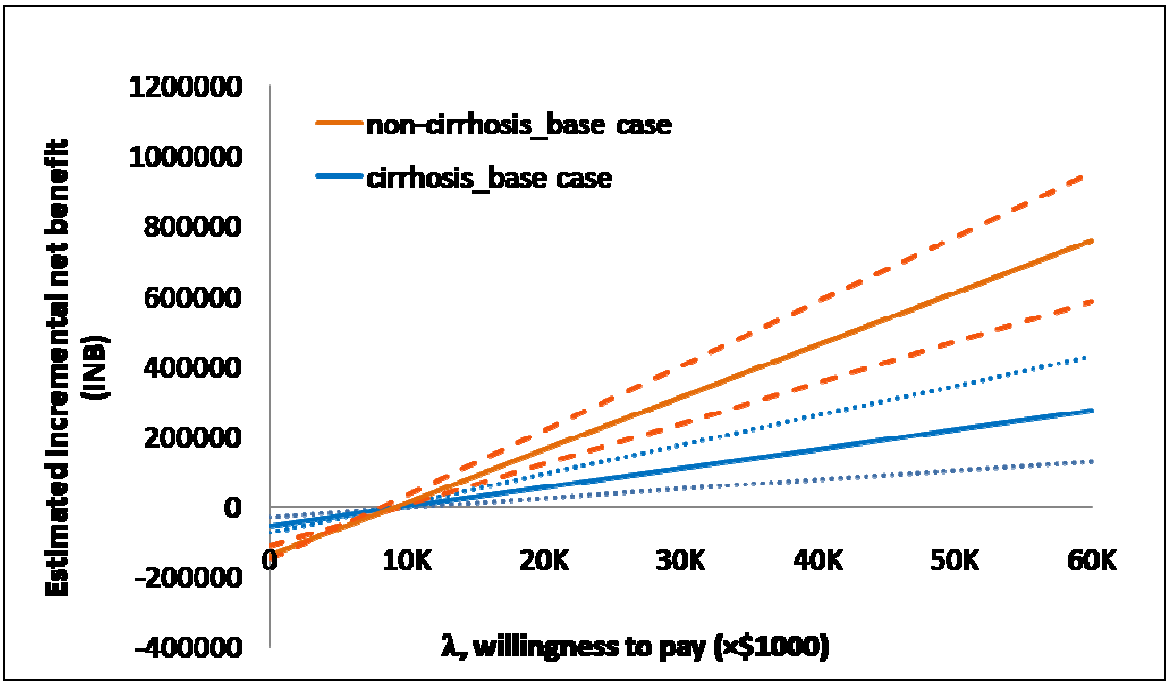

Figure 5-1. Plot of INB (95% CI) between treatment and control among patients with and without cirrhosis in base case analyses. Patients with cirrhosis, treatment is cost-effective was found at WTP≥$15,000 (δ= 11471, 95% CI=16822 to 22173, one-sided test with p<0.001). For patients without cirrhosis, treatment is cost-effective was found at the same threshold as cirrhotic patients (WTP≥$15,000, δ= 24815, 95% CI=11601 to 38030, one-sided test with p<0.001).

APPENDIX A
NET BENEFIT OF INITIAL COMBINATION ANTIVIRAL THERAPY IN BASE CASE ANALYSIS

Patients with Cirrhosis

Abbreviations for variables in multivariate net benefit regression models are: tx (treatment indicator), age_HCV (age at the year of HCV diagnosis), plan1 (health plan: POS), plan2 (health plan: PPO), plan3 (health plan: HMO), geo1 (census region: New England and Middle Atlantic), geo2 (census region: East North Central and West North Central), geo3 (census region: South Atlantic, East South Central, and Mountain and Pacific), geo4 (census region: West South Central), geo5 (census region: National and Other in the dataset), yr_hcv0=1998, yr_hcv1=1999, yr_hcv2=2000, yr_hcv3=2001, yr_hcv4=2002, yr_hcv5=2003, yr_hcv6=2004, yr_hcv7=2005, yr_hcv8=2006, yr_hcv9=2007, DC2 (severe decompensated cirrhosis), CC (compensated cirrhosis), Ddpend (Drug Dependence), dpress_late (depression after HCV diagnosis), DM (diabetes), HBV (Hepatitis B virus infection), HIV (Human Immunodeficiency Virus), anncost_b4 (prior annual medical expenditure),Hx_b4 (prior hospitalization history), FG_cnt (family practice physician visits), GS_cnt (gastroenterologist visits), Intern_cnt (internal medicine physician visits). out_cnt (outpatient/physician visits), InMed_cnt (internal medicine physician visits), TT_lab (time to treatment initiation), anti_dpress (antidepressants use).

Table A-1. WTP=$15,000 [Regression with robust standard errors]

Linear regression	Number of obs	=	2712
	F(34, 2677)	=	331.16
	Prob > F	=	0
	R-squared	=	0.767
	Root MSE	=	64773

Table A-1. Continued

nmb15	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf. Interval]	
tx	16821.7	2728.957	6.16	0.000	11470.63	22172.78
gender	-20220.2	2722.791	-7.43	0.000	-25559.2	-14881.2
plan2	8761.94	2840.408	3.08	0.002	3192.324	14331.56
plan3	9414.779	4060.917	2.32	0.021	1451.928	17377.63
geo1	109218.5	11020.52	9.91	0.000	87608.96	130828.1
geo2	55715.18	11932.39	4.67	0.000	32317.55	79112.81
geo3	48726.8	11614.74	4.2	0.000	25952.02	71501.58
geo4	29257.76	11579.62	2.53	0.012	6551.855	51963.67
yr_hcv0	121568.5	10771.16	11.29	0.000	100447.9	142689.2
yr_hcv1	26197.69	11353.87	2.31	0.021	3934.451	48460.92
yr_hcv2	314579.6	9836.25	31.98	0.000	295292.1	333867
yr_hcv3	291805.4	8700.85	33.54	0.000	274744.3	308866.4
yr_hcv4	245859.2	8216.327	29.92	0.000	229748.2	261970.2
yr_hcv5	233697.3	8191.592	28.53	0.000	217634.8	249759.8
yr_hcv6	171584.9	7899.448	21.72	0.000	156095.2	187074.5
yr_hcv7	131007.3	7330.31	17.87	0.000	116633.7	145381
yr_hcv8	54667.04	7580.78	7.21	0.000	39802.27	69531.82
dc2_b4	-105626	5466.337	-19.32	0.000	-116345	-94907.2
cvd_b4	-8032.27	11445.24	-0.7	0.483	-30474.7	14410.14
dm_b4	-44598.8	3884.881	-11.48	0.000	-52216.5	-36981.1
dpress_late	-18514.3	7308.986	-2.53	0.011	-32846.1	-4182.45
hbv_b4	-25504	4229.048	-6.03	0.000	-33796.5	-17211.5
hiv_b4	-22908.5	15020.64	-1.53	0.127	-52361.7	6544.732
heart_b4	-13590.3	5391.578	-2.52	0.012	-24162.3	-3018.19
psych_b4	4096.716	3715.612	1.1	0.270	-3189.04	11382.48
anncost_b4	-21234.6	2993.917	-7.09	0.000	-27105.2	-15364
biopsy_b4	34476.32	3208.884	10.74	0.000	28184.17	40768.46
hx_b4	-27465.5	3731.875	-7.36	0.000	-34783.1	-20147.8
out_cnt	257.1462	62.32477	4.13	0.000	134.9366	379.3557
fg_cnt	-437.296	231.9167	-1.89	0.059	-892.05	17.45824
gs_cnt	-814.7	350.2614	-2.33	0.020	-1501.51	-127.889
intern_cnt	-1017.16	209.5522	-4.85	0.000	-1428.06	-606.257
tt_lab	32037.25	2628.9	12.19	0.000	26882.37	37192.13
anti_dpress	-8111.76	3978.39	-2.04	0.042	-15912.8	-310.734
_cons	-33116.6	13725.67	-2.41	0.016	-60030.6	-6202.59

Table A-2. WTP=$20,000 [Regression with robust standard errors]

Linear regression	Number of obs	=	2712
	F(34, 2677)	=	455.28
	Prob > F	=	0
	R-squared	=	0.8284
	Root MSE	=	72627

Table A-2. Continued

nmb20	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
tx	30846.78	3051.888	10.11	0.000	24862.49	36831.08
gender	-26709.1	3036.589	-8.8	0.000	-32663.4	-20754.8
plan2	11961.62	3230.367	3.7	0.000	5627.352	18295.89
plan3	14846.63	4441.379	3.34	0.001	6137.747	23555.51
geo1	131806.7	11633.42	11.33	0.000	108995.3	154618.1
geo2	57326.92	12660.64	4.53	0.000	32501.29	82152.54
geo3	48068.33	12263.61	3.92	0.000	24021.22	72115.44
geo4	22732.16	12295.96	1.85	0.065	-1378.37	46842.7
yr_hcv0	166468.3	13230.87	12.58	0.000	140524.5	192412
yr_hcv1	34219.98	14372.88	2.38	0.017	6036.909	62403.05
yr_hcv2	431578.3	12152.21	35.51	0.000	407749.6	455407
yr_hcv3	401601.3	10944.66	36.69	0.000	380140.4	423062.1
yr_hcv4	336498.7	10455.03	32.19	0.000	315997.9	356999.4
yr_hcv5	321516.6	10416.86	30.87	0.000	301090.7	341942.5
yr_hcv6	236227.6	10090.25	23.41	0.000	216442.2	256013.1
yr_hcv7	180173.2	9546.064	18.87	0.000	161454.8	198891.6
yr_hcv8	75859.32	9730.541	7.8	0.000	56779.19	94939.46
dc2_b4	-141674	6585.536	-21.51	0.000	-154588	-128761
cvd_b4	-3903.61	12001.02	-0.33	0.745	-27435.8	19628.59
dm_b4	-57360.8	4313.362	-13.3	0.000	-65818.7	-48903
dpress_late	-25481.6	7966.455	-3.2	0.001	-41102.7	-9860.61
hbv_b4	-35590.6	5027.923	-7.08	0.000	-45449.6	-25731.6
hiv_b4	-17915	15688.11	-1.14	0.254	-48677	12847.03
heart_b4	-14339.3	5769.076	-2.49	0.013	-25651.5	-3026.95
psych_b4	2997.224	4177.419	0.72	0.473	-5194.07	11188.52
anncost_b4	-25552.7	3368.349	-7.59	0.000	-32157.5	-18947.9
biopsy_b4	45488.52	3757.836	12.1	0.000	38119.96	52857.07
hx_b4	-36729.6	4187.679	-8.77	0.000	-44941	-28518.2
out_cnt	275.7892	71.04098	3.88	0.000	136.4884	415.0899
fg_cnt	-381.161	253.6577	-1.5	0.133	-878.546	116.2237
gs_cnt	-1079.29	424.6812	-2.54	0.011	-1912.03	-246.558

Table A-2. Continued

nmb20	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
intern_cnt	-1265.4	228.7712	-5.53	0.000	-1713.99	-816.817
tt_lab	45444	2913.952	15.6	0.000	39730.18	51157.83
anti_dpress	-4354.88	4266.119	-1.02	0.307	-12720.1	4010.347
_cons	-33864.4	15477.69	-2.19	0.029	-64213.8	-3514.94

Table A-3.WTP=$30,000 [Regression with robust standard errors]

Linear regression	Number of obs	=	2712
	F(34, 2677)	=	638.61
	Prob > F	=	0
	R-squared	=	0.8763
	Root MSE	=	91785

Table A-3. Continued

nmb30	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
tx	58896.94	3850.989	15.29	0.000	51345.73	66448.16
gender	-39686.9	3813.648	-10.41	0.000	-47164.9	-32208.9
plan2	18360.97	4166.253	4.41	0.000	10191.57	26530.38
plan3	25710.32	5395.001	4.77	0.000	15131.53	36289.11
geo1	176983	13247.61	13.36	0.000	151006.4	202959.6
geo2	60550.39	14553.78	4.16	0.000	32012.6	89088.18
geo3	46751.4	13961.19	3.35	0.001	19375.6	74127.2
geo4	9680.964	14152.33	0.68	0.494	-18069.6	37431.56
yr_hcv0	256267.7	18503.08	13.85	0.000	219986	292549.5
yr_hcv1	50264.56	20632.84	2.44	0.015	9806.647	90722.46
yr_hcv2	665575.8	17194.47	38.71	0.000	631860	699291.5
yr_hcv3	621193	15743.06	39.46	0.000	590323.2	652062.8
yr_hcv4	517777.6	15178.11	34.11	0.000	488015.6	547539.6
yr_hcv5	497155.2	15113.4	32.89	0.000	467520	526790.3
yr_hcv6	365513.2	14696.11	24.87	0.000	336696.4	394330.1
yr_hcv7	278504.8	14129.13	19.71	0.000	250799.7	306210
yr_hcv8	118243.9	14239	8.3	0.000	90323.34	146164.4
dc2_b4	-213771	9099.484	-23.49	0.000	-231614	-195929
cvd_b4	4353.729	13468.07	0.32	0.747	-22055.1	30762.6
dm_b4	-82884.9	5375.667	-15.42	0.000	-93425.8	-72344
dpress_late	-39416.4	9669.947	-4.08	0.000	-58377.7	-20455
hbv_b4	-55763.8	6871.283	-8.12	0.000	-69237.3	-42290.2
hiv_b4	-7928.02	17489.89	-0.45	0.650	-42223.1	26367.05

Table A-3. Continued

nmb30	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
heart_b4	-15837.2	6760.871	-2.34	0.019	-29094.3	-2580.16
psych_b4	798.2403	5285.823	0.15	0.880	-9566.47	11162.95
anncost_b4	-34188.9	4286.413	-7.98	0.000	-42593.9	-25783.9
biopsy_b4	67512.92	5042.604	13.39	0.000	57625.13	77400.71
hx_b4	-55257.8	5307.81	-10.41	0.000	-65665.6	-44850
out_cnt	313.0752	92.60896	3.38	0.001	131.4829	494.6676
fg_cnt	-268.892	307.1223	-0.88	0.381	-871.113	333.3289
gs_cnt	-1608.48	592.9698	-2.71	0.007	-2771.21	-445.758
intern_cnt	-1761.9	277.0762	-6.36	0.000	-2305.2	-1218.59
tt_lab	72257.5	3619.644	19.96	0.000	65159.92	79355.08
anti_dpress	3158.897	5024.785	0.63	0.530	-6693.96	13011.75
_cons	-35360	19685.67	-1.8	0.073	-73960.6	3240.659

Table A-4.WTP=$40,000 [Regression with robust standard errors]

Linear regression	Number of obs	=	2712
	F(34, 2677)	=	752.91
	Prob > F	=	0
	R-squared	=	0.8938
	Root MSE	=	1.10E+05

Table A-4. Continued

nmb40	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
tx	86947.1	4766.846	18.24	0.000	77600.03	96294.18
gender	-52664.7	4705.84	-11.19	0.000	-61892.1	-43437.2
plan2	24760.33	5215.073	4.75	0.000	14534.35	34986.31
plan3	36574.02	6508.996	5.62	0.000	23810.85	49337.18
geo1	222159.3	15237.66	14.58	0.000	192280.5	252038.1
geo2	63773.87	16860.24	3.78	0.000	30713.45	96834.28
geo3	45434.46	16046.01	2.83	0.005	13970.65	76898.28
geo4	-3370.24	16408.61	-0.21	0.837	-35545.1	28804.59
yr_hcv0	346067.2	23985.72	14.43	0.000	299034.8	393099.6
yr_hcv1	66309.13	27016.83	2.45	0.014	13333.17	119285.1
yr_hcv2	899573.2	22474.96	40.03	0.000	855503.2	943643.3
yr_hcv3	840784.8	20714.68	40.59	0.000	800166.4	881403.2
yr_hcv4	699056.6	20034.95	34.89	0.000	659771	738342.1
yr_hcv5	672793.8	19944.11	33.73	0.000	633686.3	711901.2

Table A-4. Continued

nmb40	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
yr_hcv6	494798.8	19423.08	25.47	0.000	456713.1	532884.6
yr_hcv7	376836.5	18790.79	20.05	0.000	339990.6	413682.4
yr_hcv8	160628.4	18859	8.52	0.000	123648.8	197608.1
dc2_b4	-285868	11782.95	-24.26	0.000	-308973	-262764
cvd_b4	12611.07	15291.3	0.82	0.410	-17372.9	42595.02
dm_b4	-108409	6598.992	-16.43	0.000	-121349	-95469.3
dpress_late	-53351.1	11697.33	-4.56	0.000	-76287.8	-30414.4
hbv_b4	-75936.9	8869.874	-8.56	0.000	-93329.4	-58544.4
hiv_b4	2058.962	19766.73	0.1	0.917	-36700.6	40818.56
heart_b4	-17335.2	7966.87	-2.18	0.030	-32957	-1713.34
psych_b4	-1400.74	6534.09	-0.21	0.830	-14213.1	11411.63
anncost_b4	-42825.1	5330.885	-8.03	0.000	-53278.2	-32372.1
biopsy_b4	89537.32	6450.685	13.88	0.000	76888.49	102186.2
hx_b4	-73786	6585.177	-11.2	0.000	-86698.5	-60873.4
out_cnt	350.3613	117.0995	2.99	0.003	120.7466	579.976
fg_cnt	-156.623	368.9582	-0.42	0.671	-880.095	566.8492
gs_cnt	-2137.67	772.9349	-2.77	0.006	-3653.28	-622.062
intern_cnt	-2258.39	333.6491	-6.77	0.000	-2912.62	-1604.15
tt_lab	99071	4432.473	22.35	0.000	90379.58	107762.4
anti_dpress	10672.67	5947.234	1.79	0.073	-988.967	22334.31
_cons	-36855.6	24420.09	-1.51	0.131	-84739.8	11028.55

Table A-5.WTP=$50,000 [Regression with robust standard errors]

Linear	regression	Number of obs	=	2712
		F(34, 2677)	=	824.66
		Prob > F	=	0
		R-squared	=	0.9019
		Root MSE	=	1.40E+05

Table A-5. Continued

nmb50	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
tx	114997.3	5743.88	20.02	0.000	103734.4	126260.2
gender	-65642.5	5658.968	-11.6	0.000	-76738.8	-54546.1
plan2	31159.69	6320.856	4.93	0.000	18765.43	43553.94
plan3	47437.71	7714.195	6.15	0.000	32311.33	62564.09
geo1	267335.6	17475.63	15.3	0.000	233068.5	301602.7
geo2	66997.34	19433.41	3.45	0.001	28891.32	105103.4

Table A-5. Continued

nmb50	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf. Interval]	
geo3	44117.53	18386.81	2.4	0.016	8063.741	80171.31
geo4	-16421.4	18922.27	-0.87	0.386	-53525.2	20682.31
yr_hcv0	435866.7	29561.93	14.74	0.000	377900.2	493833.2
yr_hcv1	82353.71	33453.92	2.46	0.014	16755.58	147951.8
yr_hcv2	1133571	27858.54	40.69	0.000	1078944	1188197
yr_hcv3	1060377	25759.43	41.16	0.000	1009866	1110887
yr_hcv4	880335.5	24947.55	35.29	0.000	831417.1	929253.9
yr_hcv5	848432.3	24830.81	34.17	0.000	799742.8	897121.8
yr_hcv6	624084.4	24200.29	25.79	0.000	576631.2	671537.5
yr_hcv7	475168.2	23484.28	20.23	0.000	429119	521217.3
yr_hcv8	203013	23524.91	8.63	0.000	156884.2	249141.8
dc2_b4	-357965	14542.39	-24.62	0.000	-386481	-329450
cvd_b4	20868.4	17358.84	1.2	0.229	-13169.7	54906.5
dm_b4	-133933	7908.969	-16.93	0.000	-149441	-118425
dpress_late	-67285.8	13907.68	-4.84	0.000	-94556.7	-40014.9
hbv_b4	-96110.1	10938.94	-8.79	0.000	-117560	-74660.5
hiv_b4	12045.95	22374.04	0.54	0.590	-31826.2	55918.1
heart_b4	-18833.2	9304.149	-2.02	0.043	-37077.2	-589.107
psych_b4	-3599.73	7855.828	-0.46	0.647	-19003.8	11804.38
anncost_b4	-51461.4	6440.556	-7.99	0.000	-64090.3	-38832.4
biopsy_b4	111561.7	7916.552	14.09	0.000	96038.55	127084.9
hx_b4	-92314.2	7944.294	-11.62	0.000	-107892	-76736.6
out_cnt	387.6474	143.0191	2.71	0.007	107.2083	668.0864
fg_cnt	-44.3535	435.615	-0.1	0.919	-898.529	809.8223
gs_cnt	-2666.86	958.0185	-2.78	0.005	-4545.39	-788.33
intern_cnt	-2754.88	394.9529	-6.98	0.000	-3529.32	-1980.43
tt_lab	125884.5	5303.403	23.74	0.000	115485.3	136283.7
anti_dpress	18186.44	6968.728	2.61	0.009	4521.807	31851.08
_cons	-38351.2	29427.97	-1.3	0.193	-96055.1	19352.64

Table A-6.WTP=$60,000 [Regression with robust standard errors]

Linear	regression	Number of obs	=	2712
		F(34, 2677)	=	871.37
		Prob > F	=	0
		R-squared	=	0.9064
		Root MSE	=	1.60E+05

Table A-6. Continued

nmb60	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
tx	143047.4	6755.598	21.17	0.000	129800.7	156294.1
gender	-78620.2	6646.87	-11.83	0.000	-91653.7	-65586.7
plan2	37559.04	7458.31	5.04	0.000	22934.41	52183.67
plan3	58301.4	8973.927	6.5	0.000	40704.88	75897.93
geo1	312511.9	19877.97	15.72	0.000	273534.2	351489.6
geo2	70220.81	22180.66	3.17	0.002	26727.85	113713.8
geo3	42800.59	20897.76	2.05	0.041	1823.218	83777.97
geo4	-29472.6	21603.67	-1.36	0.173	-71834.2	12888.93
yr_hcv0	525666.2	35187.27	14.94	0.000	456669.2	594663.1
yr_hcv1	98398.29	39918.43	2.46	0.014	20124.21	176672.4
yr_hcv2	1367568	33295.24	41.07	0.000	1302281	1432855
yr_hcv3	1279968	30841.44	41.5	0.000	1219493	1340444
yr_hcv4	1061614	29888.44	35.52	0.000	1003008	1120221
yr_hcv5	1024071	29745.91	34.43	0.000	965743.6	1082398
yr_hcv6	753370	29002.94	25.98	0.000	696499.5	810240.4
yr_hcv7	573499.8	28193.72	20.34	0.000	518216.2	628783.5
yr_hcv8	245397.6	28213.97	8.7	0.000	190074.2	300720.9
dc2_b4	-430062	17341.57	-24.8	0.000	-464067	-396058
cvd_b4	29125.73	19593.51	1.49	0.137	-9294.21	67545.68
dm_b4	-159457	9268.93	-17.2	0.000	-177632	-141282
dpress_late	-81220.5	16226.39	-5.01	0.000	-113038	-49403
hbv_b4	-116283	13044.99	-8.91	0.000	-141863	-90704
hiv_b4	22032.92	25209.51	0.87	0.382	-27399.2	71465
heart_b4	-20331.1	10723.71	-1.9	0.058	-41358.7	696.4649
psych_b4	-5798.71	9219.493	-0.63	0.529	-23876.8	12279.34
anncost_b4	-60097.6	7586.872	-7.92	0.000	-74974.3	-45220.8
biopsy_b4	133586.1	9413.246	14.19	0.000	115128.2	152044.1
hx_b4	-110842	9349.577	-11.86	0.000	-129176	-92509.3
out_cnt	424.9334	169.7142	2.5	0.012	92.14926	757.7176
fg_cnt	67.9157	505.188	0.13	0.893	-922.682	1058.514
gs_cnt	-3196.05	1145.743	-2.79	0.005	-5442.68	-949.419
intern_cnt	-3251.37	459.0963	-7.08	0.000	-4151.59	-2351.15
tt_lab	152698	6208.03	24.6	0.000	140525	164871
anti_dpress	25700.22	8051.657	3.19	0.001	9912.123	41488.31
_cons	-39846.8	34590.73	-1.15	0.249	-107674	27980.43

Table A-7. WTP=$70,000 [Regression with robust standard errors]

Linear	regression	Number of obs	=	2712
		F(34, 2677)	=	903.04
		Prob > F	=	0
		R-squared	=	0.9091
		Root MSE	=	1.90E+05

Table A-7. Continued

nmb70	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf. Interval]	
tx	171097.6	7788.495	21.97	0.000	155825.5	186369.7
gender	-91598	7656.097	-11.96	0.000	-106611	-76585.6
plan2	43958.4	8614.898	5.1	0.000	27065.87	60850.93
plan3	69165.1	10268.14	6.74	0.000	49030.81	89299.39
geo1	357688.2	22391.82	15.97	0.000	313781.2	401595.2
geo2	73444.29	25044.77	2.93	0.003	24335.24	122553.3
geo3	41483.66	23524.43	1.76	0.078	-4644.22	87611.54
geo4	-42523.8	24397.55	-1.74	0.081	-90363.8	5316.121
yr_hcv0	615465.6	40841.43	15.07	0.000	535381.7	695549.6
yr_hcv1	114442.9	46398.91	2.47	0.014	23461.54	205424.2
yr_hcv2	1601566	38762.71	41.32	0.000	1525558	1677573
yr_hcv3	1499560	35944.91	41.72	0.000	1429078	1570043
yr_hcv4	1242893	34845.57	35.67	0.000	1174566	1311220
yr_hcv5	1199710	34677.35	34.6	0.000	1131712	1267707
yr_hcv6	882655.6	33820.18	26.1	0.000	816339.2	948971.9
yr_hcv7	671831.5	32912.25	20.41	0.000	607295.5	736367.5
yr_hcv8	287782.1	32916.28	8.74	0.000	223238.2	352326
dc2_b4	-502159	20163.96	-24.9	0.000	-541698	-462621
cvd_b4	37383.08	21944.3	1.7	0.089	-5646.42	80412.57
dm_b4	-184981	10659.76	-17.35	0.000	-205883	-164079
dpress_late	-95155.3	18613.01	-5.11	0.000	-131653	-58657.9
hbv_b4	-136456	15172.63	-8.99	0.000	-166208	-106705
hiv_b4	32019.91	28204.4	1.14	0.256	-23284.7	87324.52
heart_b4	-21829.1	12196.85	-1.79	0.074	-45745.3	2087.103
psych_b4	-7997.69	10608.93	-0.75	0.451	-28800.2	12804.83
anncost_b4	-68733.8	8755.452	-7.85	0.000	-85901.9	-51565.7
biopsy_b4	155610.5	10928.11	14.24	0.000	134182.1	177038.9
hx_b4	-129371	10782.99	-12	0.000	-150514	-108227
out_cnt	462.2195	196.8696	2.35	0.019	76.18764	848.2513
fg_cnt	180.185	576.6225	0.31	0.755	-950.486	1310.856

Table A-7. Continued

nmb70	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf. Interval]	
gs_cnt	-3725.24	1334.994	-2.79	0.005	-6342.96	-1107.52
intern_cnt	-3747.86	525.0396	-7.14	0.000	-4777.38	-2718.34
tt_lab	179511.5	7133.545	25.16	0.000	165523.7	193499.3
anti_dpress	33213.99	9174.292	3.62	0.000	15224.58	51203.41
_cons	-41342.4	39848.22	-1.04	0.300	-119479	36793.98

Table A-8. WTP=$80,000 [Regression with robust standard errors]:

Linear	regression	Number of obs	=	2712
		F(34, 2677)	=	925.33
		Prob > F	=	0
		R-squared	=	0.9108
		Root MSE	=	2.10E+05

Table A-8. Continued

nmb80	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf. Interval]	
tx	199147.7	8835.148	22.54	0.000	181823.3	216472.1
gender	-104576	8679.212	-12.05	0.000	-121594	-87557.2
plan2	50357.76	9783.837	5.15	0.000	31173.11	69542.4
plan3	80028.8	11585.29	6.91	0.000	57311.78	102745.8
geo1	402864.5	24983.56	16.13	0.000	353875.5	451853.5
geo2	76667.76	27989.89	2.74	0.006	21783.76	131551.7
geo3	40166.72	26232.08	1.53	0.126	-11270.5	91603.9
geo4	-55575	27269.38	-2.04	0.042	-109046	-2103.87
yr_hcv0	705265.1	46513.9	15.16	0.000	614058.3	796471.9
yr_hcv1	130487.4	52889.47	2.47	0.014	26779.09	234195.8
yr_hcv2	1835563	44249.55	41.48	0.000	1748796	1922330
yr_hcv3	1719152	41061.83	41.87	0.000	1638636	1799668
yr_hcv4	1424172	39812.89	35.77	0.000	1346105	1502239
yr_hcv5	1375348	39619.01	34.71	0.000	1297661	1453035
yr_hcv6	1011941	38646.56	26.18	0.000	936161	1087721
yr_hcv7	770163.2	37636.46	20.46	0.000	696363.7	843962.6
yr_hcv8	330166.7	37626.88	8.77	0.000	256386	403947.4
dc2_b4	-574256	23001	-24.97	0.000	-619358	-529155
cvd_b4	45640.42	24377.65	1.87	0.061	-2160.51	93441.34
dm_b4	-210505	12070.8	-17.44	0.000	-234174	-186836
dpress_late	-109090	21044.45	-5.18	0.000	-150355	-67825
hbv_b4	-156630	17313.9	-9.05	0.000	-190580	-122680

Table A-8. Continued

nmb80	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
hiv_b4	42006.89	31313	1.34	0.180	-19393.2	103407
heart_b4	-23327.1	13706.3	-1.7	0.089	-50203.1	3548.957
psych_b4	-10196.7	12015.2	-0.85	0.396	-33756.7	13363.33
anncost_b4	-77370	9938.444	-7.78	0.000	-96857.8	-57882.2
biopsy_b4	177634.9	12454.51	14.26	0.000	153213.5	202056.4
hx_b4	-147899	12234.65	-12.09	0.000	-171889	-123909
out_cnt	499.5055	224.3182	2.23	0.026	59.65112	939.3599
fg_cnt	292.4541	649.3045	0.45	0.652	-980.735	1565.643
gs_cnt	-4254.43	1525.204	-2.79	0.005	-7245.13	-1263.73
intern_cnt	-4244.35	592.1818	-7.17	0.000	-5405.53	-3083.17
tt_lab	206325	8072.768	25.56	0.000	190495.5	222154.5
anti_dpress	40727.76	10323.69	3.95	0.000	20484.55	60970.97
_cons	-42838	45167.38	-0.95	0.343	-131405	45728.45

APPENDIX B
NET BENEFIT OF INITIAL COMBINATION ANTIVIRAL THERAPY IN USUAL CARE ANALYSIS

Patients with Cirrhosis

Table B-1.WTP=$60,000 [Regression with robust standard errors]

Linear regression

Number of obs	=	688
F(29, 658)	=	679.56
Prob > F	=	0
R-squared	=	0.9395
Root MSE	=	1.60E+05

Table B-1. Continued

nmb60	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
tx	24553.18	14449.28	1.7	0.090	-3819.08	52925.44
age_hcv	7765.249	771.3688	10.07	0.000	6250.608	9279.89
gender	-97516.9	11840.45	-8.24	0.000	-120767	-74267.3
plan2	2424.332	13296.06	0.18	0.855	-23683.5	28532.16
plan3	-14988.1	19655.15	-0.76	0.446	-53582.5	23606.28
geo1	751448	77222.32	9.73	0.000	599816.1	903079.9
geo2	709134.5	79850.31	8.88	0.000	552342.4	865926.6
geo3	596005.5	79044.08	7.54	0.000	440796.5	751214.6
geo4	473508.8	85739.56	5.52	0.000	305152.6	641864.9
yr_hcv2	1846462	32003.91	57.69	0.000	1783620	1909304
yr_hcv3	1497774	33430.19	44.8	0.000	1432131	1563416
yr_hcv4	1273787	32053.95	39.74	0.000	1210847	1336728
yr_hcv5	1123307	27492.58	40.86	0.000	1069323	1177290
yr_hcv6	627206.1	26622.28	23.56	0.000	574931.2	679481
yr_hcv7	282946.5	24303.12	11.64	0.000	235225.5	330667.5
cvd_b4	-163934	43714.5	-3.75	0.000	-249771	-78097.2
ddpend_b4	-167609	54657.07	-3.07	0.002	-274933	-60286
dpress_late	-81898.2	24472.09	-3.35	0.001	-129951	-33845.4
hbv_b4	-230982	37899.76	-6.09	0.000	-305401	-156563
hiv_b4	345897.5	58768.04	5.89	0.000	230502	461293
heart_b4	-84579.6	21986.24	-3.85	0.000	-127751	-41408
anncost_b4	-218698	14964.41	-14.61	0.000	-248082	-189314
biopsy_b4	-122201	15581.73	-7.84	0.000	-152797	-91605.3
hx_b4	-3656.45	22680.72	-0.16	0.872	-48191.8	40878.85

Table B-1.Continued

nmb60	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
er_cnt	15310.89	4223.963	3.62	0.000	7016.819	23604.96
gs_cnt	-10777.3	1182.831	-9.11	0.000	-13099.9	-8454.76
inf_cnt	13641.2	4361.463	3.13	0.002	5077.136	22205.26
tt_lab	-22027.4	13997.64	-1.57	0.116	-49512.8	5458.081
anti_dpress	8039.544	15049.86	0.53	0.593	-21512	37591.09
_cons	-195392	93331.24	-2.09	0.037	-378655	-12128.9

Table B-2.WTP=$70,000 [Regression with robust standard errors]

Linear regression	Number of obs	=	688
	F(29, 658)	=	704.02
	Prob > F	=	0
	R-squared	=	0.9407
	Root MSE	=	1.80E+05

Table B-2. Continued

nmb70	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
tx	34154.09	16795.46	2.03	0.042	1174.934	67133.24
age_hcv	9068.86	878.7297	10.32	0.000	7343.408	10794.31
gender	-112865	13692.65	-8.24	0.000	-139751	-85978.1
plan2	2209.612	15339.71	0.14	0.886	-27911.1	32330.3
plan3	-18761.9	22911.23	-0.82	0.413	-63749.9	26226.03
geo1	858748	89934.71	9.55	0.000	682154.4	1035342
geo2	808519.5	93146.84	8.68	0.000	625618.6	991420.4
geo3	676598.9	92047.61	7.35	0.000	495856.4	857341.3
geo4	533988	99782.48	5.35	0.000	338057.5	729918.5
yr_hcv2	2158136	37052.51	58.25	0.000	2085380	2230891
yr_hcv3	1753124	38877.44	45.09	0.000	1676786	1829463
yr_hcv4	1491513	37275.52	40.01	0.000	1418320	1564707
yr_hcv5	1315166	31917.77	41.2	0.000	1252493	1377839
yr_hcv6	735039.8	30839.07	23.83	0.000	674485	795594.7
yr_hcv7	330720.2	28252.65	11.71	0.000	275243.9	386196.4
cvd_b4	-183320	49300.35	-3.72	0.000	-280125	-86515.1
ddpend_b4	-181639	58512.37	-3.1	0.002	-296533	-66745.9
dpress_late	-95670.7	28006.91	-3.42	0.001	-150664	-40677
hbv_b4	-269201	44364.02	-6.07	0.000	-356313	-182089
hiv_b4	417507.3	66161.9	6.31	0.000	287593.4	547421.2
heart_b4	-95706.5	25384.01	-3.77	0.000	-145550	-45863
anncost_b4	-254427	17367.86	-14.65	0.000	-288531	-220324

Table B-2. Continued

nmb70	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
biopsy_b4	-141851	17999.63	-7.88	0.000	-177195	-106507
hx_b4	-4400.33	26364.36	-0.17	0.867	-56168.8	47368.1
er_cnt	18668.84	4929.514	3.79	0.000	8989.368	28348.32
gs_cnt	-12573.8	1365.31	-9.21	0.000	-15254.7	-9892.91
inf_cnt	15661.32	5065.108	3.09	0.002	5715.598	25607.05
tt_lab	-23118.1	16219.07	-1.43	0.155	-54965.5	8729.229
anti_dpress	12863.32	17287.15	0.74	0.457	-21081.3	46807.96
_cons	-212157	108340.9	-1.96	0.051	-424893	578.4189

Table B-3.WTP=$80,000 [Regression with robust standard errors]:

Linear regression	Number of obs	=	688
	F(29, 658)	=	721.16
	Prob > F	=	0
	R-squared	=	0.9413
	Root MSE	=	2.10E+05

Table B-3. Continued

nmb80	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
tx	43754.97	19171.06	2.28	0.023	6111.142	81398.81
age_hcv	10372.47	989.5831	10.48	0.000	8429.348	12315.59
gender	-128212	15573.27	-8.23	0.000	-158792	-97633.1
plan2	1994.913	17418.34	0.11	0.909	-32207.3	36197.15
plan3	-22535.7	26213.34	-0.86	0.390	-74007.6	28936.16
geo1	966048	102890.1	9.39	0.000	764015.4	1168081
geo2	907904.5	106671.3	8.51	0.000	698447.3	1117362
geo3	757192.2	105307.7	7.19	0.000	550412.6	963971.7
geo4	594467.3	114070.3	5.21	0.000	370481.6	818453
yr_hcv2	2469809	42145.07	58.6	0.000	2387054	2552564
yr_hcv3	2008475	44376.03	45.26	0.000	1921339	2095611
yr_hcv4	1709239	42546.7	40.17	0.000	1625696	1792783
yr_hcv5	1507025	36387.25	41.42	0.000	1435576	1578474
yr_hcv6	842873.5	35105.52	24.01	0.000	773941.2	911805.9
yr_hcv7	378493.9	32235.47	11.74	0.000	315197.1	441790.6
cvd_b4	-202706	55187.34	-3.67	0.000	-311071	-94341.7
ddpend_b4	-195669	63313.89	-3.09	0.002	-319991	-71347.8
dpress_late	-109443	31675.21	-3.46	0.001	-171640	-47246.6
hbv_b4	-307421	50879.28	-6.04	0.000	-407326	-207515
hiv_b4	489117.1	74143.35	6.6	0.000	343531	634703.1

Table B-3. Continued

nmb80	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf. Interval]	
heart_b4	-106833	28908	-3.7	0.000	-163596	-50070.2
anncost_b4	-290157	19791.44	-14.66	0.000	-329019	-251295
biopsy_b4	-161501	20442.66	-7.9	0.000	-201641	-121360
hx_b4	-5144.19	30104.94	-0.17	0.864	-64257.5	53969.14
er_cnt	22026.79	5657.764	3.89	0.000	10917.35	33136.24
gs_cnt	-14370.3	1558.136	-9.22	0.000	-17429.8	-11310.7
inf_cnt	17681.45	5777.268	3.06	0.002	6337.342	29025.55
tt_lab	-24208.9	18475.3	-1.31	0.191	-60486.6	12068.73
anti_dpress	17687.11	19569.97	0.9	0.366	-20740	56114.23
_cons	-228923	123564.5	-1.85	0.064	-471551	13705.59

APPENDIX C
COVARIATES EFFECTS ON THE INB OF ANTIVIRAL THERAPY IN BASE CASE ANALYSIS

Patients with Cirrhosis

Table C-1. WTP=$15,000 in multivariate adjusted model

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	65	3.73E+13	5.7E+11	139.92	<.0001
Error	2646	1.09E+13	4.1E+09		
Corrected Total	2711	4.82E+13			

Table C-1. Continued

R-Square	Coeff Var	Root MSE	nmb15 Mean
0.774629	31.05834	64078.62	206317

Table C-1. Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	-36469.3677	12438.10721	-2.93	0.0034
tx	9204.1647	25610.3859	0.36	0.7193
gender	-18017.7124	3298.44668	-5.46	<.0001
plan2	8288.1011	3733.40191	2.22	0.0265
plan3	5953.159	4168.86551	1.43	0.1534
geo1	113456.6709	6804.35439	16.67	<.0001
geo2	63050.7942	9039.53957	6.98	<.0001
geo3	55463.8981	7730.71576	7.17	<.0001
geo4	32147.5459	8724.19127	3.68	0.0002
Yr_HCV0	118007.3069	12980.71633	9.09	<.0001
Yr_HCV1	23287.5459	14774.22977	1.58	0.1151
Yr_HCV2	325084.8049	10391.29195	31.28	<.0001
Yr_HCV3	301823.0893	10391.71037	29.04	<.0001
Yr_HCV4	234707.5723	10010.37824	23.45	<.0001
Yr_HCV5	225987.1133	10388.70709	21.75	<.0001
Yr_HCV6	163253.2482	10003.51003	16.32	<.0001
Yr_HCV7	126093.8127	9308.54005	13.55	<.0001
Yr_HCV8	47868.1947	9497.74716	5.04	<.0001
TT_lab	32811.8868	3348.13885	9.8	<.0001
anti_dpress	-572.6307	5150.20931	-0.11	0.9115
dc2_b4	-98775.8346	5406.42585	-18.27	<.0001
CVD_b4	-16583.1798	7852.21672	-2.11	0.0348
dm_b4	-42241.8645	4237.48045	-9.97	<.0001

Table C-1. Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
dpress_late	-24766.7491	7495.66356	-3.3	0.001
HBV_b4	-23122.2943	6020.84308	-3.84	0.0001
HIV_b4	-10345.5297	9979.47786	-1.04	0.3
Heart_b4	-11934.4791	4943.55556	-2.41	0.0158
Psych_b4	5247.1489	4276.28642	1.23	0.2199
anncost_b4	-26565.2432	4082.80224	-6.51	<.0001
Biopsy_b4	36111.7884	5908.52153	6.11	<.0001
hx_b4	-23284.7067	4253.11438	-5.47	<.0001
out_cnt	264.2758	58.93145	4.48	<.0001
FG_cnt	-387.6183	201.21125	-1.93	0.0542
GS_cnt	-744.6424	252.19984	-2.95	0.0032
Intern_cnt	-1083.7346	162.28813	-6.68	<.0001
tx*gender	-5402.9622	5535.79027	-0.98	0.3292
tx*plan2	1747.3051	6157.53147	0.28	0.7766
tx*plan3	11150.8333	7092.06624	1.57	0.116
tx*geo1	-9480.4046	11636.53077	-0.81	0.4153
tx*geo2	-20012.3084	14938.17917	-1.34	0.1805
tx*geo3	-15389.2383	13255.09511	-1.16	0.2457
tx*geo4	-7748.0757	15394.85756	-0.5	0.6148
tx*Yr_HCV0	0	.	.	.
tx*Yr_HCV1	0	.	.	.
tx*Yr_HCV2	-19006.3496	23472.91247	-0.81	0.4182
tx*Yr_HCV3	-9064.794	22887.3573	-0.4	0.6921
tx*Yr_HCV4	45943.8304	22364.45175	2.05	0.04
tx*Yr_HCV5	36244.7018	22588.63053	1.6	0.1087
tx*Yr_HCV6	40262.42	22296.51948	1.81	0.0711
tx*Yr_HCV7	31253.1163	21442.88246	1.46	0.1451
tx*Yr_HCV8	35264.0971	21706.1946	1.62	0.1044
tx*TT_lab	-8266.7883	5731.10679	-1.44	0.1493
tx*anti_dpress	-12950.6725	6967.7045	-1.86	0.0632
tx*dc2_b4	-30947.0551	11959.51191	-2.59	0.0097
tx*CVD_b4	22557.0877	14897.37978	1.51	0.1301
tx*dm_b4	-7888.1295	7450.70302	-1.06	0.2898
tx*dpress_late	13658.6629	10638.68935	1.28	0.1993
tx*HBV_b4	-9648.5506	13287.67281	-0.73	0.4678
tx*HIV_b4	-37299.5449	18270.05731	-2.04	0.0413
tx*Heart_b4	-1711.9281	8357.14464	-0.2	0.8377
tx*Psych_b4	-6987.1078	7235.11436	-0.97	0.3343

Table C-1. Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
tx*anncost_b4	9989.9821	6214.74627	1.61	0.1081
tx*Biopsy_b4	-4411.2926	8054.42177	-0.55	0.584
tx*hx_b4	-9575.7569	7592.0073	-1.26	0.2073
tx*out_cnt	-6.3201	124.66759	-0.05	0.9596
tx*FG_cnt	52.2929	389.45439	0.13	0.8932
tx*GS_cnt	-220.7435	583.56762	-0.38	0.7053
tx*Intern_cnt	289.9506	311.4351	0.93	0.3519

Table C-2. WTP=$20,000 in multivariate adjusted model

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	65	6.8620811E13	1.0557048E12	204.50	<.0001
Error	2646	1.3659916E13	5162477545.6		
Corrected Total	2711	8.2280726E13			

Table C-2. Continued

R-Square	Coeff Var	Root MSE	nmb20 Mean
0.833984	25.02755	71850.38	287085.2

Table C-2. Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	-36459.6073	13946.66054	-2.61	0.0090
tx	14211.0852	28716.53640	0.49	0.6207
gender	-24239.5692	3698.49812	-6.55	<.0001
plan2	11503.1705	4186.20680	2.75	0.0060
plan3	11096.6596	4674.48553	2.37	0.0177
geo1	136540.0685	7629.61914	17.90	<.0001
geo2	65679.8027	10135.89831	6.48	<.0001
geo3	56151.0881	8668.33406	6.48	<.0001
geo4	26643.9191	9782.30305	2.72	0.0065
Yr_HCV0	160146.4826	14555.07990	11.00	<.0001

Table C-2. Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Yr_HCV1	28958.5586	16566.11926	1.75	0.0806
Yr_HCV2	440710.9484	11651.59770	37.82	<.0001
Yr_HCV3	409043.3662	11652.06687	35.10	<.0001
Yr_HCV4	321306.2793	11224.48495	28.63	<.0001
Yr_HCV5	309705.9957	11648.69934	26.59	<.0001
Yr_HCV6	224452.6458	11216.78373	20.01	<.0001
Yr_HCV7	173094.7787	10437.52446	16.58	<.0001
Yr_HCV8	67388.4747	10649.67951	6.33	<.0001
TT_lab	46253.1894	3754.21720	12.32	<.0001
anti_dpress	4496.6294	5774.85141	0.78	0.4363
dc2_b4	-133141.2397	6062.14312	-21.96	<.0001
CVD_b4	-13743.7483	8804.57124	-1.56	0.1186
dm_b4	-53362.1098	4751.42241	-11.23	<.0001
dpress_late	-31892.4821	8404.77361	-3.79	0.0002
HBV_b4	-32289.7341	6751.07982	-4.78	<.0001
HIV_b4	-5923.5452	11189.83683	-0.53	0.5966
Heart_b4	-12737.2042	5543.13370	-2.30	0.0216
Psych_b4	4092.6355	4794.93496	0.85	0.3934
anncost_b4	-30993.2979	4577.98409	-6.77	<.0001
Biopsy_b4	47044.3960	6625.13537	7.10	<.0001
hx_b4	-32361.2336	4768.95251	-6.79	<.0001
out_cnt	286.4273	66.07894	4.33	<.0001
FG_cnt	-326.3682	225.61511	-1.45	0.1481
GS_cnt	-999.1202	282.78785	-3.53	0.0004
Intern_cnt	-1301.6706	181.97121	-7.15	<.0001

Table C-2. Continued

Parameter	Estimate		Standard Error	t Value	Pr > |t|
tx*gender	-6183.0086		6207.19748	-1.00	0.3193
tx*plan2	1369.8456		6904.34643	0.20	0.8427
tx*plan3	12583.5437		7952.22606	1.58	0.1137
tx*geo1	-11448.1062		13047.86506	-0.88	0.3804
tx*geo2	-23708.0700		16749.95322	-1.42	0.1571
tx*geo3	-19733.5520		14862.73665	-1.33	0.1844
tx*geo4	-11364.3832		17262.01976	-0.66	0.5104
tx*Yr_HCV0	0.0000	B	.	.	.
tx*Yr_HCV1	0.0000	B	.	.	.
tx*Yr_HCV2	-7042.0726		26319.81993	-0.27	0.7891
tx*Yr_HCV3	6274.8907		25663.24582	0.24	0.8069
tx*Yr_HCV4	65095.8987		25076.91977	2.60	0.0095
tx*Yr_HCV5	55034.2762		25328.28804	2.17	0.0299
tx*Yr_HCV6	57884.1436		25000.74835	2.32	0.0207
tx*Yr_HCV7	45359.7958		24043.57814	1.89	0.0593
tx*Yr_HCV8	47595.8873		24338.82604	1.96	0.0506
tx*TT_lab	-8823.8716		6426.20292	-1.37	0.1698
tx*anti_dpress	-15809.3471		7812.78114	-2.02	0.0431
tx*dc2_b4	-40044.8418		13410.01890	-2.99	0.0029
tx*CVD_b4	26437.9191		16704.20549	1.58	0.1136
tx*dm_b4	-13236.8288		8354.36004	-1.58	0.1132
tx*dpress_late	14896.1648		11929.00065	1.25	0.2119
tx*HBV_b4	-13672.3772		14899.26553	-0.92	0.3589
tx*HIV_b4	-34539.4245		20485.93753	-1.69	0.0919
tx*Heart_b4	-1194.5661		9370.73924	-0.13	0.8986

Table C-2. Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
tx*Psych_b4	-7596.9544	8112.62375	-0.94	0.3491
tx*anncost_b4	9785.5729	6968.50052	1.40	0.1604
tx*Biopsy_b4	-4688.9641	9031.30069	-0.52	0.6037
tx*hx_b4	-11019.3758	8512.80238	-1.29	0.1956
tx*out_cnt	-12.0880	139.78787	-0.09	0.9311
tx*FG_cnt	28.5072	436.68929	0.07	0.9480
tx*GS_cnt	-214.3022	654.34550	-0.33	0.7433
tx*Intern_cnt	181.6982	349.20744	0.52	0.6029

Table C-3.WTP=$30,000 in multivariate adjusted model

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	65	1.6054228E14	2.4698812E12	299.66	<.0001
Error	2646	2.180933E13	8242377217.9		
Corrected Total	2711	1.8235161E14			

Table C-3. Continued

R-Square	Coeff Var	Root MSE	nmb30 Mean
0.880400	20.23700	90787.54	448621.6

Table C-3. Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	-36440.0865	17622.49458	-2.07	0.0388
tx	24224.9261	36285.17420	0.67	0.5044
gender	-36683.2827	4673.28813	-7.85	<.0001
plan2	17933.3093	5289.53914	3.39	0.0007
plan3	21383.6609	5906.51042	3.62	0.0003
geo1	182706.8638	9640.51011	18.95	<.0001

Table C-3. Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
geo2	70937.8196	12807.35360	5.54	<.0001
geo3	57525.4683	10952.99262	5.25	<.0001
geo4	15636.6655	12360.56345	1.27	0.2060
Yr_HCV0	244424.8339	18391.27122	13.29	<.0001
Yr_HCV1	40300.5840	20932.34764	1.93	0.0543
Yr_HCV2	671963.2355	14722.53640	45.64	<.0001
Yr_HCV3	623483.9199	14723.12922	42.35	<.0001
Yr_HCV4	494503.6934	14182.85221	34.87	<.0001
Yr_HCV5	477143.7604	14718.87413	32.42	<.0001
Yr_HCV6	346851.4408	14173.12123	24.47	<.0001
Yr_HCV7	267096.7107	13188.47746	20.25	<.0001
Yr_HCV8	106429.0346	13456.54890	7.91	<.0001
TT_lab	73135.7945	4743.69274	15.42	<.0001
anti_dpress	14635.1496	7296.89286	2.01	0.0450
dc2_b4	-201872.0499	7659.90424	-26.35	<.0001
CVD_b4	-8064.8852	11125.13699	-0.72	0.4686
dm_b4	-75602.6005	6003.72508	-12.59	<.0001
dpress_late	-46143.9480	10619.96719	-4.35	<.0001
HBV_b4	-50624.6139	8530.41968	-5.93	<.0001
HIV_b4	2920.4239	14139.07210	0.21	0.8364
Heart_b4	-14342.6546	7004.10276	-2.05	0.0407
Psych_b4	1783.6085	6058.70596	0.29	0.7685
anncost_b4	-39849.4073	5784.57470	-6.89	<.0001
Biopsy_b4	68909.6113	8371.28084	8.23	<.0001
hx_b4	-50514.2876	6025.87547	-8.38	<.0001

Table C-3. Continued

Parameter	Estimate		Standard Error	t Value	Pr > |t|
out_cnt	330.7304		83.49496	3.96	<.0001
FG_cnt	-203.8680		285.07907	-0.72	0.4746
GS_cnt	-1508.0757		357.32047	-4.22	<.0001
Intern_cnt	-1737.5426		229.93223	-7.56	<.0001
tx*gender	-7743.1015		7843.18968	-0.99	0.3236
tx*plan2	614.9267		8724.08181	0.07	0.9438
tx*plan3	15448.9646		10048.14452	1.54	0.1243
tx*geo1	-15383.5094		16486.80921	-0.93	0.3509
tx*geo2	-31099.5934		21164.63358	-1.47	0.1418
tx*geo3	-28422.1794		18780.01514	-1.51	0.1303
tx*geo4	-18596.9982		21811.66229	-0.85	0.3939
tx*Yr_HCV0	0.0000	B	.	.	.
tx*Yr_HCV1	0.0000	B	.	.	.
tx*Yr_HCV2	16886.4813		33256.77017	0.51	0.6117
tx*Yr_HCV3	36954.2600		32427.14692	1.14	0.2546
tx*Yr_HCV4	103400.0354		31686.28659	3.26	0.0011
tx*Yr_HCV5	92613.4251		32003.90642	2.89	0.0038
tx*Yr_HCV6	93127.5909		31590.03915	2.95	0.0032
tx*Yr_HCV7	73573.1547		30380.59357	2.42	0.0155
tx*Yr_HCV8	72259.4678		30753.65811	2.35	0.0189
tx*TT_lab	-9938.0382		8119.91701	-1.22	0.2211
tx*anti_dpress	-21526.6963		9871.94697	-2.18	0.0293
tx*dc2_b4	-58240.4152		16944.41367	-3.44	0.0006

Table C-3. Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
tx*CVD_b4	34199.5817	21106.82840	1.62	0.1053
tx*dm_b4	-23934.2273	10556.26643	-2.27	0.0235
tx*dpress_late	17371.1686	15073.05270	1.15	0.2492
tx*HBV_b4	-21720.0302	18826.17171	-1.15	0.2487
tx*HIV_b4	-29019.1839	25885.28789	-1.12	0.2624
tx*Heart_b4	-159.8423	11840.52634	-0.01	0.9892
tx*Psych_b4	-8816.6475	10250.81723	-0.86	0.3898
tx*anncost_b4	9376.7545	8805.14460	1.06	0.2870
tx*Biopsy_b4	-5244.3071	11411.62410	-0.46	0.6459
tx*hx_b4	-13906.6136	10756.46843	-1.29	0.1962
tx*out_cnt	-23.6239	176.63089	-0.13	0.8936
tx*FG_cnt	-19.0642	551.78475	-0.03	0.9724
tx*GS_cnt	-201.4195	826.80725	-0.24	0.8076
tx*Intern_cnt	-34.8065	441.24586	-0.08	0.9371

APPENDIX D
COVARIATES EFFECTS ON THE INB OF ANTIVIRAL THERAPY IN USUAL CARE ANALYSIS

Patients with Cirrhosis

Table D-1.WTP=$60,000 in multivariate adjusted model

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	55	2.579578E14	4.6901419E12	187.42	<.0001
Error	632	1.5815912E13	25025177897		
Corrected Total	687	2.7377372E14			

Table D-1. Continued

R-Square	Coeff Var	Root MSE	nmb60 Mean
0.942230	9.899500	158193.5	1597995

Table D-1.Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	-259711.502	80461.0874	-3.23	0.0013
tx	203740.419	138586.3807	1.47	0.1420
age_HCV	7593.419	1028.1910	7.39	<.0001
gender	-96599.750	16533.8761	-5.84	<.0001
plan2	6348.906	17791.1090	0.36	0.7213
plan3	-12813.356	22291.6185	-0.57	0.5656
geo1	778069.450	39313.3358	19.79	<.0001
geo2	719749.530	49664.2000	14.49	<.0001
geo3	634346.631	46100.4208	13.76	<.0001
geo4	528966.435	52746.5169	10.03	<.0001
Yr_HCV2	1888435.362	48331.4487	39.07	<.0001
Yr_HCV3	1558921.691	48070.3645	32.43	<.0001
Yr_HCV4	1335553.608	45851.7925	29.13	<.0001

Table D-1.Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Yr_HCV5	1162222.878	48353.7954	24.04	<.0001
Yr_HCV6	673258.104	45836.3536	14.69	<.0001
Yr_HCV7	319770.258	43963.8600	7.27	<.0001
TT_lab	-7577.496	17016.7303	-0.45	0.6563
anti_dpress	-999.866	21856.4325	-0.05	0.9635
CVD_b4	-125584.067	39756.5540	-3.16	0.0017
Ddpend_b4	-259707.002	73149.3149	-3.55	0.0004
dpress_late	-82604.096	35601.0061	-2.32	0.0206
HBV_b4	-247787.557	30055.4557	-8.24	<.0001
HIV_b4	348971.477	43645.8483	8.00	<.0001
Heart_b4	-79373.805	19895.2364	-3.99	<.0001
anncost_b4	-218197.255	19242.4886	-11.34	<.0001
Biopsy_b4	-138893.642	29607.3173	-4.69	<.0001
hx_b4	-13724.934	22981.9157	-0.60	0.5506
er_cnt	12100.671	4030.0518	3.00	0.0028
GS_cnt	-11282.810	1653.1250	-6.83	<.0001
INF_cnt	13066.204	2378.0170	5.49	<.0001
tx*age_HCV	45.725	1852.8664	0.02	0.9803
tx*gender	-6165.051	27573.2092	-0.22	0.8231
tx*plan2	-8532.278	29508.7688	-0.29	0.7726
tx*plan3	-2602.547	36455.5171	-0.07	0.9431
tx*geo1	-76328.842	65369.9483	-1.17	0.2434
tx*geo2	-24840.183	85391.8975	-0.29	0.7712
tx*geo3	-97961.991	75736.6598	-1.29	0.1963
tx*geo4	-136104.490	91500.2253	-1.49	0.1374

Table D-1.Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
tx*Yr_HCV2	-126560.769	75475.1684	-1.68	0.0941
tx*Yr_HCV3	-146770.633	68895.5328	-2.13	0.0335
tx*Yr_HCV4	-155103.517	67504.5314	-2.30	0.0219
tx*Yr_HCV5	-98926.618	69293.0868	-1.43	0.1539
tx*Yr_HCV6	-110989.617	67399.1787	-1.65	0.1001
tx*Yr_HCV7	-81946.379	62609.8711	-1.31	0.1911
tx*TT_lab	-36913.225	29067.1091	-1.27	0.2046
tx*anti_dpress	20711.654	32213.4639	0.64	0.5205
tx*CVD_b4	-70615.031	85111.5195	-0.83	0.4070
tx*Ddpend_b4	170790.707	100510.2050	1.70	0.0898
tx*dpress_late	-3182.146	51420.6915	-0.06	0.9507
tx*HBV_b4	130599.804	79808.3612	1.64	0.1023
tx*anncost_b4	-12149.771	30485.0424	-0.40	0.6904
tx*Biopsy_b4	29230.771	39401.1151	0.74	0.4584
tx*hx_b4	39091.311	42700.6332	0.92	0.3603
tx*er_cnt	16448.168	9118.6581	1.80	0.0717
tx*GS_cnt	440.567	2574.5997	0.17	0.8642
tx*INF_cnt	9479.151	8328.5263	1.14	0.2555

Table D-2.WTP=$70,000 in multivariate adjusted model

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	55	3.5171446E14	6.3948083E12	191.58	<.0001
Error	632	2.1095309E13	33378654023		
Corrected Total	687	3.7280977E14			

Table D-2. Continued

R-Square	Coeff Var	Root MSE	nmb70 Mean
0.943415	9.751631	182698.3	1873515

Table D-2. Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	-284491.261	92924.8184	-3.06	0.0023
tx	240611.500	160053.9425	1.50	0.1333
age_HCV	8833.757	1187.4617	7.44	<.0001
gender	-112091.059	19095.0369	-5.87	<.0001
plan2	6345.039	20547.0201	0.31	0.7576
plan3	-18380.388	25744.6757	-0.71	0.4755
geo1	887074.041	45403.1222	19.54	<.0001
geo2	818983.124	57357.3750	14.28	<.0001
geo3	719724.740	53241.5528	13.52	<.0001
geo4	596420.605	60917.1547	9.79	<.0001
Yr_HCV2	2207426.202	55818.1754	39.55	<.0001
Yr_HCV3	1823032.109	55516.6483	32.84	<.0001
Yr_HCV4	1566273.808	52954.4110	29.58	<.0001
Yr_HCV5	1363016.425	55843.9837	24.41	<.0001
Yr_HCV6	790095.318	52936.5805	14.93	<.0001
Yr_HCV7	375234.088	50774.0305	7.39	<.0001
TT_lab	-5669.810	19652.6871	-0.29	0.7731
anti_dpress	2468.726	25242.0778	0.10	0.9221
CVD_b4	-139498.775	45914.9966	-3.04	0.0025
Ddpend_b4	-279821.133	84480.4243	-3.31	0.0010
dpress_late	-98773.741	41115.7385	-2.40	0.0166
HBV_b4	-290266.144	34711.1611	-8.36	<.0001

Table D-2. Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
HIV_b4	420869.329	50406.7575	8.35	<.0001
Heart_b4	-89550.954	22977.0848	-3.90	0.0001
anncost_b4	-253315.590	22223.2238	-11.40	<.0001
Biopsy_b4	-161164.028	34193.6043	-4.71	<.0001
hx_b4	-14993.543	26541.9026	-0.56	0.5723
er_cnt	14777.082	4654.3223	3.17	0.0016
GS_cnt	-13048.314	1909.2004	-6.83	<.0001
INF_cnt	14706.615	2746.3809	5.35	<.0001
tx*age_HCV	45.725	2139.8825	0.02	0.9830
tx*gender	-7103.752	31844.4051	-0.22	0.8235
tx*plan2	-9397.905	34079.7902	-0.28	0.7828
tx*plan3	1579.052	42102.6165	0.04	0.9701
tx*geo1	-83385.423	75496.0040	-1.10	0.2698
tx*geo2	-26216.610	98619.4299	-0.27	0.7905
tx*geo3	-110673.296	87468.5588	-1.27	0.2062
tx*geo4	-155338.739	105673.9610	-1.47	0.1421
tx*Yr_HCV2	-145535.925	87166.5614	-1.67	0.0955
tx*Yr_HCV3	-166746.890	79567.7150	-2.10	0.0365
tx*Yr_HCV4	-186276.852	77961.2421	-2.39	0.0172
tx*Yr_HCV5	-117210.576	80026.8517	-1.46	0.1435
tx*Yr_HCV6	-129820.072	77839.5699	-1.67	0.0959
tx*Yr_HCV7	-96036.507	72308.3802	-1.33	0.1846
tx*TT_lab	-44826.923	33569.7158	-1.34	0.1822
tx*anti_dpress	23869.100	37203.4529	0.64	0.5214
tx*CVD_b4	-84017.895	98295.6202	-0.85	0.3930

Table D-2. Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
tx*Ddpend_b4	182655.522	116079.6211	1.57	0.1161
tx*dpress_late	-185.871	59385.9538	-0.00	0.9975
tx*HBV_b4	156443.140	92170.9823	1.70	0.0901
tx*anncost_b4	-14761.799	35207.2924	-0.42	0.6752
tx*Biopsy_b4	34357.036	45504.4989	0.76	0.4505
tx*hx_b4	40323.117	49315.1251	0.82	0.4139
tx*er_cnt	18692.177	10531.1732	1.77	0.0764
tx*GS_cnt	200.668	2973.4151	0.07	0.9462
tx*INF_cnt	13819.171	9618.6470	1.44	0.1513

Table D-3. WTP=$80,000 in multivariate adjusted model

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	55	4.6005228E14	8.364587E12	194.03	<.0001
Error	632	2.7245554E13	43110054101		
Corrected Total	687	4.8729784E14			

Table D-3. Continued

R-Square	Coeff Var	Root MSE	nmb80 Mean
0.944088	9.661527	207629.6	2149035

Table D-3.Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	-309271.021	105605.5140	-2.93	0.0035
tx	277482.581	181895.2049	1.53	0.1276
age_HCV	10074.096	1349.5050	7.47	<.0001
gender	-127582.369	21700.7816	-5.88	<.0001

Table D-3.Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
plan2	6341.171	23350.9051	0.27	0.7860
plan3	-23947.420	29257.8426	-0.82	0.4134
geo1	996078.632	51598.9178	19.30	<.0001
geo2	918216.718	65184.4704	14.09	<.0001
geo3	805102.850	60506.9953	13.31	<.0001
geo4	663874.775	69230.0243	9.59	<.0001
Yr_HCV2	2526417.041	63435.2287	39.83	<.0001
Yr_HCV3	2087142.527	63092.5546	33.08	<.0001
Yr_HCV4	1796994.008	60180.6696	29.86	<.0001
Yr_HCV5	1563809.972	63464.5589	24.64	<.0001
Yr_HCV6	906932.532	60160.4060	15.08	<.0001
Yr_HCV7	430697.918	57702.7503	7.46	<.0001
TT_lab	-3762.124	22334.5298	-0.17	0.8663
anti_dpress	5937.319	28686.6592	0.21	0.8361
CVD_b4	-153413.484	52180.6435	-2.94	0.0034
Ddpend_b4	-299935.265	96008.7821	-3.12	0.0019
dpress_late	-114943.385	46726.4696	-2.46	0.0142
HBV_b4	-332744.732	39447.9114	-8.44	<.0001
HIV_b4	492767.181	57285.3586	8.60	<.0001
Heart_b4	-99728.102	26112.5810	-3.82	0.0001
anncost_b4	-288433.925	25255.8468	-11.42	<.0001
Biopsy_b4	-183434.415	38859.7279	-4.72	<.0001
hx_b4	-16262.152	30163.8606	-0.54	0.5900
er_cnt	17453.493	5289.4599	3.30	0.0010
GS_cnt	-14813.817	2169.7335	-6.83	<.0001
INF_cnt	16347.025	3121.1572	5.24	<.0001

Table D-3.Continued

Parameter	Estimate	Standard Error	t Value	Pr > |t|
tx*age_HCV	45.724	2431.8949	0.02	0.9850
tx*gender	-8042.454	36189.9526	-0.22	0.8242
tx*plan2	-10263.533	38730.3826	-0.26	0.7911
tx*plan3	5760.650	47848.0189	0.12	0.9042
tx*geo1	-90442.004	85798.3308	-1.05	0.2922
tx*geo2	-27593.037	112077.2229	-0.25	0.8056
tx*geo3	-123384.601	99404.6830	-1.24	0.2150
tx*geo4	-174572.988	120094.4287	-1.45	0.1465
tx*Yr_HCV2	-164511.081	99061.4745	-1.66	0.0973
tx*Yr_HCV3	-186723.147	90425.6752	-2.06	0.0393
tx*Yr_HCV4	-217450.188	88599.9800	-2.45	0.0144
tx*Yr_HCV5	-135494.535	90947.4665	-1.49	0.1368
tx*Yr_HCV6	-148650.526	88461.7042	-1.68	0.0934
tx*Yr_HCV7	-110126.635	82175.7179	-1.34	0.1807
tx*TT_lab	-52740.620	38150.7024	-1.38	0.1673
tx*anti_dpress	27026.545	42280.3062	0.64	0.5229
tx*CVD_b4	-97420.759	111709.2256	-0.87	0.3835
tx*Ddpend_b4	194520.336	131920.0647	1.47	0.1408
tx*dpress_late	2810.403	67489.8728	0.04	0.9668
tx*HBV_b4	182286.476	104748.8081	1.74	0.0823
tx*anncost_b4	-17373.827	40011.7458	-0.43	0.6643
tx*Biopsy_b4	39483.301	51714.1285	0.76	0.4455
tx*hx_b4	41554.923	56044.7599	0.74	0.4587
tx*er_cnt	20936.186	11968.2769	1.75	0.0807
tx*GS_cnt	-39.231	3379.1729	-0.01	0.9907
tx*INF_cnt	18159.191	10931.2257	1.66	0.0972

LIST OF REFERENCES

1. Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol 2007;13(17):2436-41.

2. The National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. National Hepatitis C Prevention Strategy: Hepatitis C Infection in the United States (2008). (Accessed May 18, 2008, at http://www.cdc.gov/ncidod/diseases/hepatitis/c/plan/HCV_infection.htm.)

3. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999;341(8):556-62.

4. Armstrong GL WA, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The Prevalence of Hepatitis C Virus Infection in the United States,1999 through 2002. Ann Intern Med 2006;144:705-14.

5. Dienstag JL, McHutchison JG. American Gastroenterological Association technical review on the management of hepatitis C. Gastroenterology 2006;130(1):231-64; quiz 14-7.

6. Armstrong GL, Wasley A, Simard EP, et al. The Prevalence of Hepatitis C Virus Infection in the United States,1999 through 2002. Ann Intern Med 2006;144:705-14.

7. Grant WC, Jhaveri RR, McHutchison JG, et al. Trends in health care resource use for hepatitis C virus infection in the United States. Hepatology 2005;42(6):1406-13.

8. Wong JB, McQuillan GM, McHutchison JG, et al. Estimating future hepatitis C morbidity, mortality, and costs in the United States. Am J Public Health 2000;90(10):1562-9.

9. Davis GL, Albright JE, Cook SF, et al. Projecting future complications of chronic hepatitis C in the United States. Liver Transpl 2003;9(4):331-8.

10. Nainan OV, Alter MJ, Kruszon-Moran D, et al. Hepatitis C virus genotypes and viral concentrations in participants of a general population survey in the United States. Gastroenterology 2006;131(2):478-84.

11. Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. Semin Liver Dis 2000;20(1):17-35.

12. Hoofnagle JH. Hepatitis C: the clinical spectrum of disease. Hepatology 1997;26(3 Suppl 1):15S-20S.

13. Seeff LB. Natural history of hepatitis C. Hepatology 1997;26(3 Suppl 1):21S-8S.

14. McHutchison JG, Bacon BR. Chronic hepatitis C: an age wave of disease burden. Am J Manag Care 2005;11(10 Suppl):S286-95; quiz S307-11.

15. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci 2006;3(2):47-52.

16. American Gastroenterological Association. American Gastroenterological Association Technical Review on the Management of Hepatitis C. Gasteroenterology 2006;130:231-64.

17. Piasecki BA, Lewis JD, Reddy KR, et al. Influence of alcohol use, race, and viral coinfections on spontaneous HCV clearance in a US veteran population. Hepatology 2004;40(4):892-9.

18. Strader DB, Wright T, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004;39(4):1147-71.

19. American Gastroenterological Association. Medical position statement on the management of Hepatitis C. Gastroenterology 2006;130:225-30.

20. Armstrong GL, Alter MJ, McQuillan GM, et al. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. Hepatology 2000;31(3):777-82.

21. Bonkovsky HL, Snow KK, Malet PF, et al. Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. J Hepatol 2007;46(3):420-31.

22. Kim WR. The burden of hepatitis C in the United States. Hepatology 2002;36(5 Suppl 1):S30-4.

23. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347(13):975-82.

24. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358(9286):958-65.

25. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute For Clinical Excellence (NICE). Lancet 2002;360(9334):711-5.

26. Younossi ZM, Singer ME, McHutchison JG, et al. Cost effectiveness of interferon alpha2b combined with ribavirin for the treatment of chronic hepatitis C. Hepatology 1999;30(5):1318-24.

27. Wong JB, Koff RS. Watchful waiting with periodic liver biopsy versus immediate empirical therapy for histologically mild chronic hepatitis C. A cost-effectiveness analysis. Ann Intern Med 2000;133(9):665-75.

28. Wong JB, Poynard T, Ling MH, et al. Cost-effectiveness of 24 or 48 weeks of interferon alpha-2b alone or with ribavirin as initial treatment of chronic hepatitis C. International Hepatitis Interventional Therapy Group. Am J Gastroenterol 2000;95(6):1524-30.

29. Salomon JA, Weinstein MC, Hammitt JK, et al. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. Jama 2003;290(2):228-37.

30. Sullivan SD, Craxi A, Alberti A, et al. Cost effectiveness of peginterferon alpha-2a plus ribavirin versus interferon alpha-2b plus ribavirin as initial therapy for treatment-naive chronic hepatitis C. Pharmacoeconomics 2004;22(4):257-65.

31. Yeh WS, Armstrong EP, Skrepnek GH, et al. Peginterferon alfa-2a versus peginterferon alfa-2b as initial treatment of hepatitis C virus infection: a cost-utility analysis from the perspective of the Veterans Affairs Health Care System. Pharmacotherapy 2007;27(6):813-24.

32. National Institutes of Health (NIH) Consensus Statement on Management of Hepatitis C: 2002. NIH Consens State Sci Statements 2002;19(3):1-46.

33. Strader DB. Understudied populations with hepatitis C. Hepatology 2002;36(5 Suppl 1):S226-36.

34. Calvert JFJ, Goldenberg PC, Schock C. Chronic hepatitis C infection in a rural Medicaid HMO. J Rural Health 2005;21(1):74-8.

35. Falck-Ytter Y, Kale H, Mullen KD, et al. Surprisingly small effect of antiviral treatment in patients with hepatitis C. Ann Intern Med 2002;136(4):288-92.

36. Markowitz JS, Gutterman EM, Hodes D, et al. Factors associated with the initiation of alpha-interferon treatment in Medicaid patients diagnosed with hepatitis C. J Viral Hepat 2005;12(2):176-85.

37. Shatin D, Schech SD, Patel K, et al. Population-based hepatitis C surveillance and treatment in a national managed care organization. Am J Manag Care 2004;10:250-25.

38. Rocca LG, Yawn BP, Wollan P, et al. Management of patients with hepatitis C in a community population: diagnosis, discussions, and decisions to treat. Ann Fam Med 2004;2(2):116-24.

39. Bini EJ, Brau N, Currie S, et al. Prospective multicenter study of eligibility for antiviral therapy among 4,084 U.S. veterans with chronic hepatitis C virus infection. Am J Gastroenterol 2005;100(8):1772-9.

40. Hare CB, Morris JA, Chu A, et al. Comparison of characteristics of treated and non-treated patients with hepatitis C infection. Pharmacoepidemiol Drug Saf 2006;15(2):71-6.

41. Butt AA, Justice AC, Skanderson M, et al. Rate and predictors of treatment prescription for hepatitis C. Gut 2007;56(3):385-9.

42. Kanwal F, Hoang T, Spiegel BM, et al. Predictors of treatment in patients with chronic hepatitis C infection - role of patient versus nonpatient factors. Hepatology 2007;46(6):1741-9.

43. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making 1998;18(2 Suppl):S68-80.

44. O'Brien BJ, Drummond MF, Labelle RJ, et al. In search of power and significance: issues in the design and analysis of stochastic cost-effectiveness studies in health care. Med Care 1994;32(2):150-63.

45. Hoch JS, Dewa CS. Lessons from Trial-Based Cost-Effectiveness Analyses of Mental Health Interventions: Why Uncertainty About the Outcome, Estimate and Willingness to Pay Matters. Pharmacoeconomics 2007;25(10):807-16.

46. Hoch JS, Briggs AH, Willan AR. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. Health Econ 2002;11(5):415-30.

47. Health Insurance Association of American. Source Book of Health Insurance Data, 1999-2000. Washington, DC: Health Insurance Association of American.; 1999.

48. National Institutes of Health (NIH). National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C. Hepatology 1997;26 (3 Suppl 1):2S-10S.

49. Ray WA. Evaluating Medication Effects Outside of Clinical Trials: New-User Designs. American Journal of Epidemiology 2003;158(9):915-20.

50. Poynard T, Yuen MF, Ratziu V, et al. Viral hepatitis C. Lancet 2003;362(9401):2095-100.

51. Reschovsky J, Kemper P, Tu H. Does type of health insurance affect health care use and assessments of care among the privately insured? Health Serv Res 2000;35(1):219-37.

52. National Institutes of Health (NIH). National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C. Hepatology 2002;19:1-46.

53. Strader DB. Coinfection with HIV and hepatitis C virus in injection drug users and minority populations. Clin Infect Dis 2005;41 Suppl 1:S7-13.

54. Soriano V, Sulkowski M, Bergin C, et al. Care of patients with chronic hepatitis C and HIV co-infection: recommendations from the HIV-HCV International Panel. Aids 2002;16(6):813-28.

55. Poynard T, Ratziu V, Charlotte F, et al. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis c. J Hepatol 2001;34(5):730-9.

56. Poynard T, Mathurin P, Lai CL, et al. A comparison of fibrosis progression in chronic liver diseases. J Hepatol 2003;38(3):257-65.

57. Torriani FJ R-TM, Rockstroh JK et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med 2004;351:438-50.

58. Poynard T, McHutchison J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002;122(5):1303-13.

59. Carrat F B-SF, Pol S et al. . Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA 2004;292:2839-48.

60. Jonsson JR, Barrie HD, O'Rourke P, et al. Obesity and steatosis influence serum and hepatic inflammatory markers in chronic hepatitis C. Hepatology 2008;48(1):80-7.

61. Leandro G, Mangia A, Hui J, et al. Relationship between steatosis, inflammation, and fibrosis in chronic hepatitis C: a meta-analysis of individual patient data. Gastroenterology 2006;130(6):1636-42.

62. Geppert CM, Arora S. Widening the door: the evolution of hepatitis C treatment in patients with psychiatric disorders. Hepatology 2007;46(4):957-9.

63. Schaefer M SM, Garkisch AS, Pich M, Hinzpeter A, Uebelhack R, et al.. Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C. J Hepatol 2005;42:793-98.

64. Kashihara D, Carper, K. National Health Care Expenses in the U.S. Civilian Noninstitutionalized Population, 2003 Rockville, MD. : Agency for Healthcare Research and Quality; 2005. Report No.: Statistical Brief #103.

65. Andriulli A, Festa V, Leandro G, et al. Usefulness of a liver biopsy in the evaluation of patients with elevated ALT values and serological markers of hepatitis viral infection: an AIGO study. Dig Dis Sci 2001;46(7):1409-15.

66. Saadeh S, Cammell G, Carey WD, et al. The role of liver biopsy in chronic hepatitis C. Hepatology 2001;33(1):196-200.

67. Andriulli A, Persico M, Iacobellis A, et al. Treatment of patients with HCV infection with or without liver biopsy. J Viral Hepat 2004;11(6):536-42.

68. Garcia G, Keeffe EB. Liver biopsy in chronic hepatitis C: routine or selective. Am J Gastroenterol 2001;96(11):3053-5.

69. Raikou M, McGuire A. Estimating medical care costs under conditions of censoring. J Health Econ 2004;23(3):443-70.

70. Lin DY, Feuer EJ, Etzioni R, et al. Estimating medical costs from incomplete follow-up data. Biometrics 1997;53(2):419-34.

71. O'Hagan A, Stevens JW. On estimators of medical costs with censored data. J Health Econ 2004;23(3):615-25.

72. Young TA. Estimating mean total costs in the presence of censoring: a comparative assessment of methods. Pharmacoeconomics 2005;23(12):1229-42.

73. Doshi JA, Glick HA, Polsky D. Analyses of cost data in economic evaluations conducted alongside randomized controlled trials. Value Health 2006;9(5):334-40.

74. Lin DY. Linear regression analysis of censored medical costs. Biostatistics 2000;1(1):35-47.

75. Willan AR, Lin DY, Manca A. Regression methods for cost-effectiveness analysis with censored data. Stat Med 2005;24(1):131-45.

76. Wooldridge JM. Introductory econometrics: a modern approach Stamford, CT: South-Western College Publishing; 2000.

77. Sloan FA, Bethel MA, Ruiz DJ, et al. The growing burden of diabetes mellitus in the US elderly population. Arch Intern Med 2008;168(2):192-9.

78. Nguyen GC, Segev DL, Thuluvath PJ. Nationwide increase in hospitalizations and hepatitis C among inpatients with cirrhosis and sequelae of portal hypertension. Clinical Gastroenterology and Hepatology 2007;5(9):1092-9.

79. Lindsay KL, Trepo C, Heintges T, et al. A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. Hepatology 2001;34(2):395-403.

80. Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology 2007;45(3):579-87.

81. Wong JB, Davis GL, McHutchison JG, et al. Economic and clinical effects of evaluating rapid viral response to peginterferon alfa-2b plus ribavirin for the initial treatment of chronic hepatitis C. Am J Gastroenterol 2003;98(11):2354-62.

82. Collett D. Modelling Survival Data in Medical Research 2nd ed. Boca Raton: Chapman & Hall/CRC; 2003.

83. Di Bisceglie AM, Shiffman ML, Everson GT, et al. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. N Engl J Med 2008;359(23):2429-41.

84. Kaiser S, Lutze B, Werner Rea. Long-term low dose treatment with pegylated interferon alpha 2b for 6 years leads to a significant reduction in fibrosis and inflammatory score in a subgroup of chronic hepatitis C nonresponder patients with fibrosis or cirrhosis In: AASLD; 2008; San Francisco; 2008.

85. Mihm U, Herrmann E, Sarrazin C, et al. Review article: predicting response in hepatitis C virus therapy. Aliment Pharmacol Ther 2006;23(8):1043-54.

86. Shiffman ML, Di Bisceglie AM, Lindsay KL, et al. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. Gastroenterology 2004;126(4):1015-23.

87. Shiffman ML, Ghany MG, Morgan TR, et al. Impact of reducing peginterferon alfa-2a and ribavirin dose during retreatment in patients with chronic hepatitis C. Gastroenterology 2007;132(1):103-12.

88. Metwally MA, Zein CO, Zein NN. Regression of hepatic fibrosis and cirrhosis in patients with chronic hepatitis C treated with interferon-based therapy. Gastroenterology 2003;124(5):1561.

89. Mallet V, Gilgenkrantz H, Serpaggi J, et al. Brief communication: the relationship of regression of cirrhosis to outcome in chronic hepatitis C. Ann Intern Med 2008;149(6):399-403.

90. Wiesner R, Sorrell M, Villamil F, et al. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. Liver Transpl 2003;9(11):S1-9.

91. Forns X, Garcia-Retortillo M, Serrano T, et al. Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver transplantation. J Hepatol 2003;39:389–96.

92. Thomas R, Brems J, Guzman-Hartman G, et al. Infection with chronic hepatitis C virus and liver transplantation: a role for interferon therapy before transplantation. Liver Transpl 2003;9:905–15.

93. Everson G, Trotter J, Forman L, et al. Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy. Hepatology 2005;42:255–62.

94. D'Souza R, Sabin C, Foster G. Insulin resistance plays a significant role in liver fibrosis in chronic hepatitis C and in the response to antiviral therapy. . Am J Gastroenterol 2005;100:1509–15.

95. Romero-Gómez M, Del Mar Viloria M, Andrade RJ. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. . Gastroenterology 2005;128:636–41.

96. Kuehne FC, Bethe U, Freedberg K, et al. Treatment for hepatitis C virus in human immunodeficiency virus-infected patients: clinical benefits and cost-effectiveness. Arch Intern Med 2002;162(22):2545-56.

97. Campos NG, Salomon JA, Servoss JC, et al. Cost-effectiveness of treatment for hepatitis C in an urban cohort co-infected with HIV. Am J Med 2007;120(3):272-9.

98. Shepherd J, Jones J, Hartwell D, et al. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. Health Technol Assess 2007;11(11):1-205, iii.

99. Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 2003;38(6):1449-57.

100. Fraenkel L, Chodkowski D, Lim J, et al. Patients' Preferences for Treatment of Hepatitis C. Med Decis Making 2009.

101. Neymark N, Adriaenssen I, Gorlia T, et al. Estimating survival gain for economic evaluations with survival time as principle endpoint: A cost-effectiveness analysis of adding early hormonal therapy to radiotherapy in patients with locally advanced prostate cancer. Health Econ 2002;11:233-48.

102. Willan AR, Lin DY, Cook RJ, et al. Using inverse-weighting in cost-effectiveness analysis with censored data. Stat Methods Med Res 2002;11(6):539-51.

BIOGRAPHICAL SKETCH

Chien-Ning Hsu was born in Kaohsiung, Taiwan. She received a Master of Science degree in clinical pharmacy from National Taiwan University, Taipei in 1996. Her thesis title was "Drug use evaluation and preliminary cost analysis of uncomplicated appendectomy clinical path." She continued her clinical pharmacy fellowship for two years at National Taiwan University Hospital. During that time, she gained experience and skills in pharmacotherapy and disease management in several areas including critical care, infectious disease, nephrology, and organ transplantation.

She worked in the drug regulatory agency, Center for Drug Evaluation (CDE) in Taiwan for 3 years before she began her doctoral program in Pharmaceutical Outcomes and Policy at the University of Florida, College of Pharmacy. She served as a project manager in the new drug application (NDA) and investigational new drug (IND) review processes. Chien-Ning has authored and coauthored peer-reviewed publications and presented at national and international academic conferences. She is interested in evaluating the appropriateness of drug use and health outcomes with special regard to economic consequences.