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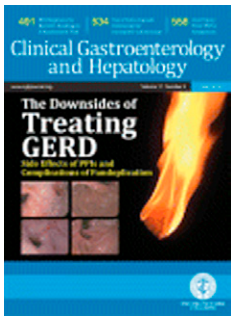

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PII: S1542-3565(13)00705-2

DOI: 10.1016/j.cgh.2013.05.014

Reference: YJCGH 53338

To appear in: *Clinical Gastroenterology and Hepatology*

Received Date: 20 December 2012

Revised Date: 17 April 2013

Accepted Date: 10 May 2013

Please cite this article as: Chan K, Lai MN, Groessl EJ, Hanchate AD, Wong JB, Clark JA, Asch SM, Gifford AL, Ho SB, Cost-Effectiveness Analysis of Direct-Acting Antiviral Therapy for Treatment-Naïve Patients with Chronic Hepatitis C Genotype 1 Infection in the Veterans Health Administration, *Clinical Gastroenterology and Hepatology* (2013), doi: 10.1016/j.cgh.2013.05.014.

Cost-Effectiveness Analysis of Direct-Acting Antiviral Therapy for Treatment-Naïve Patients with Chronic Hepatitis C Genotype 1 Infection in the Veterans Health Administration

Short title: DAA cost effectiveness in VHA

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Grant Support: Department of Veterans Affairs HSR&D Quality Enhancement Research Initiative RRP 10-228

Abbreviations: Boc, boceprevir; DAA, direct-acting antiviral; HCV, hepatitis C virus; ICER, incremental cost effectiveness ratio; PR, pegylated interferon alfa and ribavirin; Tel, telaprevir; VHA, Veterans Health Administration

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Disclosures:
Samuel B. Ho, MD: research and grant support: Genetech, Inc., Vital Therapies, Inc., Aspire Bariatrics, Inc.; Expert panel fees: Roche Pharmaceuticals, Inc.
Other authors: nothing to disclose.

Author Contributions:

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ABSTRACT

BACKGROUND AND AIM: The Veterans Health Administration (VHA) is the largest single provider of care for hepatitis C virus (HCV) infection in the US. We analyzed the cost-effectiveness of treatment with the HCV protease inhibitors boceprevir and telaprevir in a defined managed care population of 102,851 patients with untreated chronic genotype 1 infection.

METHODS: We used a decision-analytic Markov model to examine 4 strategies: standard dual-therapy with pegylated interferon-alfa and ribavirin (PR), the combination of boceprevir and PR triple therapy, the combination of telaprevir and PR, or no antiviral treatment; sensitivity analysis was performed. Sources of data included published rates of disease progression, the census bureau, and VHA pharmacy and hospitalization cost databases.

RESULTS: The estimated costs for treating each patient were $8000 for PR, $31,300 for boceprevier and PR, and $41,700 for telaprevir and PR. Assuming VHA treatment rates of 22% and optimal rates of sustained viral response, PR, boceprevir and PR, and telaprevir and PR would reduce relative liver-related deaths by 5.2%, 10.9%, and 11.5%, respectively. Increasing treatment rates to 50% would reduce liver-related deaths by 12%, 24.7%, and 26.1%, respectively. The incremental cost-effectiveness ratios were $29,184/quality of adjusted-life years (QALY) for boceprevir and PR and $44,247/QALY for telaprevir and PR vs only PR. With the current 22% treatment rate, total system-wide costs to adopt boceprevir and PR or telaprevir and PR would range from $708 million to $943 million.

CONCLUSIONS: Despite substantial upfront costs of treating HCV-infected patients in the VHA with PR, or telaprevir and PR, each regimen improves quality of life and extends life

expectancy, by reducing liver-related morbidity and mortality, and should be cost effective. Further efforts to expand access to direct-acting antiviral therapy are warranted.

KEYWORDS: liver disease; cirrhosis; prevention; health care costs

INTRODUCTION

The Veterans Health Administration (VHA) is the largest single provider of hepatitis C (HCV) care in the United States. Between 2000 and 2008, 287,410 Veterans in VHA care screened positive for antibodies to HCV and 189,065 (65%) were identified with chronic HCV infection. Of these, 80% have genotype 1 infection, and the large majority has never received antiviral treatment[1-3]. Population projections suggest increasing HCV burden from progression to cirrhosis and development of hepatocellular carcinoma and liver failure [4]. Consequently, the VHA and other healthcare systems expect a substantial rise in health care costs for patients with complications from HCV-related complications in the near future. Antiviral treatment has been shown to eradicate the HCV virus and thus, reduce the complications and mortality from liver disease in HCV patients [5-9]. Available since 2001, pegylated interferon combined with ribavirin resulted in 41-44% sustained viral response (SVR) rates for genotype 1 in clinical trials [10, 11] with lower real-world SVR rates[3].

In 2011, the FDA approved two new HCV protease inhibitors, Telaprevir and Boceprevir, for use in combination with the previous standard of care pegylated interferon alfa and ribavirin (PR). These drugs represent a new category known as direct acting antivirals (DAA). Phase III clinical trials demonstrate improvement in SVR rates for genotype 1: 68-75% for treatment-naïve patients, and 53% for patients that have failed previous PR treatment [12-15]. In addition, these SVR rates can be obtained with a shorter duration of therapy (24-28 weeks) in a larger proportion of patients. However, these new treatment regimens are considerably more expensive than the previous standard of care, and the overall impact on the population of HCV genotype 1 patients in the VHA remains unknown. The VHA represents a unique population of patients with HCV, with an increased prevalence of patients with more advanced fibrosis and

other characteristics that correlate with both decreased antiviral treatment response and increased long-term morbidities. Further data are needed to determine the relative costs and benefits of new therapies in this population [1, 3]. Cost analyses within the VHA are relevant to managed care systems and practices with disadvantaged populations.

The objective of our research is to investigate the estimated costs and effects of the new DAA triple therapy in VHA medical practice. The target population for this analysis is the current cohort of viremic and untreated chronic hepatitis C genotype 1 patients in the VHA system. We use a decision analytic model based on natural history data and progression rates to estimate the current distribution of fibrosis among VHA patients with HCV. Sensitivity analyses examine the impact of variation in drug costs, treatment efficacy, overall treatment rates, transition probabilities, and annual disease costs on the results of the model. The results presented will assist policymakers, stakeholders, clinicians, and patients at the VHA and similar managed care systems to critically evaluate the costs and benefits of the emerging DAA therapies.

METHODS:

Strategies in Decision-Analytic Model

A decision-analytic Markov model was constructed to evaluate the disease and antiviral costs associated with different drug therapies strategies to the VHA healthcare system (Figure 1), using transition probabilities from published literature as described below. We compared the cost and the effectiveness of no antiviral HCV treatment versus three currently FDA approved treatment strategies with availability in VHA medical centers: (1) pegylated interferon alfa and ribavirin dual therapy (PR) (2) Boceprevir (Boc) and PR triple therapy, and (3) Telaprevir (Tel) and PR triple therapy. Our main outcomes measures were lifetime costs, life expectancy, projected clinical outcomes, and the incremental cost-effectiveness ratios between the different treatment strategies.

Markov Models Transition State

Figure 1 displays the Markov model of the natural history model of chronic HCV [4, 16-18], representing the possible progression of a typical patient with HCV. The detailed procedural steps in the development of our model design and ascertainment of data input are described in the Technical Appendix.

VHA target population characteristics

To determine the number of active viremic patients with hepatitis C in the VHA, we used the VA Hepatitis C Clinical Case Registry, a centralized database including diagnostic codes, and laboratory, pharmacy and demographic data (http://vaww.hepatitis.va.gov/data-reports/ccr-index.asp) [19], which incorporates data from VISTA (Veterans Health Information Systems and

Technology Architecture) and CPRS (Computerized Patient Record System) from 128 reporting facilities. We estimated current fibrosis stage distribution on our VHA patient population by applying standard fibrosis progression rates from the medical literature[21] to averages of published fibrosis distributions of VHA hepatitis C patient populations. (Technical Appendix and Supplemental Tables 1). Projected SVR rates expected in VHA patients and estimated duration of antiviral treatments were derived from previous studies (Technical Appendix and Supplemental Tables 2-3).

Transition Probabilities.

There are no published natural history studies of fibrosis progression rates in VHA patients, therefore, transition probabilities for the different health states were obtained from the medical literature and published studies (Table 2), including a meta-analysis of fibrosis progression rates in patients with chronic hepatitis C [20]. The Markov model projected this pattern until all the individuals were in the death state resulting from liver related death or from death from age and sex determined natural history death rates [21]. For patients undergoing antiviral treatment we estimated the SVR rates and assumed that patients with cirrhosis with a SVR have markedly reduced rates of subsequent decompensated disease and HCC, based on recent long term follow up studies [5-9].

Cost and Health Care Resource Utilization Data

Cost associated with each health state in the Markov model included inpatient stays, outpatient visits, laboratory tests, and medications utilized by the patient for the different therapy

strategies. The primary sources were obtained from 1) published data, 2) national VHA administrative data (inpatient, outpatient and pharmacy) of health care resources, 3) published and unpublished VHA clinical care utilization data for treated patients with hepatitis C[17, 22-25, 26], and 4) HERC cost data [22, 25]. The costs of antiviral medications were obtained from the publicly available Federal Schedule Supply pricing displayed in the drug monographs available at the Veterans Affairs Pharmacy Benefits Management Services website (www.pbm.va.gov), and reflects pricing of antiviral drugs as of September 2011. (Technical Appendix and Supplemental Tables 4-5).

Utilities

To compare the effectiveness in term of quality of adjusted-life years (QALYs) between the strategies, we used the utilities associated with the different health states derived from actual patients with chronic hepatitis C derived by Chong et al [27] (Supplemental Table 4). These were measured by HUI-3, which was chosen because it is widely used, is derived from actual patients, and it is more comprehensive than the shorter EQ5D. Adverse side effects associated with both PR and DAA antiviral treatment decreased each health state utility value by 0.05[28]. Since a range of utilities are possible, for example potential increased side effects with different antiviral therapies, we used a sensitivity analysis to test a range of utilities that encompass other previous reported values in chronic hepatitis C studies[22, 27, 28].

Data Analysis.

TreeAge Pro software (TreeAge Software, Williamstown, MA) was used to calculate the costs and life expectancies associated with each Markov cycle [29, 30]. By tracking each individual

in our hypothetical cohort until death, the software calculates the average life expectancy, quality-adjusted life expectancy and lifetime costs for the cohort[29]. The incremental cost-effectiveness ratio (ICER) is calculated by rank ordering strategies from low to high cost and then taking the difference in total cost between strategy 1 and strategy 2 then dividing by the difference in health outcomes from strategy 1 and strategy 2 to yield

$$\text{ICER} = \frac{\text{Cost strategy 1} - \text{Cost strategy 2}}{\text{Effectiveness strategy 1} - \text{Effectiveness strategy 2}}$$

The analysis is taken from a VHA healthcare organizational perspective and does not account for out-of-pocket patient and time-related cost factors except for those incorporated in quality of life adjustments. Following the recommendations of the US Panel on Cost-Effectiveness in Health and Medicine [31], we discounted costs and QALY at an annual rate of 3%.

Sensitivity Analysis.

Sensitivity analyses were performed to assess the extent to which uncertainties in our assumptions affected results. The ranges for our sensitivity analyses were derived from medical literature. We assessed the cost impact due to the range of variability on multiple parameters, using a probabilistic sensitivity analysis assuming a Gaussian distribution for the different ranges. Parameters tested included: 1) SVR rates (calculated range), 2) transition probabilities (95% confidence intervals if available and ranges of 50%-150% if 95% confidence interval were not available), utilities of different HCV states (95% confidence intervals), and 4) costs of care for HCV states with ranges spanning from 50% to 150% of base costs.

RESULTS

Baseline Treatment Results

The target population included 102,851 patients with HCV genotype 1 infection in VHA as of 2010 who were not previously treated, with an average age of approximately 58 years and 97% male. Estimates of baseline fibrosis in VHA patients were made from prior published case series, and initial probabilities for fibrosis were estimated to be 4.2% (F0), 18% (F1), 22.2% (F2), 27.6% (F3), and 28% (F4) (Technical Appendix and Supplemental Table 1). Under the four different strategies, we calculated and compared lifetime health outcomes for a range of potential SVR rates (44-57%) estimated from actual VHA antiviral treatment experience and phase III trial results (Supplemental Tables 2,3), using a range of possible lifetime treatment rates (22-50%) for the cohort of 102,851 HCV genotype 1 treatment naïve patients. Compared to no treatment, use of standard PR therapy in the patient population at the treatment rate of 22% previously achieved among VA patients initiated on antiviral therapy between 2000-2008[1, 19] will decrease overall liver-related mortality by 5.0% (Table 2 and Figure 2). In contrast, treatment with DAA triple therapies at this same treatment rate, assuming the highest expected SVR rates (Boc/PR 54 % and Tel/PR 57%), will result in a 10.4 to 11.0% reduction in liver related death, respectively. If a treatment rates with PR, Boc/PR or Tel/PR can be increased to 50% of patients, the long-term reduction liver-related deaths will be 11.4%, 23.7% and 25.0%, respectively.

Cost and cost-effectiveness of antiviral treatments

With the previously achieved inital treatment rate of 22 %, total system-wide costs to adopt Boc/PR or Tel/PR would be $708 million and $943 million, respectively. Increasing treatment rates to 50% would result in the total cost of antiviral therapies PR, Boc/PR and Tel/PR treatment to be $411 million, $1,610 million and $2,144 million, respectively (Figure 3). Without antiviral treatment, the expected total cost of care for hepatitis C-related liver disease is $3,729 million. Compared with no treatment using PR at a 50% treatment rate results in overall cost savings of $30 million over the VHA cohort lifetime. In contrast, using Boc/PR or Tel/PR at a 50% treatment rate results in net cost expenditures of $692 million or $1,175 million, respectively.

The estimated cost and effectiveness (QALY) for the average treatment-naïve genotype 1 VHA patient and the incremental cost effectiveness ratio of DAA triple therapies compared with no therapy and PR therapy are given in Table 3A. Assuming the higher estimated SVR rates, the ICER for BocPR vs. PR = $29,184/QALY gained and TelPR vs. PR = $44,247/QALY gained.

Erythropoetin use was considered optional in the Boc licensing trial and not used in Tel licensing trials, and no SVR data is available for patients treated with TelPR when erythropoietin is used. Table 3B demonstrates the changes in ICER for DAA and PR therapies if potential costs of erythropoietin are included, which is common in clinical practice, although not universal.

For comparison purposes, the corresponding ICERs calculated using the average wholesale prices for Ribavirin, Peginterferon alfa, Boceprevir and Telaprevir are listed in Supplemental Table 6. The cost effectiveness for the four treatment strategies based on patient age and fibrosis stage are listed in Supplemental Table 7, and indicate that treating subgroups with younger age and more advanced fibrosis stage will be more cost-effective. As of 2010

there were approximately 21,466 genotype 1 patients that failed previous interferon treatment in the VHA. There is little data available concerning treatment of prior PR treatment failures in VHA populations, therefore we have used data from published phase III trials to make preliminary estimates related to incremental cost effectiveness ratios of DAA re-treatment in this patient population (Technical Appendix and Supplemental Table 8) [14, 15, 32].

Sensitivity Analyses

To evaluate the robustness and sensitivity of our parameters used in our models, we conducted a series of one-way sensitivity analyses on different factors. The upper and lower limit of the range that are most sensitive in affecting the ICER are compared between dual therapy vs. BocPR (Figure 3A) and dual therapy vs. TelPR (Figure 3B). The ICER between triple therapy and dual therapy is most sensitive to quality of life for the SVR state, quality of life for chronic hepatitis C, SVR rate of triple therapy, transitional probabilities from F4 to HCC and F4 to decompensation. Future research in VHA populations to obtain accurate data related to quality of life will improve our ability to more accurately define the cost effectiveness of DAA treatments. Supplemental Figure 1 illustrates a sensitivity analyses of the effect on ICERs related to a range of possible costs for DAA therapies and a range of possible SVR rates of Boc/PR and Tel/PR in the VHA system. The results of varying possible transition probabilities from decompensated cirrhosis to liver transplantation in VHA are indicated in the Technical Appendix.

DISCUSSION

Our model projects cost-effectiveness analysis of the new DAAs therapy in the veteran population. Our simulated cohort of 102,851 treatment-naïve US veteran patients with HCV genotype 1 infection had more than 2-fold reduction in liver related death when they were treated with either Boc/PR or Tel/PR strategies compared to treatment with PR alone. When we used VHA contract FSS pricing, the incremental cost effectiveness ratio (ICER) of Boc/PR and Tel/PR compared with PR are $29,184/QALY gained and $44,247/QALY gained, respectively. The ICER of Boc/PR and Tel/PR compared to no treatment are $15,027/QALY gained and $24,467/QALY gained, respectively. For patients in their 40's and 50's with early fibrosis stage 1 and 2, the ICERs for DAA treatments compared with PR are within the oft cited $50,000/QALY gained threshold for consideration of acceptable ICERs for medical interventions. Our results indicate that these therapies are cost-effective for the majority of US veteran patients.

Other recent studies have showed similar cost-effectiveness results using wholesale pricing of the new DAA therapy. Liu et al. used average wholesale pricing for DAA therapy of $1100 per week [33]. They projected the ICER of triple therapy vs. dual therapy would be $102,600 for patients with mild fibrosis and $51,000 for patients with advanced fibrosis, which is considerably higher than our projected cost effectiveness as would be expected given their higher pharmaceutical costs. Strategies to improve the ICERs of HCV antiviral treatments in the community setting may include selecting patients (such as those with advanced fibrosis) who would be more likely to benefit from therapy. In addition, they evaluated the use of the strategy of IL28 genotyping to guide therapy, with IL28 CC genotypes receiving PR therapy first. IL28-guided triple therapy treatment strategy results in reduced ICER for triple therapy treatment,

although reductions in lifetime decompensated cirrhosis and HCC obtained with this strategy were only approximately 83% of those achieved with universal triple therapy. Recent data has demonstrated that IL28 CC patients treated with Tel/PR for 12 weeks achieve a 100% SVR rate compared with 64% SVR for these patients treated with PR for 48 weeks[34]. These data appear to mitigate the benefits of an IL28-guided strategy and lessen the likelihood that this would be an acceptable clinical alternative, yet further efforts to select patients most likely to benefit would be warranted under these scenarios. Further comparisons and limitations of our study are listed in the Technical Appendix.

We accounted for uncertainties regarding DAA treatment by estimating a range of possible SVR rates based on SVR rates attained in the VHA population with dual therapy pegylated interferon alfa and ribavirin. A recent meta-analysis by Cooper et al. compared SVR rates of BocPR and TelPR based on all data from phase II and phase III trials using a network meta-analysis and indirect comparisons to relative risk for SVR, and resulted in similar results as our analysis using phase III trial data[35]. For estimating duration of therapy with DAA treatments we used data from registration trials to calculate the percentage of patients with early treatment discontinuation and the percentage eligible to receive shorter durations of therapy. Because data from the Boceprevir registration trial was reported for Non-black and Black populations separately, we adjusted the treatment duration estimates for the known Non-black and Black patient distribution in VHA HCV patients, and therefore this data may be more accurate than the estimated treatment durations obtained from the Telaprevir registration trial.

A critical question for health care systems is the percentage of patients that are able to receive current antiviral therapies. Our data reflects the optimistic treatment rate of 50%, with the potential consequence of a 24-25% reduction in liver-related deaths. Such treatment rates in

a VHA population may be attained with the use of integrated care protocols, which have surpassed 40% of VHA patients with pre-existing risk factors for psychiatric and substance use conditions in a recent study[36, 37]. Future interferon-free regimens are likely necessary for maximizing the number of HCV patients that can receive antiviral therapy.

In conclusion, our model indicates the upfront costs required for treatment with Boc/PR or Tel/PR are high; however the offsetting benefits of extending quality of life and lower costs due to liver-related morbidity indicate that these therapies have very acceptable incremental cost-effectiveness ratios compared to previous therapies in this managed care health care system. Further efforts to expand access to DAA therapy are warranted. In our study, we evaluated cost effectiveness of DAA treatment strategies in a defined managed care population with pharmaceutical pricing based on large group negotiated prices. In the future, integrated care systems may be more common with the evolution of the Affordable Care Act and similar heath care reforms[38], and drug pricing advantages will play an important role in determining overall cost effectiveness of new medications. In addition, our data is more relevant to health care systems in other countries with similar large group negotiated prices.

Cost-effectiveness ratios are one very important, but not sufficient, factor for making health policy decisions. Other factors such as system adaptability, budgetary issues, and patient preferences should also be considered in addition to our findings. This model will continue to be of use to evaluate future DAA therapies for HCV treatment, which may demonstrate increased efficacy albeit with significant costs.

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Table 1. Transition probabilities

Initial state	Progression to	Transition probabilities		
		base value	**lower limit**	**upper limit**
F0	F1	0.117[20]	0.104	0.13
F1	F2	0.085 [20]	0.075	0.096
F2	F3	0.12[20]	0.109	0.133
F3	F4	0.116[20]	0.104	0.129
F4	Decompensated	0.0637[39]	0.0318	0.0955
F4	HCC	0.0336[39]	0.0168	0.0504
Decompensated	OLT	0.023[4, 40]	0.012	0.035
HCC -1st year, for patients<65 years old	OLT	0.04 [41]	0.02	0.06
F4 (post SVR)	HCC	0.01 [5, 7]	0.005	0.015
F4 (post SVR)	Decompensated	0.00[5, 7]	0.00	0.00
Decompensated cirrhosis, year 1	Death	0.14 [42]	0.07	0.21
Decompensated cirrhosis, year 2+	Death	0.103 [42]	0.0515	0.1545
HCC Year 1	Death	0.53 [43]	0.27	0.80
HCC Year 2+	Death	0.26 [43]	0.13	0.39
Post-OLT, year1	Death	0.11 [44]	0.055	0.165
post-OLT year2+	Death	0.0375 [44]	0.019	0.056
Non HCV-related death	Death	Adjusted U.S life tables [21] (for VHA patients)		

Table 2. Project Lifetime Outcomes (numbers of patients)

	No therapy	Dual therapy		BocPR		BocPR		TelPR		TelPR	
SVR rate	0%	26%		45%		54%		44%		57%	
Treatment rate		22%	50%	22%	50%	22%	50%	22%	50%	22%	50%
DC	29,135	27,468	25,347	26,237	22,550	25,673	21,268	26,295	22,681	25,481	20,831
HCC	15,368	14,736	13,932	14,270	12,872	14,056	12,387	14,292	12,922	13,983	12,221
OLT	3,036	2,864	2,645	2,737	2,356	2,679	2,224	2,743	2,370	2,659	2,179
Liver death	30,828	29,282	27,314	28,140	24,718	27,617	23,530	28,193	24,841	27,438	23,125
Reduction in Liver Death %		5.0%	11.4%	8.7%	19.8%	10.4%	23.7%	8.5%	19.4%	11.0%	25.0%

DC = decompensated cirrhosis; HCC=hepatocellular cancer; OLT = orthotopic liver transplant

Table 3A. Cost, Effectiveness, and Incremental Cost-Effectiveness Ratio (ICER) **without** cost of EPO

	No treatment	**Dual therapy**	**BOC+PR**		**TEL+PR**	
SVR rates	0%	26%	45%	54%	44%	57%
Cost	38,189	37,337	54,107	51,112	64,801	60,478
QALY	8.297	8.685	9.009	9.157	8.994	9.208
Life-year gained	14.177	14.836	15.323	15.546	15.3	15.622

Incremental Cost-Effectiveness Ratio (ICER) between different strategies

	If SVR for BocPR=45% and TelPR=44%	**If SVR rates for BocPR = 54% and Tel+ PR = 57%**
BocPR vs No Treatment	$ 22,357/QALY	$ 15,027/QALY
TelPR vs. No Treatment	$ 38,181/QALY	$ 24,467/QALY
BocPR vs Dual Therapy	$ 51,759/QALY	$ 29,184/QALY
TelPR vs. Dual Therapy	$ 88,880/QALY	$ 44,247/QALY

TnQTable5Incremental Cost-Effectiveness Ratio (ICER) between different strategies

	If SVR for BocPR=45% and TelPR=44%	**If SVR for BocPR=54% and TelPR=57%**
BocPR vs. no treatment	$31,747/QALY	$22,776
TelPR vs. No treatment	$38,181/QALY	$24,467
BocPR vs. Dual Therapy	$57,552/QALY	$33,161
TelPR vs. Dual Therapy	$73,388/QALY	$35,094

FIGURE LEGENDS

Figure 1 Decision tree and Markov model (A). Decision tree describing different strategies with their associated outcomes. All the branches of the decision tree will terminate into the Markov process that follows up patients long term. (B). Markov model describing transitions of patients to different states of health. Note, the model also incorporates competing or non-HCV-related mortality risks (not pictured).

Figure 2. Outcomes and Costs for DAA therapies in the VHA. (A). The number of cases for decompensated, HCC, Liver Transplantation, and Liver-related death were compared for antiviral treatment rate of 21 % vs. 50% with assumed overall SVR for BocPR = 54% and TelPR = 57%. DC = decompensated cirrhosis; HCC=hepatocellular cancer; OLT = orthotopic liver transplant. (B). Total annual costs of HCV medical care for 102,851 genotype 1 treatment naïve VHA patients, assuming a potential treatment rate of 50%, a discounted rate of 3%/year, and SVR rates BocPR = 54% and TelPR = 57%. Treatment strategies include: 1) no treatment, 2) PR dual therapy, 3) BocPR, and 4) TelPR. The proportion of care includes cost associated with antiviral therapy, compensated, decompensated, HCC, and liver transplantation.

Figure 3. One-way Sensitivity Analyses were compared between (A) dual PR vs. BocPR and (B) dual PR vs. TelPR treatments in order to determine the critical parameters and their range that are sensitive for ICERs. The four parameters utility of SVR state, utility of chronic hepatitis C, SVR rate of DAA/PR therapy, and transition probability of F4 to HCC have the most significant affect on ICERs. Range of parameters used for Quality of Life (QoL), SVR rates, transition rate probabilities are listed in Tables 2,3, supplementary table 2A.

Figure 1.

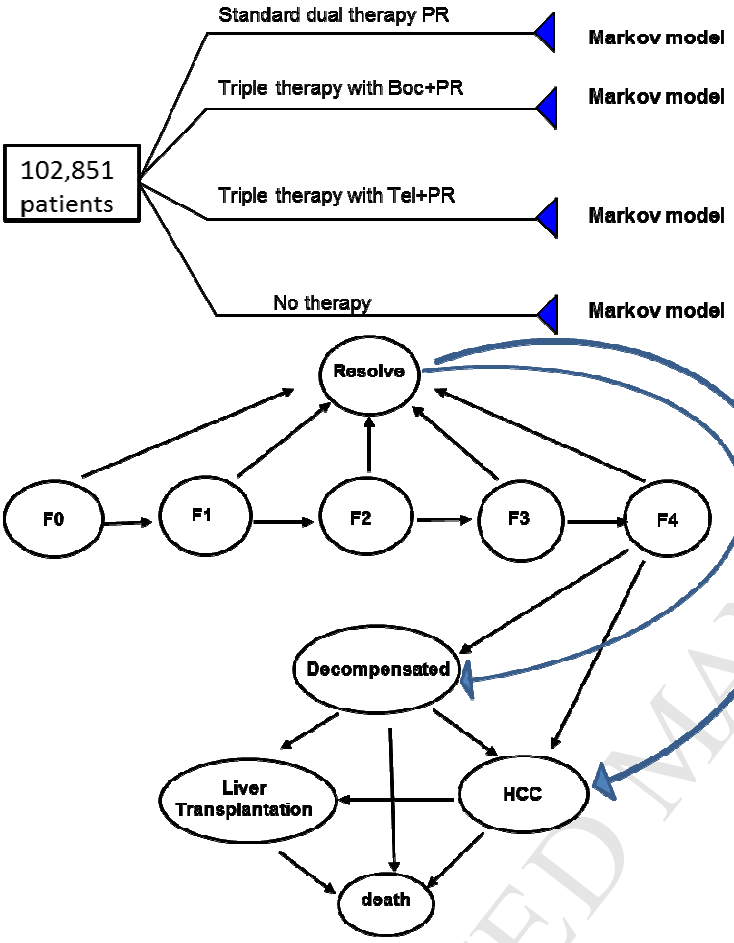
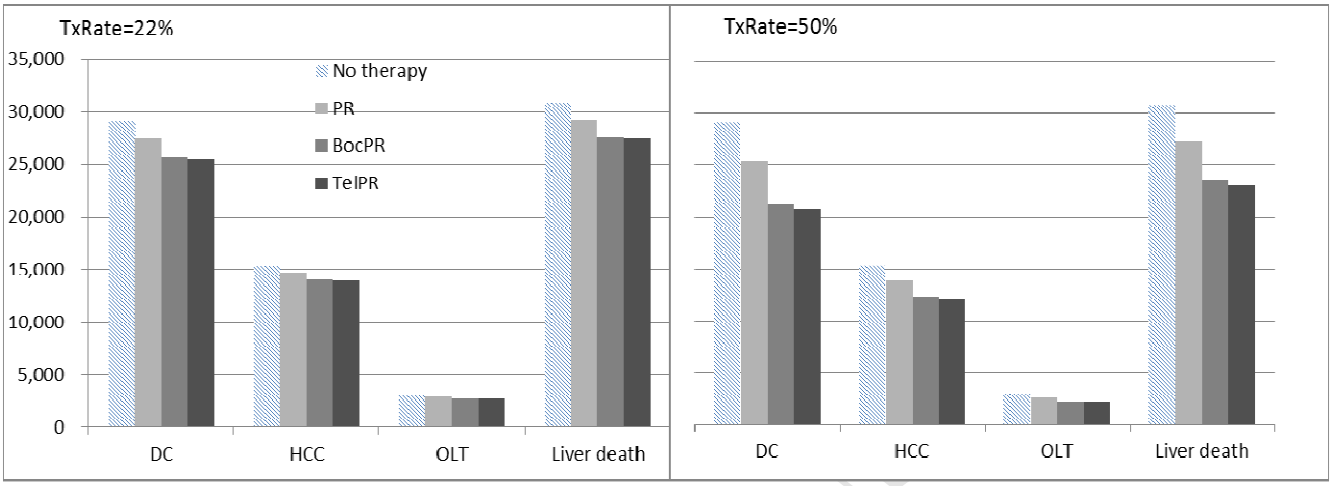


Figure 2

A.


TxRate=22%
TxRate=50%
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
No therapy
PR
BocPR
TelPR
DC
HCC
OLT
Liver death

B.

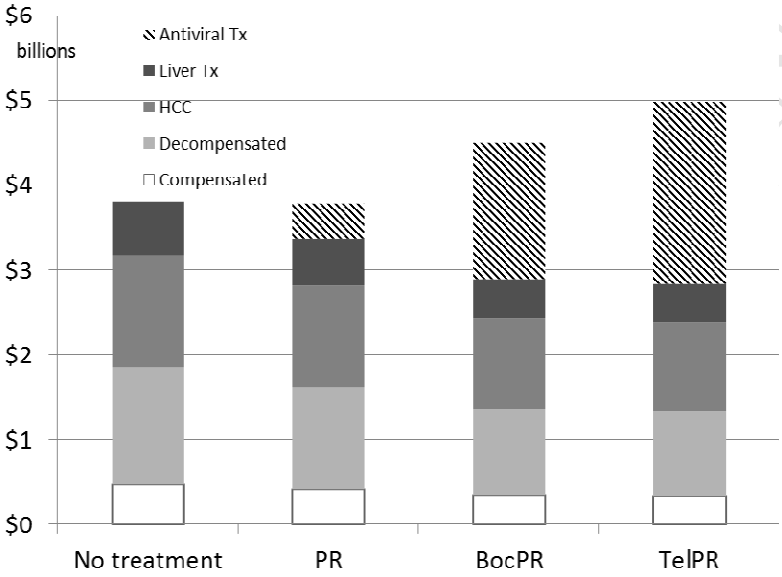
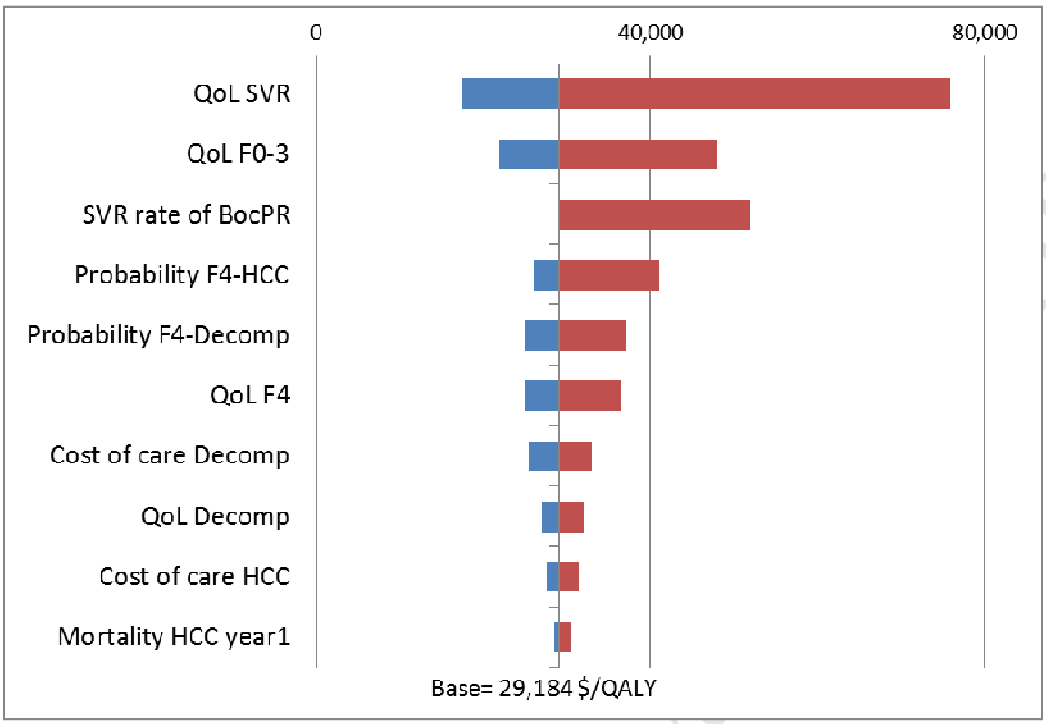

$6
billions
$5
$4
$3
$2
$1
$0
Antiviral Tx
Liver Tx
HCC
Decompensated
Compensated
No treatment
PR
BocPR
TelPR

Figure 3.

A. BocPR vs. PR



B. TelPR vs. PR