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QUERI

Assessment of Alternative Treatment Strategies for Chronic Genotype 1 Hepatitis C

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PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help to:

- develop clinical policies informed by evidence
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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BACKGROUND

There is great potential to improve health outcomes for Veterans and other patients with chronic genotype 1 (GT1) Hepatitis C (HCV) infections through the use of newly-available triple combination therapies that include directly acting antivirals (DAA) along with recently developed patient genotyping (IL-28B) which is predictive of HCV treatment response. Chronic GT1 HCV infections have been historically difficult to treat, with low cure rates on standard two drug therapy (Pegylated Interferon + Ribavirin), high rates of side-effects and treatment discontinuation, and low rates of uptake. Recently, FDA approved two DAAs (boceprevir and telaprevir). Used in combination with standard two drug therapy as triple therapy, these DAAs show higher rates of sustained viral response, though they are also more costly and have more severe side-effect profiles. IL-28B genotyping can help to identify patients least likely to respond to standard therapy and hence who stand to benefit the most from triple therapy and for whom, therefore, the increased risks of side-effects may be most justified.

METHODS

We addressed four related questions:

- Key Question #1: What are the current usage patterns of directly acting antivirals and of IL-28B patient genotyping in the VA health system? And how do these patterns differ by VISN?
- Key Question #2: What will be the health impacts of using either of two available directly acting antivirals combined with pegylated interferon and ribavirin (triple therapy)?
- Key Question #3: How will be the magnitudes of the health impacts measured in Key Question #2 change if IL-28B patient genotyping is used to offer triple therapy to those less likely to benefit from two-drug pegylated interferon + ribavirin?
- Key Question #4: What will be the cost and resource use patterns when using either triple therapy or IL-28B-guided triple therapy?

We used analysis of observational data and decision analysis to answer these questions over a 5 year time horizon, all in comparison to health outcomes and costs if standard two-drug treatment were continued without adoption of either of the new technologies. Importantly, these results are appropriate for short-term budgeting and planning considerations but are not appropriate for formal cost-effectiveness analyses as they do not represent the full costs and benefits experienced over a life time.

PEER REVIEW

A draft version of this report was reviewed by six technical experts, as well as clinical leadership. Reviewer comments were addressed and our responses were incorporated in the final report (Appendix A)

RESULTS

Key Question #1: What are the current usage patterns of directly acting antivirals and of IL-28B patient genotyping in the VA health system? And how do these patterns differ by VISN?

Between July 2011 and June 2012 nearly 3,000 people initiated DAA treatment, with approximately 80% using on-formulary boceprevir (Boceprevir N=2,366, Telaprevir N=501). During this same period, 2,171 individuals had an IL-28B test. There was heterogeneity in the number of people taking up DAA therapies and IL-28B testing across VISNs.

VISNs differed in their rate of use of IL-28B testing in patients receiving DAAs, with a national average just above 10 percent. VISN 22 had the greatest number of IL-28B tests, while VISNs 8, 16, and 21 had the greatest number of patients initiating DAA therapy. In some VISNs there are more patients initiating DAA therapy than getting IL-28B tests, while in other VISNs the reverse was true. Seven VISNs used testing in five percent or less of patients receiving DAA medications, whereas three VISNs tested 30 percent or more of their patients.

The median length of boceprevir treatments was just under 28 weeks. Of those who initiated boceprevir, 89% continued to 8 weeks, 81% to 12 weeks, 76% to 16 weeks, and 29% to 32 weeks. Telaprevir treatment episodes were much shorter per its therapeutic protocol. The median length of telaprevir treatment was between 12 and 16 weeks. None lasted beyond 28 weeks.

Key Question #2: What will be the health impacts of using either of two available directly acting antivirals combined with pegylated interferon and ribavirin (triple therapy)?

We used simulation modeling analysis over five years to project the likely effect of universal triple therapy compared to standard therapy. Universal triple therapy was likely to reduce the annual number of cases of decompensated cirrhosis by 10-29 (current uptake: 10; doubled uptake: 29; quadrupled uptake: 50), the annual number of cases of hepatocellular carcinoma by 5-16 (current: 5; doubled: 16; quadrupled: 27) and the annual number of liver transplants by 0-1 (current: 0; doubled: 1; quadrupled: 2). Compared to standard therapy, adoption of universal triple therapy is likely to increase the annual number of quality adjusted life years (QALYs) by 148-213 (current: 148; doubled: 213; quadrupled: 322).

Key Question #3: How will the magnitudes of the health impacts measured in Key Question #2 change if IL-28B patient genotyping is used to offer triple therapy to those less likely to benefit from two-drug pegylated interferon + ribavirin?

We used simulation modeling analysis over 5 years to compare IL-28B guided triple therapy to standard two-drug therapy. IL-28B guide triple therapy was likely to reduce the annual

number of cases of decompensated cirrhosis by 8-26 (current uptake: 8; doubled uptake: 26; quadrupled uptake: 45), annual cases of hepatocellular carcinoma by 4-14 (current: 4; doubled: 14; quadrupled: 25), and annual numbers of liver transplants by 0-1 (current: 0; doubled: 1; quadrupled: 2). Compared to standard therapy, IB-28B guided triple therapy is likely to result in an annual increase in QALYs of 110-145 (current: 110; doubled: 145; quadrupled: 225).

Key Question #4: What will be the cost and resource use patterns when using either triple therapy or IL-28B-guided triple therapy?

Based on our simulation modeling analysis, replacement of standard two-drug therapy with triple therapy was likely to increase total expenditures for HCV treatment and care for individuals with GT1 HCV by $32-$100 million annually, depending on treatment strategy and uptake patterns. At the current uptake rate of 2 percent per year, universal triple drug therapy would be expected to cost $43 million more than standard two-drug therapy. IL-28B guided therapy would cost $32 million more.

ABBREVIATIONS TABLE

Abbreviation	Meaning
DAA	Directly Acting Antiviral
DSS	Decision Support System
FDA	U.S. Food and Drug Administration
FY	Fiscal Year
GT1	Genotype 1
HCV	Hepatitis C Virus
IEN	Internal Entry Number
IL-28B	Interleukin 28-B
NDC	National Drug Code
PEG	Pegylated Interferon
QALY	Quality Adjusted Life Year
RIB	Ribavirin
SVR	Sustained Viral Response
VISN	Veterans Integrated Service Network

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EVIDENCE REPORT

INTRODUCTION

There is great potential to improve health outcomes for Veterans and other patients with chronic genotype 1 (GT1) Hepatitis C (HCV) infections through the use of newly-available directly acting antiviral (DAA) medications and patient genotyping (IL-28B). Chronic GT1 HCV infections have been historically difficult to treat with low cure rates on standard two drug therapy (Pegylated Interferon + Ribavirin), high rates of side-effects and treatment discontinuation, and low rates of uptake. Recently, FDA approved two DAAs (boceprevir and telaprevir). Used in combination with standard two drug therapy as triple therapy, these DAAs show higher rates of sustained viral response, though they are also more costly and have more severe side-effect profiles. IL-28B genotyping can help to identify patients least likely to respond to standard therapy and hence who stand to benefit the most from triple therapy and for whom, therefore, the increased risks of side-effects may be most justified.

To achieve the potential health benefits from DAAs and IL-28B genotyping while acknowledging very real budgetary and resource constraints, proactive planning supported by appropriate analyses is needed. VA added boceprevir to its formulary approximately a year ago, allows the use of telaprevir off formulary for a number of reasons, and has the capability to use IL-28B patient genotyping as well. Responding to a request for guidance submitted to the VA Evidence-based Synthesis Program (ESP), we undertook a set of preliminary studies aimed at providing rapid, timely estimates of cost, resource and health impacts of using DAAs and/or IL-28B genotyping within VA over a 5 year time horizon.

Specifically, we addressed four related questions:

- Key Question #1: What are the current usage patterns of directly acting antivirals and of IL-28B patient genotyping in the VA health system? And how do these patterns differ by VISN?
- Key Question #2: What will be the health impacts of using either of two available directly acting antivirals combined with pegylated interferon and ribavirin (triple therapy)?
- Key Question #3: How will the magnitudes of the health impacts measured in Question #2 change if IL-28B patient genotyping is used to offer triple therapy to those less likely to benefit from two-drug pegylated interferon + ribavirin?
- Key Question #4: What will be the cost and resource use patterns when using either triple therapy or IL-28B-guided triple therapy?

We answered these questions over a 5 year time horizon, comparing health outcomes and costs of standard two-drug treatment to adoption of these new technologies. Importantly, these results are appropriate for short-term budgeting and planning considerations but they should not be used for formal cost-effectiveness analyses as they do not represent the full costs and benefits experienced over a life time.

METHODS

We undertook three main activities to answer these questions.

First, we performed an observational analysis of VA data to evaluate the uptake, use, and costs of therapies for HCV. This characterized the current state of DAA and IL-28B testing within VA in roughly the first year since adoption. Observational analysis was also used to estimate the cost of care for patients with liver disease.

Second, we adapted our previously-developed HCV computer model1 to more closely reflect VA patient populations with chronic GT1 HCV infections and patterns of HCV care in VA. In order to adapt this model, we performed a rapid literature review for chronic HCV-related studies from 2000-2012 that focused on VA populations. This review included peer-reviewed literature and for other reports. We performed preliminary analyses of VA administrative data to examine the usage patterns of DAAs and IL-28B in VA in the past year and the cost of care of patients with HCV. We used this information in the computer model so that it would reflect the VA patient population and care practices.

Third, using the adapted model, we then performed model-based projections of health outcomes and costs of alternative HCV treatment strategies.

ADAPTING PREVIOUSLY DEVELOPED HCV MODEL TO VA

Brief description of the HCV computer model

The computer simulation model of HCV we use here has been described in detail previously.[1] For convenience, we describe it here briefly. The model has two main parts:

1. Decision model that incorporates alternative treatment strategies for chronic GT1 HCV and potentially uses IL-28B genotyping to select the most appropriate treatment for a patient based on the IL-28B genotype results (Figure 1 Panel A).
2. HCV natural history model that projects the course of future health prior to initiating, during, and after treatment and also tracks clinical events, resource utilization, costs, morbidities, and mortality (Figure 1 Panel B).

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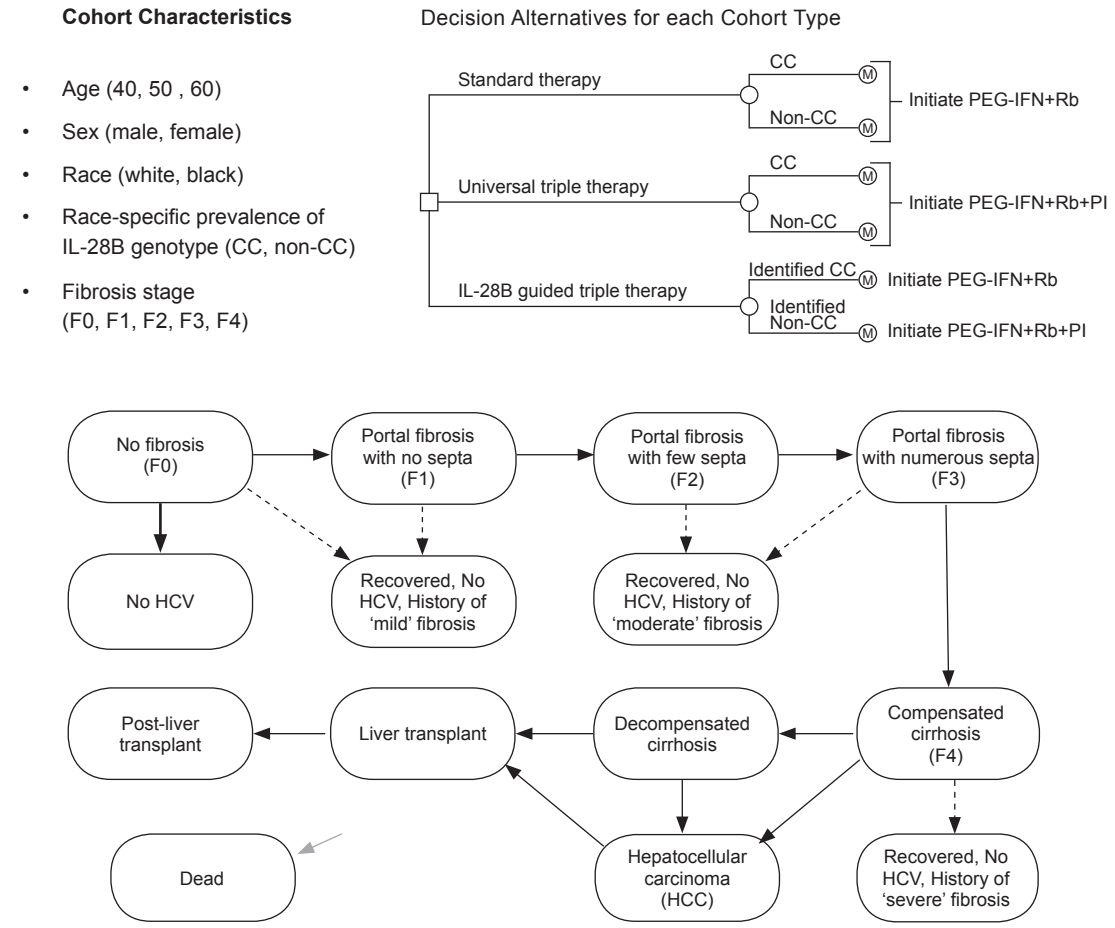
Figure 1. Decision Model (Panel A) and HCV Natural History Model (Panel B)



The model is stratified by a set of cohort characteristics including age, sex, race, IL-28B genotype, and stage of liver fibrosis (Metavir score F0-F4). While IL-28B genotypes include CC, CT, and TT, the similarity of response to therapy for CT and TT and the relatively limited amount of data on these types, especially when further stratified by race, led us to combine them into non-CC.

Three main strategies are included in the model. The first is standard therapy, the continued use of 48 weeks of Pegylated Interferon + Ribavirin for all patients regardless of IL-28B genotype (i.e., without genotyping them). The second strategy is universal triple therapy, the use of DAAs in combination triple therapy for all patients regardless of IL-28B genotype (i.e., without genotyping them). The third strategy considered is IL-28B guided triple therapy. In the strategy, patients are first tested for the IL-28B genotype. Patients with CC type are most likely to respond to standard therapy and are directed to the treatment. Those with non-CC types are provided with triple therapy. All strategies use specific response guided protocols (not shown). Models for all strategies include risks, costs, and quality-of-life reductions due to side-effects as well as the possibility of non-adherence and discontinuation above and beyond response guided protocols.

The HCV natural history model tracks individuals at 4 week intervals. During each interval, people have the chance of transition along the solid black arrows which represent progression through various states of liver fibrosis, advanced liver disease including decompensated cirrhosis,

hepatocellular carcinoma, and liver transplantation. At all times, people have an age, sex, and race specific risk of death with elevated risks for advanced liver disease. Successful treatment that leads to SVR and cure allows individuals to transition along the dashed arrows to "recovered" states that are stratified by fibrosis severity. In recovered states, individuals have lower mortality risks and lower ongoing medical care costs than in the corresponding states prior to recovery.

The model considers chronic GT1 HCV individuals who are HCV treatment naïve who do not have a co-occurring HIV infection.

Literature Review of Veteran-related Chronic HCV-related Studies from 2000-2012

We conducted a rapid evaluation of references for information on chronic HCV infection in U.S. Veterans. Because of the limited time available, we did not undertake the formal methods of a systematic literature review. We searched PubMed for published studies from 2000-2012 on topics that included both "chronic HCV" and "veterans." Identified abstracts were reviewed and full text of articles obtained. We further reviewed these articles' bibliographies for other important sources that the search may have missed. Additionally, we performed web searches and VA-specific website searches to locate VA reports and other public, non-journal-published data relevant to these topics. We then extracted information from these sources. When we combined information from the studies and sources described above, we gave precedence to recent studies, large studies, representative studies, and high-quality studies. We did not assess articles formally for quality and attempted to be as inclusive as possible. Articles were excluded that did not report provide sufficient detail on a needed parameter.

Mortality in Veterans regardless of HCV has been modeled actuarially as reflected in the VA's VetPop 2007 model (www.va.gov/VETDATA/Demographics/Demographics.asp).

Additional information on mortality relating to HCV and liver disease is reported in a number of studies.[23,29,31] We combined this information on VA-specific age and sex-stratified mortality rates, using NHANES (National Health and Nutrition Examination Survey) III linked estimates of hazard rate ratios for mortality due to HCV by race/ethnicity to reflect the background mortality patterns of individuals within VA with chronic HCV infections.

Preparing the Model for Performing Preliminary Projections on Cost and Outcomes for the VA's Chronic HCV GT1 Population

The preliminary resource analysis considered a representative cohort of chronic HCV GT1 infected individuals in VA. In the analysis, scenarios are considered that use DAAs (Key Question 2, Key Question 4) alone or with IL-28B patient genotyping (Key Question 3, Key Question 4) as an alternative to standard two drug therapy and in which treatment uptake may differ from the past. Each scenario examines the costs of delivering such treatments over a 5 year window of time as well as the health benefits within this 5 year window.

Importantly, costs and benefits are reported for these 5 particular years only. As they do not include subsequent costs or benefits beyond these 5 years, this analysis CANNOT be used to assess the cost-effectiveness of these treatment strategies. Cost-effectiveness analysis employs a lifetime time horizon, considering all costs and benefits over the patients' lifetimes.

Representative Cohort of Chronic HCV GT1 Infected Individuals in VA

We defined a representative cohort of chronic HCV GT1 infected individuals in VA based on published studies of VA HCV populations and other VA-specific documents and data that are described in the results.

Treatment-eligible Patient Population and Uptake Scenarios

To provide estimates of total costs due to DAAs and IL-28B genotyping, it is necessary to determine the size of the treatment-eligible patient population and likely patterns of treatment uptake. We then combined the update scenarios with the treatment-eligible population for analyses.

PRELIMINARY ANALYSES OF VA ADMINISTRATIVE DATA

The VA Health Economics Resource Center examined national data extracts from the VA Decision Support System (DSS) to identify use of DAA medications and IL-28B testing VA for the period of July 2011 through June 2012. Administrative data were also used to identify the size of the population with HCV infection. VA cost data from the 2010 federal fiscal year were analyzed to determine the cost of care for patients with different stages of liver disease.

VA Population with Chronic HCV Receiving VHA Care

The VA hospital discharge and outpatient visit files for the year ending 9/30/2011 were used to identify all persons who received at least one service that was assigned an ICD-9 diagnosis code for HCV. For this time period, the national prevalence of an HCV ICD-9 diagnosis code is approximately 2.6%.

Prescription Data on DAA Medication Use

The VA DSS National Data Extract of prescription data was analyzed for the use of DAA medications boceprevir or telaprevir. A record was considered to refer to a DAA if all of the following were true:

- National Drug Code (NDC) was for one of these DAA medications
- Internal entry number (IEN) from the VA drug file was for one of the DAA medications
- The DSS Intermediate Product (IPNUMBER) was either for a specific DAA or for a "new drug."

The text in the drug description field was not used to identify DAA medications. The text "telaprevir" did not appear in any record. The text "boceprevir" did not appear in the drug description field of these records until the 2012 fiscal year. An additional 169 records that had text description that included the string "boceprevir FY12", and DSS intermediate product number for pegylated interferon, were reviewed. Records that had a quantity of medication that was consistent with boceprevir were included in the analysis.

Data on IL-2B Genotype Testing Use

The DSS National Data Extract of laboratory orders was evaluated. All records with a laboratory test description containing the text "IL-28" were included in the analysis.

VISN-level Analyses

To enable VISN-level analyses, we assigned VISN number using the VISN recorded in the first record for a DAA prescription fill in the pharmacy data, or the first IL-28B test in the laboratory data. We used the first record in order to be consistent in characterizing number of new treatments and the length of treatment episodes. When we combined the lab data (on IL-28B testing) with prescription data (on DAA fills), if the VISN was not the same in the two sources, the conflict was resolved by using the VISN in the earlier record.

Key Question #1 Analysis Plan: What are the current usage patterns of directly acting antivirals and of IL-28B patient genotyping in the VA health system? And how do these patterns differ by VISN?

We divided this overarching question into a number of related sub-questions answered individually below.

Sub-question 1.1: How many people initiated DAAs during 07/1/11-06/30/12? How did this differ across VISNs? How has this changed since the introduction of DAAs into VA?

We created a person-level file using prescription records during the year 7/1/11-6/30/12. We summarized the data so that there was one record per patient. The summary record included a patient identifier, a variable to indicate if the patient initiated boceprevir, and the month when this medication was first dispensed. Each summary record also included a variable to indicate whether telaprevir was initiated and the month that this medication was first dispensed. This patient-level file was used to determine the number of unique persons initiating DAA, and the number initiating each medication.

Sub-question 1.2: How many unique people had an IL-28B test during 07/1/11-06/30/12? How did this differ across VISNs?

We created a person-level file from qualifying IL-28B laboratory records from the study year. The file included the patient identifier and an indicator that the patient received at least one IL-28B test during the study year. We report the total number of patients who had an IL-28B test.

Sub-question 1.3: Among people receiving DAA, how many had IL-28B testing? Among those with IL-28B testing, how many received DAA therapy? How does this differ across VISNs?

We approached this question in two ways. We first compared the counts of individuals initiating DAA therapy and being tested with IL-28B testing by VISN without examining whether the counts were of the same individuals or not. Second, we combined the person-level prescription and laboratory files from the study year, and created a 2 x 2 table to show the number receiving a DAA medication, an IL-28B test, or both. Note that the cell for neither is not included, as persons had to receive either a DAA medication or an IL-28B test to be included.

Sub-question 1.4: Among persons who initiated DAA treatment during the study year, what is the length of their treatment episode?

We examined how long individuals initiating DAAs were on treatment before ending it. From the data available, we could not ascertain the reason for ending treatment (e.g., treatment success, discontinuation because of an adverse event, etc.). Our analysis considered the incomplete nature of the data available. We extracted data from 7/1/2011 until 5/31/2012. In this analysis, we excluded data from June, 2012, to be certain that results would not be affected by possible incomplete processing of prescriptions filled at the end of the study period. We had between one month and one year of prescription data on those who initiated DAA treatment in this period.

We evaluated treatment duration using a method similar to a survival analysis. We used these data to characterize the percentage of persons with available data who were still in treatment at each interval of time. We created one record for each patient for each medication, and called this a treatment episode. We found the length of treatment and the length of follow-up. We ignored any treatment gaps resulting from delays in filling prescriptions in defining the duration of treatment. We use the following procedure:

First, we excluded cases with uncertain data. Most records reported the days' supply of medication that was dispensed. If this field was missing, we estimated the days of supply by dividing the quantity of drug by the recommended daily dose (12 pills for boceprevir or 6 pills for telaprevir). We excluded 3% of the records with a value of more than 90 days of supply dispensed at single prescription fill date.

Second, we then created an episode data base with one record for combination of person and drug (a small number of persons initiated treatment with both drugs, and when this occurred we included both starts in our data). Although data were extracted for the month of June, 2012, we excluded these data as we were uncertain if all records from that month had been processed. We created an episode database with the following variables:

- Medication: The medication for this episode, either boceprevir or telaprevir.
- Total days supply: The total day supply in all prescription fills.
- Days of treatment: The number of days of treatment was defined as the greater of two numbers: the total number of days' supply of medication that was dispensed, or the number of days between the date the prescription was first dispensed and the date that the last prescription would have been exhausted. The first number, days' supply of medication, represents the length of treatment in patients who were prompt in filling prescriptions. The second number represents the duration of treatment in patients who were not prompt in refilling prescriptions, and includes some days in which medication doses were missed.
- Medication possession ratio: The medication possession ratio was the total days of supply divided by the number of days from treatment initiation to exhaustion of last prescription. This number was less than 100% in patients who did not fill prescriptions on time. This number was more than 100% when prescriptions were

refilled promptly. In this case, there was an accumulated a supply of medication available to take when this last fill would otherwise have been exhausted.

- Days of follow-up: The days of follow-up was the number of days from treatment initiation to the end of follow-up (5/31/12), that is, the date that information about this treatment episode was censored by limits of the data extract. Episodes in which days of supply exceeded the days of follow-up are censored; there is insufficient information to know the length of that treatment episode. There is sufficient information to know that the treatment lasted at least as long as the number of days of follow-up.
- Month in which treatment was initiated: The month in which the first prescription was filled. We used this information to see if there was a trend in the number of individuals starting treatment.

Third, we characterized length of treatment, considering the limitation of follow-up. We considered the percentage of people who were still receiving the DAA in each 4 week interval (after 4 weeks, after 8 weeks, after 12 weeks, etc.). For each interval, we computed: 1) the denominator (number who could have been treated this long, that is, whose follow-up was not yet censored); and 2) the numerator (number actually treated this long). For example, we evaluated the episode database for boceprevir to see treatments that lasted at least 4 weeks. We counted as the denominator the number of persons still being followed, those who initiated treatment more than 28 days before the last date in the prescription data. We counted in the numerator the number of these persons (with 28 days of follow-up) who had at least 28 days of treatment. Note that it was possible for an individual to have more days of medication than days of follow-up, and that we only included in the numerator those eligible for the denominator. This analysis was repeated for subsequent 4 weeks intervals, until there were no more cases that met the criteria for the denominator (52 weeks).

Key Question #2: What will be the health impacts of using either of two available directly acting antivirals combined with pegylated interferon and ribavirin (triple therapy)?

The analytic plan for addressing Key Question #2 involved three steps:

1. Synthesizing VA-specific data into model-usable inputs: Information from administrative data analyses and literature reviews were combined to produce inputs usable by the model.
2. Running VA-specific cohorts through the simulation model under each treatment strategy at various rates of uptake for the new DAAs: Simulations were conducted using computers and TreeAge modeling software. Under each combination of treatment and uptake rate, the model produced a set of outputs that were then analyzed to address the Key Question.
3. Computing multiple, annual health impacts over a 5 year horizon: Improving treatment efficacy has the potential to ameliorate a variety of non-fatal and fatal outcomes. Non-fatal outcomes included decompensated cirrhosis, hepatocellular carcinoma, and the need for liver transplant. We considered mortality due to chronic HCV in general and to advanced liver disease in particular. We combined the effects of non-fatal and fatal outcomes into a single,

standard measure – quality-adjusted life years (QALYs). All outcomes were computed over a 5 year horizon and reflect the annualized difference between standard two-drug therapy and alternatives that included a DAA as part of HCV treatment. As the goal was to consider short-term effects within the VA Health System, results DO NOT consider lost life years or reduced quality-of-life for individuals in years after the 5 year horizon and therefore likely underestimate the full health benefits of patients' lifetimes.

Key Question #3: How will the magnitudes of the health impacts measured in Key Question #2 change if IL-28B patient genotyping is used to offer triple therapy to those less likely to benefit from two-drug pegylated interferon + ribavirin?

The analytic plan for Key Question #3 was the same as that of Key Question #2 except that instead of evaluating universal triple therapy, the treatment strategy that was evaluated was IL-28B patient genotyping to guide who receives standard two-drug therapy and who receives triple therapy with a DAA.

Key Question #4: What will be the cost and resource use patterns when using either triple therapy or IL-28B-guided triple therapy?

The analytic plan for Key Question #4 was the same as that of Key Questions #2 and #3 except that the cost impacts over a 5 year horizon were considered. This meant that costs of treatment, contingent on response guided therapy protocols and adherence, were tallied for individuals initiating treatment. Costs depended on treatment effectiveness, as the model tallied the effect of sustained viral response in averted treatment of advanced liver disease. Like health benefits, costs were only considered for a 5 year period. The effectiveness of treatment strategies after the 5 year horizon were not considered, and therefore the estimates are likely underestimate the full lifetime cost effects and do not represent lifetime horizon needed to estimate cost-effectiveness.

The costs of inpatient and outpatient care are based on relative values of the national average Medicare reimbursement rate, adjusted to correspond to actual VA expenditures (the HERC average cost estimates). These estimates were based on an analysis of cost of care provided to VA patients with HCV who received care in the 2010 federal fiscal year conducted by the Health Economics Resource Center. Pharmacy costs were based on data in the DSS prescription-level national data extract from the same period, with the exception of cost of DAA medications. All cost estimates include both the direct costs of care and the indirect (overhead) costs of providing that care.

PEER REVIEW

A draft version of this report was reviewed by six technical experts as well as clinical leadership. Their comments and our responses are presented in Appendix A.

RESULTS

RESULTS USED TO INFORM THE MODEL

Table 1 below shows the number of sources with information relevant to various parts of the topic.

Table 1. Number of Sources Identified for Each Model Attribute/Area

Attribute	# of Sources	Attribute	# of Sources
Age	28	Treatment eligibility	10
Sex	27	Treatment uptake	9
Race/ethnicity	25	Treatment completion	11
Fibrosis stage	11	Treatment effectiveness	13
HCV genotype	15	Side-effects	4
Liver transplant	2	HCV care costs	1
Liver cancer	3	Drug costs	1
Mortality	4	Side-effect costs	1
HCV clearance	4	Advanced liver disease costs	1
		Quality of life	8

We now describe the information from the published studies within the sources noted in the table above. Many studies describe the demographic and health characteristics of Veterans with chronic HCV infections. The mean age of individuals with chronic HCV infections is between 45-55 years in most studies with the majority in the low to mid 50s.[2–26] Most individuals with chronic HCV in VA are male, with study means falling between 90-100% with the majority at 97%.[2–4,6,7,9–19,21–25,27] Race/ethnicity reports tend to be complete in smaller clinical studies with substantial portions marked as missing or unknown in very large registry and administrative studies. Even so, if one looks at the proportion of White to African American individuals among those whose race/ethnicity is reported, there is reasonable stability across studies with a ratio of between 2.0:1 and 2.5:1 being common – hence for the analysis we assume that of African American and White individuals, the percentage that were White was assumed to be 69%.[2–4,6,11,13–16,18–21,23–28] HCV genotype is reported in a number of studies, though often not all individuals in the study have their HCV infection genotyped and sometimes genotypes 1 and 4 are grouped together as are genotypes 2 and 3. In these studies, typically 70-85% of chronic HCV infections are genotype 1.[2,5,7,10,11,13,15,17,19,22,24–27] Liver fibrosis stage distribution is important information that is not reported in many studies, with F0-F2 often grouped together and F3-F4 grouped together. In some studies, only F4 and decompensated cirrhosis are reported. Typically the F2 and F3 fibrosis stages are the most common in these studies.[6,7,10,13,17,19,24–27,29] Clearance rates of chronic HCV infection are reported in one study.[20] These data inputs to the model are summarized in Table 2, below.

Table 2. Demographic Characteristics Assumed for VA HCV GT1 Population

Model Input	Value
Age (years)	55
Sex	
Male	97%
Female	3%
Race	
White	69%
African American	31%
Fibrosis Distribution (see below for alternatives)	8%
F0	25%
F1	33%
F2	20%
F3	14%
F4	

Fewer studies provide detailed data on advanced liver disease. Few studies report data on liver transplantation, though a review of liver transplant outcomes in African Americans includes information on African American Veterans.[30] Likewise, there is relatively little information on hepatocellular carcinoma in the chronic HCV infected Veterans.[29–31] These data inputs to the model are summarized in Table 3, below.

Table 3. Transplantation for Advanced Liver Disease related to HCV

Model Input	Value	Sources/Notes
Rate of liver transplantation for individuals with decompensated cirrhosis (chronic genotype 1 HCV who are treatment eligible) (# per 100,000 person years)	2,500	Based on preliminary analyses of VA administrative data for 2010 prepared by HERC, it appears that approximately 0.5% have liver transplants within VA itself. However, these data rely on a very small sample size and only 6 months of follow-up on average. Specifically, among 16,234 VA patients with cirrhosis in FY10, 79 (.49%) had a liver transplant during the year. This count includes transplants provided by non-VA providers if these were sponsored by VA. Given that the model tracks post-transplant care within VA even if transplants themselves occur outside VA, we assume a higher rate so as not to undercount costs in the model.

Model Input	Value	Sources/Notes
Rate of liver transplantation for individuals with HCC (chronic genotype 1 HCV who are treatment eligible) (# per 100,000 person years)	8,000	Based on preliminary analyses of VA administrative data for 2010 prepared by HERC, it appears that approximately 0.5% have liver transplants within VA itself. However, these data rely on a very small sample size and only 6 months of follow-up on average. Specifically, among 2,883 VA patients with HCC in FY10, 42 (1.5%) had a liver transplant. This count includes transplants provided by non-VA providers if these were sponsored by VA. Given that the model tracks post-transplant care within VA even if transplants themselves occur outside VA, we assume a higher rate so as not to undercount costs in the model.

A number of studies provide information on HCV treatment-related parameters within VA. Consistent information on the proportion of Veterans who are treatment eligible is less available as the definition of treatment eligibility differs between studies and between clinician assessment as well as official VA guidance over time in this regard. In general, treatment eligibility ranges from approximately 30-55% and is most commonly in the 40-45% range,[2,4,7,15–18,27,28,32] though this may be somewhat lower in the VA population if the studies were conducted in populations who are more likely to be eligible for treatment. Studies on treatment uptake also are less straightforward to compare as some report uptake among those who are treatment eligible and some report on uptake among all participants. Furthermore, uptake is often reported as a cumulative percentage with different lengths of follow-up. Long-term uptake among treatment eligible individuals ranges from approximately 20-50% in studies with 30-35% being the most common.[2,4,7,10,15,17,18,27] For similar reasons, treatment completion rates reported in various studies are difficult to compare,[2,4,7,15,19,24,26–28,33,34] as are treatment success rates.[2,6,7,10,11,15,19,24,26–28,30,32,33] Given these challenges, we describe how we estimate treatment completion and success rates for the VA population we model below.

HCV treatment completion and success rate information for the VA population, especially for very recently introduced triple therapy that includes a DAA, is not readily available. We estimated these parameters using the following methods for both standard two-drug treatment and triple therapy. For both standard treatment and triple therapy, we used the race/ethnicity distributions derived as described in the preceding paragraphs. Because, treatment effectiveness was predicated on IL-28B genotype, we used the distribution of CC versus non-CC (CT and TT) IL-28B genotypes by race/ethnicity reported in Thompson (2010).[34]

For standard two-drug treatment, overall rates of treatment completion were similar across multiple studies within VA.[15,24,33] Because the data from Beste (2010) provides information on which individuals quit due to treatment failure versus an unspecified reason, we used this study in particular to estimate the overall rate of treatment non-completion for a reason other than treatment failure.[33] Butt (2010) showed that African Americans were 10% less likely to complete treatment than individuals of other races, so we calculated race-specific treatment non-completion rates.[4] Beste (2010) also identified the overall proportion of patients who terminated

treatment due to treatment failure at 12 and 24 weeks.[33] We estimated the race- and IL-28B-genotype stratified relative risks of treatment failure at 12 and 24 weeks based on Thompson (2010).[34] Using these new race- and IL-28B genotype-stratified probabilities of treatment failure at 12 and 24 weeks, we computed the race- and IL-28B genotype stratified rates of SVR for patients who completed 48 weeks of treatment such that these SVR rates satisfied race-specific SVR rate ratios for CC to non-CC types (Thompson 2010) and the overall intent to treat SVR rate observed in Kramer (2012) (i.e., 27% in non-African Americans and 15.8% in African Americans).[15] These data inputs to the model are summarized in Table 4, below.

For triple therapy, we used a very similar process to that for standard two-drug therapy. Importantly, no studies report on treatment completion rates for triple therapy in VA since these treatments have only recently been introduced. The assumptions we used, therefore, were less VA-specific than for standard two-drug therapy and more closely resembled our previously published analysis.[1] We assumed that patients do not complete treatment for reasons other than treatment failure at the same rate whether they are receiving standard or triple therapy, using standard therapy VA-specific discontinuation rates described above. We assumed that the race- and IL-28B-genotype specific 12 week treatment failure rate was the same for patients receiving standard or triple therapy, also as described above. These small changes in assumptions, while maintaining all of other assumptions from the prior analysis,[1] resulted in triple therapy intent to treat SVR rates of 48.9% in non-African Americans and 37.3% in African Americans. These data inputs to the model are summarized in Table 4, below.

Table 4. Treatment Parameters Estimates for the VA HCV GT1 Population

Model Input	Value for Whites	Value for African Americans
Treatment dropout rate (# per 100,000 person years)	37,040	48,534
Standard Two-Drug Therapy Parameters		
Early Virologic Response (EVR) at 12 weeks		
CC genotype	98%	97%
Non-CC genotype	91%	86%
Continue treatment beyond 24 weeks (conditional on EVR at 12 weeks)		
CC genotype	97%	89%
Non-CC genotype	86%	82%
Sustained Virologic Response (SVR) (conditional on 48 weeks of treatment)		
CC genotype	60%	60%
Non-CC genotype	34%	27%
Triple Therapy Parameters		
No virologic failure at 12 weeks		
CC genotype	98%	97%
Non-CC genotype	91%	86%

Model Input	Value for Whites	Value for African Americans
No virologic failure at 24 weeks (conditional on no failure at 12 weeks)	62%	48%
CC genotype	43%	48%
Non-CC genotype		
No virologic failure at 48 weeks (conditional on no failure at 12 weeks)		
CC genotype	28%	38%
Non-CC genotype	42%	38%
Sustained virologic response given 24 weeks of treatment		
CC genotype	98%	95%
Non-CC genotype	95%	89%
Sustained virologic response given 48 weeks of treatment		
CC genotype	75%	70%
Non-CC genotype	65%	60%

A number of studies report quality-of-life for Veterans with chronic HCV infections both for those not on treatment as well as those while on treatment (including rates of side-effects).[19,21,22,27,28,35–40]

Notably, very limited information appears in the published literature on the cost of HCV treatment and care for Veterans in VA. For costs we relied on prior communications with the Office of Pharmacy Benefits Management as well as preliminary analyses performed by HERC. Additionally, both for costs and other information, we relied on the VA State of Care report on HCV.[1] The cost data included in the model are summarized in Table 5, below.

Table 5. VA-specific Cost Inputs

Cost Type	Amount	Sources/Notes
Cost of Peg-RIB 48 weeks and care/monitoring during that time*	$15,281	Peg-RIB costs $9,120 to which we add costs of care during the 48 weeks of treatment of $6,161 (assuming a full 48 weeks) assumed to be 1.5 times the costs of HCV care prior to treatment success to account for other monitoring, etc.
Additional Cost of Boceprevir (24 weeks) (to be added to the Cost of Peg-RIB 48 weeks above)	$18,753	Assumed Boceprevir (provisional) FSS price is $3,125.49 per 28 day supply
Additional Cost of Telaprevir (12 weeks) (to be added to the Cost of Peg-RIB 48 weeks above)	$36,828	Assumed Telaprevir (provisional) FSS price is $12,276.10 per 28 day supply
Average adverse events costs 2 drug therapy	$1,920	

Cost Type	Amount	Sources/Notes
Average adverse events costs 3 drug therapies	$2,586	The mix of adverse events is different for Boceprevir and Telaprevir but the average costs (likelihood times cost of dealing with the side-effects, summed over all side-effects) for both drugs have been observed to be quite similar (see for example, Stephens, et. al. AASLD poster, 38).
Annual HCV care (w/o Peg-RIB or other treatment costs)	$4,450	HERC preliminary analysis of 2010 data: Since this is just care that is related to HCV and liver disease we take the difference of the total cost of care for people with uncomplicated chronic HCV ($11,486) and subtract the average cost of care for people in VA ($7,036)
Annual post-successful treatment HCV care costs	$2,225	HERC preliminary analysis of 2010 data, per note above: We assume that this care is roughly 50% of the cost of care prior to achieving treatment success as seen in studies not specific to VA HCV patient populations.
Annual decompensated cirrhosis care costs (w/o Peg-RIB or other Tx)	$13,093	HERC preliminary analysis of 2010 data, per note above: We subtract from the costs for those with decompensated cirrhosis ($20,129) the average costs of care for people in VA ($7,036).
Annual HCC costs (w/o Peg-RIB or other Tx)	$71,954	HERC preliminary analysis of 2010 data suggests an annual cost of $33,096 among all individuals, including those who died and did not complete full year of treatment. Since our cost is conditional on survival (model cycle length much shorter than 1 year), we used a VA report and other data that suggest a roughly 15% 3-year survival. *(http://www.hepatitis.va.gov/provider/reviews/HCC.asp* and Surveillance, Epidemiology and End Results (SEER)) which implies that the cost should be multiplied by [1.00/0.46], implying the cost of $71,954.
Year of Liver Transplant cost of care	$152,313	HERC preliminary analysis of 2010 data, adjusted for censoring of people who die and do not complete full year of treatment: $134,036 (using 1.00/0.88 again as the survival multiplier as above) Other sources suggest that costs are closer to: $250,000 but may include the transplant itself as well as a 7-day hospital stay. Still other sources suggest $150,000 - $250,000 range (*http://www.hepatitis.va.gov/pdf/feedback-forum.pdf from 2007*)

Cost Type	Amount	Sources/Notes
Years post Liver Transplant cost of care	$32,903	HERC preliminary analysis of 2010 data, adjusted for censoring of people who die and do not complete full year of treatment: $31,587 (here we use a 1.00/0.96 survival multiplier) Other sources suggest $12,000 as the annual medication cost alone (*http://www.hepatitis.va.gov/patient/complications/transplant-basics.asp*)

* Note: For the costs of treatment using response guided algorithms (i.e., triple therapies), costs are scaled for early stopping due to Early Virologic Response or failure to achieve sufficient reductions per response guided therapy in the model itself.

We defined a representative cohort of chronic HCV GT1 infected individuals in VA based on published studies of VA HCV populations and other VA-specific documents and data which are described in the results. The cohort's age is 55 years with 97% male, 69% white, and 31% African American. These characteristics as well as the liver fibrosis distribution assumed are shown in Table 2 above.

Treatment-eligible Patient Population

The total population of chronic HCV infected Veterans is approximately 189,065 according to the VA's State of Care 2010 report. The report also notes that this number has stayed stable over the preceding 5 years. Of these, based on the literature review, we assume that approximately 80% are genotype 1 HCV infections – the major genotype with the lowest overall response rate to standard two-drug therapy, for which DAAs appear to offer the greatest benefit, and in which they have been best studied to date. Of these individuals, again based on the literature review, approximately 45% are treatment-eligible. Finally, since the analysis focuses on treatment-naïve individuals and based on the State of Care 2010 report as well as the published literature, we assume that approximately 70% of individuals have not been treated previously.

$$8{,}000 \cong 189{,}065 * 0.80 * 0.45 * 0.70$$

Based on these calculations, the analysis uses an estimate of approximately 48,000 GT1 chronic HCV-infected, treatment-eligible, treatment-naïve Veterans for determining total costs and health benefits.

Uptake Scenarios

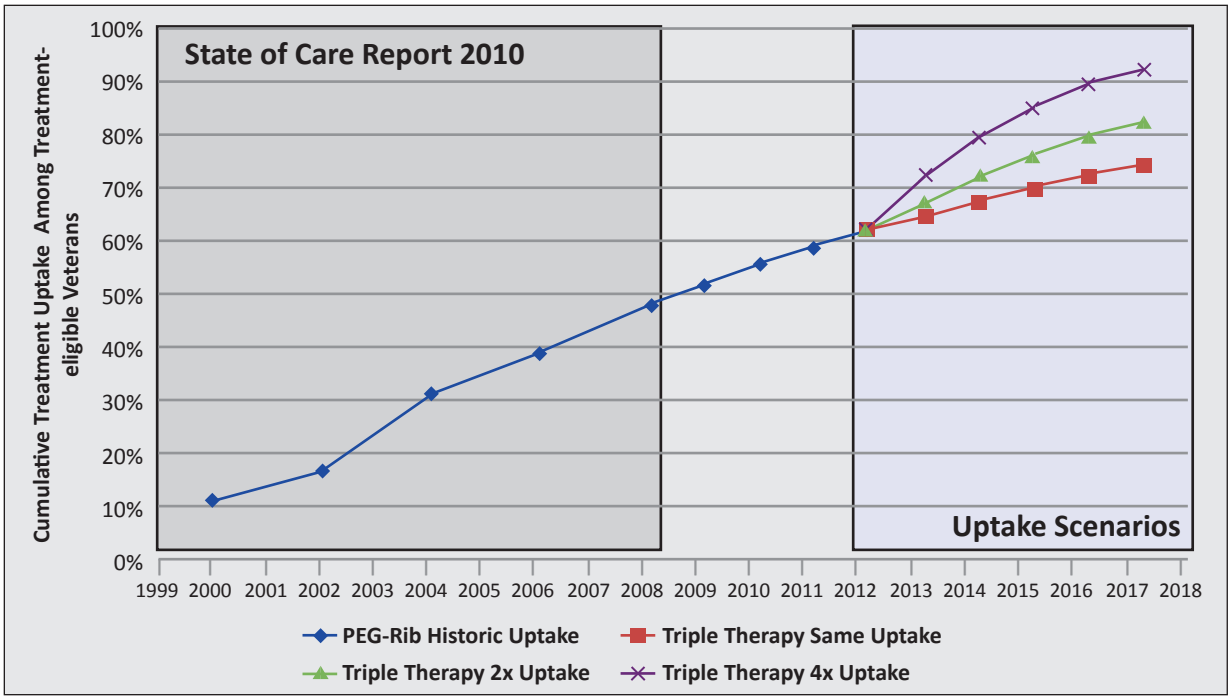
The analysis considered multiple uptake scenarios. In all scenarios, the comparator was standard two-drug therapy offered to all treatment-eligible patients with the assumption that 2% of this group took up therapy annually over the 5 year window considered in the analysis. Uptake scenarios considered the effects of DAAs possibly combined with IL-28B genotyping at three different levels of uptake:

- Approximately 2% of treatment-eligible chronic HCV GT1 infected Veterans take-up HCV treatment each year, similar to uptake rates for standard two-drug therapy

- Approximately 4% each year, double the uptake rates for standard two-drug therapy – slightly above those actually observed in VA towards the latter half of FY2008, based on the preliminary analyses reported below (Figure 2)
- Approximately 8% each year, quadruple the uptake rates for standard two-drug therapy

Multiple uptake scenarios were explored because future uptake is highly uncertain. There is little experience with DAAs and IL-28B genotyping as they have only recently become available in VA. The effect of newer treatments and technologies currently in clinical testing contributes to this uncertainty. Figure 2 below compares historical rates of uptake of standard two drug therapy to the uptake scenarios we consider for DAA strategies.

Figure 2. Cumulative Proportion of Treatment-eligible, Chronic HCV Individuals Taking Up Therapy



Combining Uptake Scenarios with the Treatment-eligible Population for Analyses

Table 6 estimates the number of individuals initiating treatment under each uptake scenario. The analyses consider what would happen over the next five years if the strategy was switched from standard two-drug therapy to each of the two other alternatives. Separate estimates are made for each strategy under each of the three uptake scenarios.

Table 6. Treatment Eligibility and Uptake over 5 Years (number of Veterans)

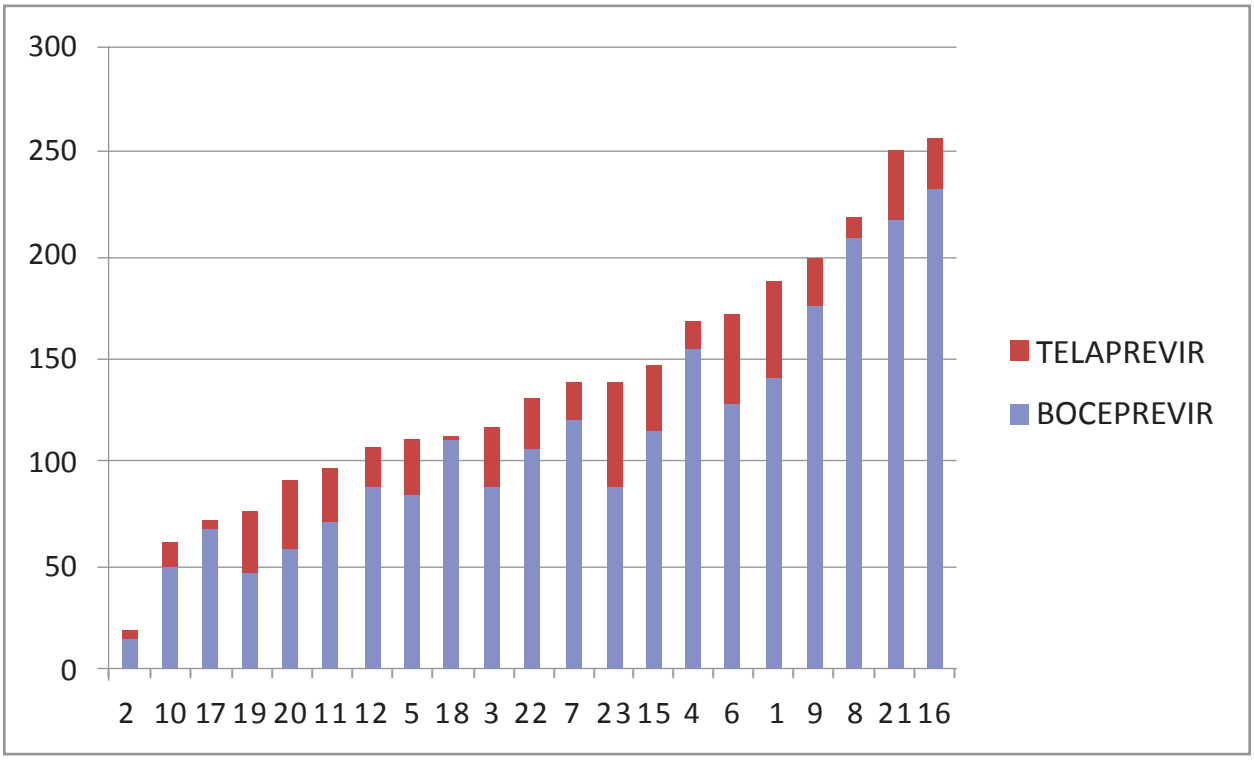
Veterans with HCV	189,065
Veterans with GT1 HCV	106,667
Veterans with GT1 HCV eligible for treatment	48,000
Current uptake rate (2%/year)	15,495
Doubled uptake rate (4%/year)	26,702
Quadrupled update rate (8%/year)	36,609

KEY QUESTION #1. What are the current usage patterns of directly acting antivirals and of IL-28B patient genotyping in the VA health system? And how do these patterns differ by VISN?

Sub-question 1.1: How many people initiated DAAs during 07/1/11-06/30/12? How did this differ across VISNs? How has this changed since the introduction of DAAs into VA?

Between July 2011 and June 2012 nearly 3,000 people initiated DAA treatment, with approximately 80% using on-formulary boceprevir (Boceprevir N=2,366, Telaprevir N=501). There was heterogeneity in the number of people taking up DAA therapies across VISNs (see Figure 3). Part of this difference must be attributed to differences in the number of treatment-eligible chronic HCV-infected Veterans in each VISN. Uptake of DAAs increased since July 2011, but seems to have stabilized at approximately 300 new people initiating DAAs per month. If the uptake pattern of approximately 300 per month continues over the next year, this would imply that approximately 3,000-4,000 new DAA treatments might be expected to be initiated annually, assuming January 2012 through May 2012 indicate longer-term average usage in VA of DAAs. This uptake rate is then slightly higher than the 3,393 standard two-drug (PEG-RIB) treatments initiated in 2008, as the State of Care 2010 report states.[41] It is however unclear if this uptake rate will continue in subsequent years (backlog vs. popularization vs. waiting for even newer drugs).

Figure 3. Uptake of DAA Therapies by VISN (x-axis denotes VISN number)

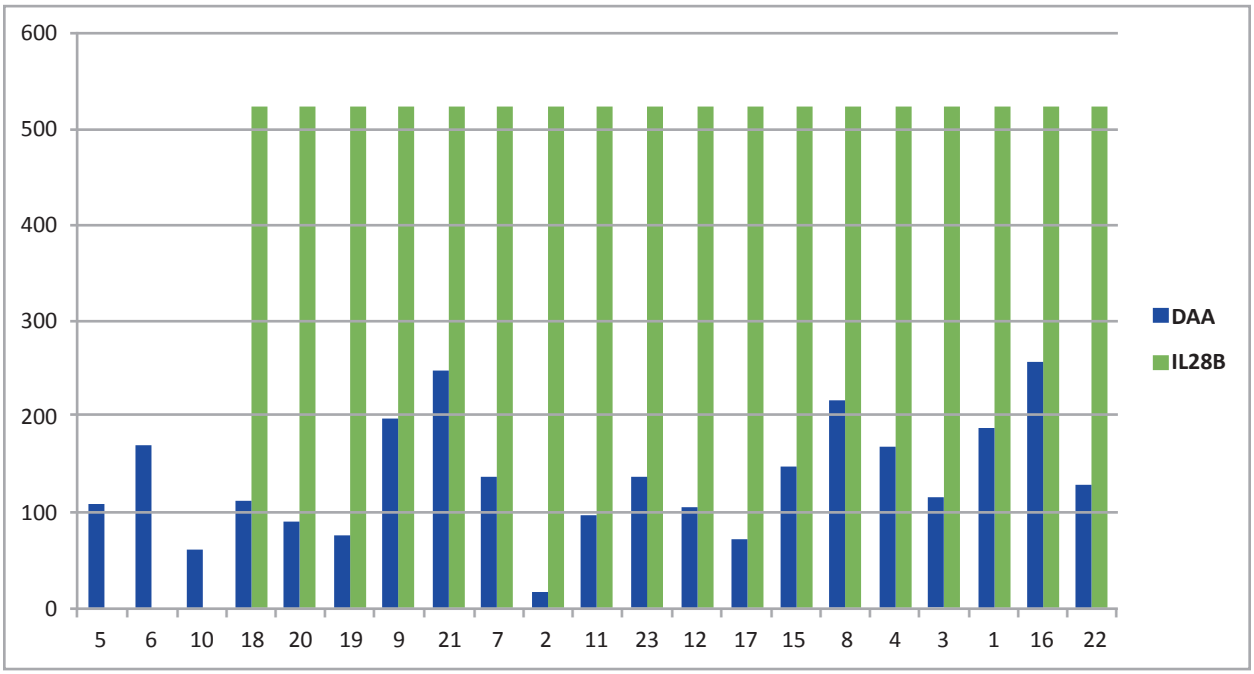


Sub-question 1.2: How many unique people had an IL-28B test during 07/1/11-06/30/12? How did this differ across VISNs?

During the period of interest, 2,171 individuals had an IL-28B test. Currently VA IL-28B tests are send-outs. There was heterogeneity in use of IL-28B testing across VISNs. Only part of this variation is explained by differences in the number of treatment-eligible chronic HCV-infected Veterans in each VISN. Use of IL-28B testing across VISNs is represented in light shading in Figure 4, below.

Sub-question 1.3: Among people receiving DAA, how many had IL-28B testing? Among those with IL-28B testing, how many received DAA therapy? How does this differ across VISNs?

Figure 4. Use of IL-28B Testing and DAAs by VISN



IL-28B testing is used for those not receiving DAAs, and DAAs are generally used without IL-28B genotyping. Only 306 patients used both, whereas 2,551 patients only used DAAs, and 1,865 patients only used IL-28B testing. VISNs differ on the rates of use of IL-28B testing in patients who received DAAs, with a national average just above 10 percent. VISN 22 had the greatest number of IL-28B tests, while VISNs 8, 16, and 21 had the greatest number of patients initiating DAA therapy. In some VISNs there were more patients initiating DAA therapy than getting IL-28B tests, while in other VISNs it was the reverse. Seven VISNs used testing in five percent or less of patients receiving DAA, whereas three VISNs used testing on 30 percent or more of these patients.

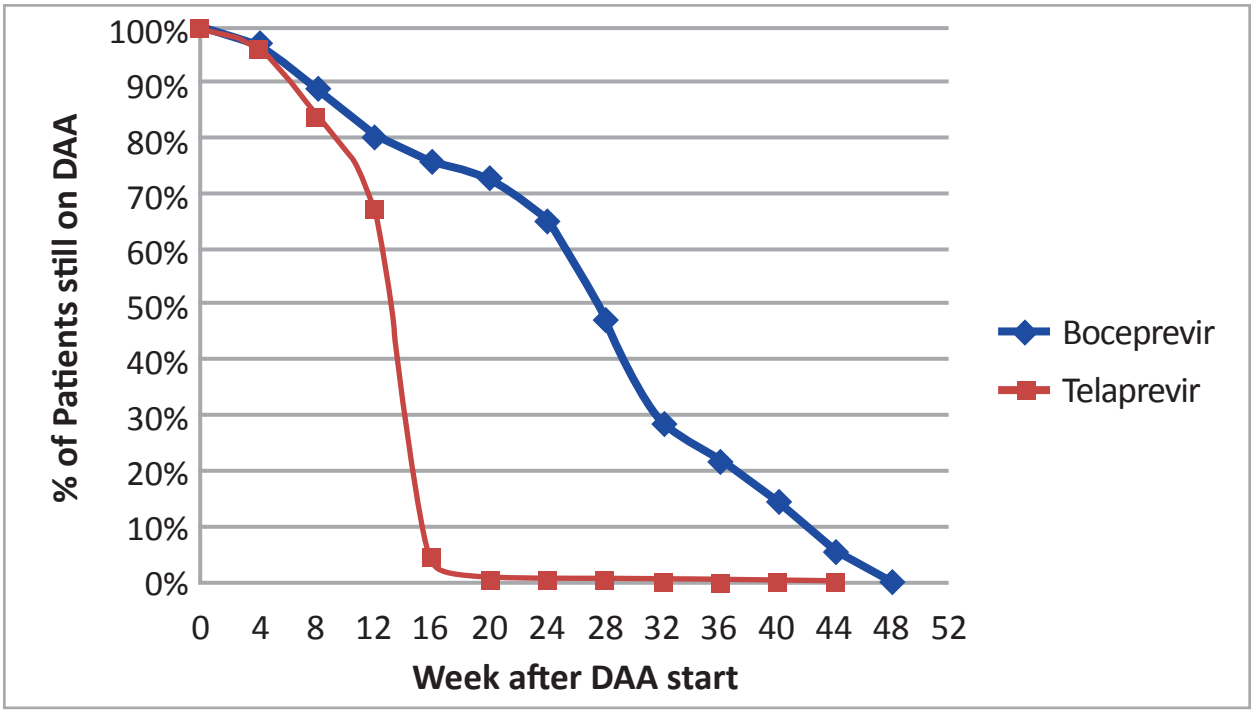
Using DAAs without information on a patient's IL-28B genotype was common in many VA care settings, although there was diversity of practice. The reasons for these differences remain to be explored. They may include other uses of the IL-28B information, such as trying to understand why a patient failed to achieve sustained virologic response to a previous treatment. Tests may be more common in some settings because they are easier to order, because some subgroups of providers are more familiar with their use, or because they are more appropriate in some patient subgroups.

Sub-question 1.4: Among persons who initiated DAA treatment during the study year, what is the length of their treatment episode?

The median length of boceprevir treatments was just under 28 weeks (see Figure 5). Of those who initiated boceprevir, 89% got to 8 weeks, 81% to 12 weeks, 76% to 16 weeks, and 29% to 32 weeks. Telaprevir episodes were much shorter per its therapeutic protocol. Median length of telaprevir treatments was between 12 and 16 weeks. None lasted beyond 28 weeks.

The medication possession ratio indicated that most patients were highly adherent and that those who continued in treatment filled prescriptions promptly.

Figure 5. The Days on Treatment for Each DAA Appear Reasonably in Line with Its Therapeutic Protocols



KEY QUESTION #2. What will be the health impacts of using either of two available directly acting antivirals combined with pegylated interferon and ribavirin (triple therapy)?

With our model, we compared universal triple therapy to standard two-drug therapy over a five year analysis period for eligible GT1 HCV patients (N=48,000) (see Table 7). This comparison was made for three potential uptake rates: the current uptake rate (two percent per year), a doubled uptake rate (four percent per year), and a quadrupled uptake rate (eight percent per year). When compared to standard therapy, universal triple therapy was likely to reduce annual cases of decompensated cirrhosis by 10-29 (current uptake: 10; doubled uptake: 29; quadrupled uptake: 50). When comparing universal triple therapy to standard therapy, annual cases of hepatocellular carcinoma were likely to be reduced by 5-16 (current: 5; doubled: 16; quadrupled: 27). Finally, when comparing universal triple therapy to standard therapy, annual numbers of liver transplants are likely to be reduced by 0-1 (current: 0; doubled: 1; quadrupled: 2). Consequently, annual quality adjusted life years (QALYs) increased by 148-213 (current: 148; doubled: 213; quadrupled: 322).

Table 7. Annual Effect of Universal Triple Therapy on Health Outcomes over 5 Years

	Current Uptake Rate (2%/yr)	2x Uptake Rate (4%/yr)	4x Uptake Rate (8%/yr)
Cases of Decompensated Cirrhosis	-10	-29	-50
Cases of Hepatocellular Carcinoma	-5	-16	-27
Number of Liver Transplants	0	-1	-2
Quality Adjusted Life Years	+148	+213	+322

N=48,000 eligible GT1 HCV

KEY QUESTION #3. How will the magnitudes of the health impacts measured in Key Question #2 change if IL-28B patient genotyping is used to offer triple therapy to those less likely to benefit from two-drug pegylated interferon + ribavirin?

Using our model, we also compared IL-28B-guided therapy to standard two-drug therapy over a five year analysis period for eligible GT1 HCV patients (N=48,000) (see Table 8). This comparison was made for the same three potential uptake rates: the current uptake rate (two percent per year), a doubled uptake rate (four percent per year), and a quadrupled uptake rate (eight percent per year). In these comparisons, annual cases of decompensated cirrhosis are likely to be reduced by 8-26 (current uptake: 8; doubled uptake: 26; quadrupled uptake: 45), annual cases of hepatocellular carcinoma are likely to be reduced by 4-14 (current: 4; doubled: 14; quadrupled: 25), and annual numbers of liver transplants are likely to be reduced by 0-1 (current: 0; doubled: 1; quadrupled: 2). Consequently, annual QALYs increased by 110-145 (current: 110; doubled: 145; quadrupled: 225).

Table 8. Annual Effect of IL-28 Guided Triple Therapy on Health Outcomes over 5 Years

	Current Uptake Rate (2%/yr)	2x Uptake Rate (4%/yr)	4x Uptake Rate (8%/yr)
Cases of Decompensated Cirrhosis	-8	-26	-45
Cases of Hepatocellular Carcinoma	-4	-14	-25
Number of Liver Transplants	0	-1	-2
Quality Adjusted Life Years	+110	+145	+225

N=48,000 eligible GT1 HCV

KEY QUESTION #4. What will be the cost and resource use patterns when using either triple therapy or IL-28B-guided triple therapy?

Depending on uptake patterns, increased total expenditures for HCV treatment and care for individuals with GT1 HCV relative to standard two-drug therapy will likely be $32-$100 million annually. Table 9 below shows the details about these annual net expenditures vary depending on strategy and scenario.

Table 9. Average Annual Net Increase in Cost by Treatment Strategy and Uptake Rate over the 5 Years of the Analysis Relative to Standard Therapy

	Current Uptake Rate (2%/yr)	2x Uptake Rate (4%/yr)	4x Uptake Rate (8%/yr)
IL-28B-guided therapy	$32M	$76M	$115M
Universal triple therapy	$43M	$96M	$144M
N=48,000 eligible GT1 HCV			

The table gives the additional cost of each treatment strategy compared to standard two-drug therapy. The costs include the direct cost of the new medications, the cost of treating side effects, as well as averted costs of advanced liver disease and lower care costs after achieving sustained virologic response. Importantly, average annual net costs, health outcomes and quality-of-life presented in these analyses should not be used for cost-effectiveness calculations as averted costs and downstream health benefits past year 5 are not counted in the 5-year projection of the effect on health care cost.

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SUMMARY AND DISCUSSION

SUMMARY OF EVIDENCE BY KEY QUESTION

Key Question #1: What are the current usage patterns of directly acting antivirals and of IL-28B patient genotyping in the VA health system? And how do these patterns differ by VISN?

Between July 2011 and the end of June 2012, nearly 3,000 people initiated DAA treatment, with approximately 80% using on-formulary boceprevir (Boceprevir N=2,366, Telaprevir N=501). During this same period, 2,171 individuals had an IL-28B test. There was heterogeneity in number of people taking up DAA therapies and IL-28B testing across VISNs

VISNs differed in the rates of use of IL-28B testing in patients who were prescribed DAA medications, with a national average just above 10 percent. VISN 22 had the greatest number of IL-28B tests, while VISNs 8, 16, and 21 had the greatest number of patients initiating DAA therapy. In some VISNs there were more patients initiating DAA therapy than getting IL-28B tests, while in other VISNs the reverse was true. Seven VISNs used testing in five percent or less of patients receiving DAA, whereas three VISNs used testing on 30 percent or more of these patients.

The median length of boceprevir treatments was just under 28 weeks. Of those who initiated boceprevir, 89% got to 8 weeks, 81% to 12 weeks, 76% to 16 weeks, and 29% to 32 weeks. Telaprevir episodes were much shorter per its therapeutic protocol. Median length of telaprevir treatments was between 12 and 16 weeks. None lasted beyond 28 weeks.

Key Question #2: What will be the health impacts of using either of two available directly acting antivirals combined with pegylated interferon and ribavirin (triple therapy)?

When compared to standard therapy, universal triple therapy was likely to reduce annual cases of decompensated cirrhosis by 10-29 (current uptake: 10; doubled uptake: 29; quadrupled uptake: 50). When comparing universal triple therapy to standard therapy, annual cases of hepatocellular carcinoma were likely to be reduced by 5-16 (current: 5; doubled: 16; quadrupled: 27). Finally, when comparing universal triple therapy to standard therapy, annual numbers of liver transplants are likely to be reduced by 0-1 (current: 0; doubled: 1; quadrupled: 2). Consequently, annual quality adjusted life years (QALYs) increased by 148-213 (current: 148; doubled: 213; quadrupled: 322).

Key Question #3: How will be the magnitudes of the health impacts measured in Key Question #2 change if IL-28B patient genotyping is used to offer triple therapy to those less likely to benefit from two-drug pegylated interferon + ribavirin?

Comparing IL-28B guided therapy to standard two-drug therapy, annual cases of decompensated cirrhosis are likely to be reduced by 8-26 (current uptake: 8; doubled uptake: 26; quadrupled uptake: 45), annual cases of hepatocellular carcinoma are likely to be reduced by 4-14 (current:

4; doubled: 14; quadrupled: 25), and annual numbers of liver transplants are likely to be reduced by 0-1 (current: 0; doubled: 1; quadrupled: 2). Consequently, annual QALYs increased by 110-145 (current: 110; doubled: 145; quadrupled: 225).

Key Question #4: What will be the cost and resource use patterns when using either triple therapy or IL-28B-guided triple therapy?

Depending on uptake patterns, increased total expenditures for HCV treatment and care for individuals with GT1 HCV relative to standard two-drug therapy will likely be $32-$100 million annually. At the current uptake rate of 2 percent per year, universal triple drug therapy would be expected to cost $43 million more, while IL-28B guided therapy would be expected to cost $32 million more, compared to standard two-drug therapy.

LIMITATIONS

Key uncertainties remain as with all studies and especially in the case of rapid, preliminary analyses. Below we summarize a number of these.

The IL-28B genotype distribution in the VA population has not yet been described. Our study uses race-specific IL-28B genotype distributions observed in other studies. The VA specific distribution might be different from that observed in other studies.

The liver fibrosis distribution in the VA population is based on diagnostic codes in administrative datasets. We did not have the more definitive results from liver biopsies, but this omission may not be very important, as biopsies are not performed in most persons with chronic HCV infection. Laboratory data can be used to estimate the stage of their fibrosis and may provide more accurate information on the distribution of fibrosis in future studies.

The modeling analysis focused on VA as a whole. It is clear from the preliminary VA administrative data analyses that there is heterogeneity in the adoption of DAAs and IL-28B between VISNs. We had insufficient information to project potential differences in uptake in these treatments by VISN. Furthermore, there are other patient, provider, and facility characteristics that may play a role in determining use of these new technologies and additionally, depending on the results from IL-28B testing may also play a role in determining subsequent clinical actions and patient behaviors. Information in this area could help to further refine the analyses presented here.

The modeling analysis is confined to treatment-naïve, HCV mono-infected individuals as evidence of effectiveness for those co-infected with HIV is only beginning to emerge and utilization data needed to support VA-specific analyses stratified by co-infection status are also needed. Analyses like those presented here for individuals with previous experience of HCV treatment would be important to conduct, though are complicated by a number of issues including fewer data on effectiveness, various types of treatment failures, and reasons for failure including lack of adherence to medication regimen versus non-response to appropriately taken medications.

The modeling analysis considers three strategies including one strategy where IL-28B genotyping is used to determine triple therapy treatment versus standard therapy treatment. IL-28B genotype

along with other predictive markers for treatment response are an exciting new avenue.[42-44] Our analysis considers one such approach, though others may also be possible. Ultimately, all such approaches attempt to optimize over treatment response, side-effects, and costs in achieving best outcomes for individual patients.

More generally, it is unclear how uptake rates may change beyond those observed in the first year of VA administrative data. Newer therapies and technologies are in clinical trials and could potentially represent even more attractive options for clinicians and Veterans, and may supplant the treatments we considered. Conversely physician education or other diffusion of information processes could increase uptake rates over time. Uncertainties in uptake scenarios can be reduced by periodically reevaluating the VA administrative data.

RECOMMENDATIONS FOR FUTURE RESEARCH

Therapy for HCV is evolving rapidly and important questions remain unanswered. As clinicians use currently approved DAAs more extensively and additional DAAs become available, future research should evaluate the health and economic outcomes that result from use of these therapies. This research should evaluate: practice patterns, including variations in care among VISNs; patient selection for treatment; effectiveness of DAAs in Veterans (in contrast to efficacy as measured in randomized trials) and in specific Veteran populations, such as patients with substance use disorders; utilization and costs from treatment and complications of HCV infection (e.g., costs); impact on specific VA budgets (pharmacy care, specialty care); cost-effectiveness of treatment and genetic testing; and barriers to diffusion of high-value therapies.

CONCLUSIONS

Approximately 3,000 Veterans initiated care with DAAs since their approval, with about 80% receiving boceprevir. Uptake of DAAs and use of IL-28B testing varies substantially among VISNs, unadjusted for the number of patients who are eligible for treatment. Our model-based analyses indicate that use of triple therapy results in better outcomes than standard therapy, but at increased costs. Use of IL-28B to select patients for triple therapy results in modest reductions in anticipated health benefits and costs. Assessment of the cost effectiveness of use of IL-28B guided therapy or universal therapy with DAAs will require projection of long-term health outcomes and costs.

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APPENDIX A. PEER REVIEW COMMENTS/AUTHOR RESPONSES

Comment	Response
The data is intriguing but in my view still somewhat preliminary. I would like to see this repeated in a year or two to see if the patterns observed hold up	We appreciate the assessment. We hope to repeat this analysis and plan to do so should funding permit.
Results of this report may influence decisions about future formulary status of boceprevir and telaprevir. Results have the potential to indirectly influence future decision making about formulary status of HCV medications as more DAA drugs are developed and come available. The VA also must review policy for future HCV antibody testing guidelines. These results are highly relevant to such guideline decisions.	Again, we appreciate this assessment and hope to be as relevant to VA decision makers.
No specific recommendations. It is appropriately structured as-is, given available data resources, to best inform decisions at hand.	Thank you.
p.18: This is a strong summary of the available data as they exist in the literature and in VA data resources. On p18, the authors discuss the sources used in concluding the estimates of number of veterans with HCV infection who are treatment eligible, and who take up treatment if eligible. As is pointed out, best estimates of these numbers vary quite a bit, and the conclusion arrived at here is that 45% of those in care are treatment eligible. I suspect that this figure may be a bit high, as it is derived quite substantially from samples selected for greater intensivity of treatment than is likely the national norm. However, pending better empiric data I suspect it is not too much of an overestimate and is reasonable.	We agree that this could be a possibility and that better data would help. We have noted this when we described this number stating “, though this may be somewhat lower in the VA population if the studies were conducted in populations who are more likely to be eligible for treatment.” (Page 18)
There are studies on the way genetic test can change behavior. In this case it is possible that knowledge of IL28B status might encourage compliance.	We have noted that this possibility exists but have not modeled this as there are no data on how IL28B changes behavior (and none specific to the VA) that we know of. We have noted this in the limitations: “Furthermore, there are other patient, provider, and facility characteristics that may play a role in determining use of these new technologies and additionally, depending on the results from IL-28B testing may also play a role in determining subsequent clinical actions and patient behaviors. Information in this area could help to further refine the analyses presented here.”

Comment	Response
It seems likely that use of DAAs and IL28B tests vary by more than just VISN (discussion). It is likely to vary among providers, and even vary within a single practitioner over time.	We have noted this in the discussion as an area of definite interest for future work. See our response to the comment above which includes how we have addressed this point in the revised text as well.
It is an early assessment of the testing for the new medications responsiveness. I would like to see a follow up in two years relative to the benefit of testing in the selection of patients for triple therapy.	We appreciate the assessment. We would love to repeat this analysis and plan to do so should funding permit.
Very good and I have no substantive recommendations. This is good work given the newness of the drugs and the brief period for which analysis can be provided. It would be good to repeat this in 2014.	Thank you.
P. 13, Sub-question 1.4 paragraph 3: Excluded cases: supply of drugs greater than 90 days. Unsure why this is excluded given that some of the patients are snow birds and may need more drugs for travel? Given this is only 3% I am ok with it. Just wanted to know the thought behind this exclusion.	The analysis of length of treatment excluded the 3% of individuals who had a dispensed prescription for a single day supply and those with prescriptions for more than 90 days' supply. This exclusion was applied only to the analysis of the length of treatment with DAA. All cases were used in estimating the number of individuals starting DAA. It was felt the including individuals who had records with extreme values of "days supply" in a single prescription record might bias the estimate of the duration of treatment, and these individuals were excluded. This exclusion is unlikely to have much effect, however, as only 3% of individuals were excluded, and the mean supply of medication dispensed to them (114 days) was similar to the mean of dispensed to individuals included in the analysis (102 days).
Page 14. The analysis uses ICD9 codes to assemble a cohort of HCV-positive patients. The report should indicate whether this approach using administrative data has been validated (either by the authors or others) or whether this is a pragmatic approach given the rapid nature of the report. It also seems that events such as decompensated cirrhosis were identified in administrative databases but the methods for identifying these are not outlined.	We identified prevalence of HCV by counting the number of persons with visits or stays assigned an ICD-9 diagnosis code for HCV during the year end 9/30/2010. This was a pragmatic (if inexact) means of identifying the relative prevalence in different regions to provide context for the utilization of the new treatments and the new genetic screening test. We did not have access to HCV test results, but will use those data to identify cases in our newly approved study.
Page 33, Paragraph 1: The report would benefit from a table outlining the breakdown of component costs.	This is a good suggestion but beyond the scope of the current study.

Comment	Response
The scope of the paper emerges upon reading but would benefit from being more clearly described near the beginning of the report.	We have made extensive edits for clarity and believe this helps the overall readability of the report per the reviewer's comments.
The report should clarify whether HIV-positive patients were excluded from the analyses (particularly the VA population with chronic HCV receiving VHA care) since the efficacy of DAAs in this population is only now emerging.	Patients with HIV were not excluded from the administrative data analyses, though due to the fact that efficacy in HIV co-infected individuals is highly uncertain we would expect utilization in this population to be relatively low. We have noted this in the appropriate section. For the simulation model, we have further highlighted the fact that HIV-infected individuals were excluded from the analyses for this same reason. The model focuses on treatment-naive, HCV monoinfected individuals only. We have added the following to the document: "The modeling analysis is confined to HCV monoinfected individuals as evidence of effectiveness for those co-infected with HIV is only beginning to emerge and utilization data needed to support VA-specific analyses stratified by co-infection status are also needed."
One of the main findings of the report is that the QALYs gained with IL-28B testing are lower than those obtained with treatment not guided by IL-28B testing. This is a counterintuitive finding to me, considering that IL-28B testing should have its maximal benefit in avoiding toxic therapy among those who would not benefit. This is worthy of discussion and clarification.	We believe the reviewer is asking about universal triple therapy versus IL-28B guided triple therapy. While the gain in efficacy in non-CC types is much higher for triple therapy compared to standard dual therapy, efficacy gains in studies for CC types is also somewhat higher. Hence, although side effects are more intense for triple therapy, its potentially shorter duration combined with increased efficacy appears to offset this though at increased overall costs.
Although it is only a one year time horizon, the report would benefit from some simple analyses to ascertain whether the use of DAAs in the VA has been stable or increasing over that time period. This is presented descriptively in the results but could also be addressed analytically.	According to the data source used, the DSS prescription dataset, the number of patients initiating DAA increased during the first 10 months of the analysis, and then decreased in the last 3 months in the dataset. It is uncertain whether the decrease represents an actual change in practice or is an artifact of the data processing. The decline in new starts at the end of the study may represent incomplete processing of VISTA pharmacy data for inclusion in the DSS extract.

Comment	Response
Several assumptions in Tables 3 and 5 are presented without justification or are presented only qualitatively without justification of the actual parameter used. For example, the report assumes a "higher rate" of liver transplants than observed but it is unclear how the value of 2500 per 100,000 person years was derived. Similar assumptions apply to some costs in Table 5, including the average adverse event costs and the annual post-successful treatment HCV care costs.	We have endeavored to clarify this point in the notes in the table, providing the numbers of the FY10 preliminary analysis to estimate liver transplantation rates. Adverse event costs were derived from studies conducted by others as cited in the notes in the relevant sections of Table 5. A number of the assumptions about costs were made based on non-VA-specific studies when no VA-specific data could be found. For example, the cost of post-successful treatment HCV care in non-VA-specific populations tends to be roughly half that of pre-treatment care costs (excluding the costs of medications and other clinical care and monitoring during treatment with two-drug or triple therapy). This is now noted more clearly in the table.
The report would benefit considerably from presenting sensitivity analyses.	Sensitivity analyses are planned for the approved HSR&D study, but are beyond the scope of this current preliminary effort.
Several abbreviations and acronyms are not fully defined (e.g. IPNUMBER). The report should be carefully edited to include these in the table of abbreviations.	We have clarified abbreviations in the appropriate places in the report.
The model considers age and race but does not present the results by these subgroups (i.e., it does not present variability in outcomes by subgroups but rather averages outcomes across the entire population). However, analyses by subgroups could be particularly beneficial for developing guidelines or targeting therapy within specific institutions.	We agree, though the main goal of the analysis was to highlight costs and resource use for the VA taking into account factors that might influence these things. The analysis also does not do a lifetime horizon cost-effectiveness analysis which would be important for considering guidelines for targeting therapy. We hope to do this contingent on appropriate funding.
Lai M, Afdhal NH. Clinical utility of Interlukin-28B testing in patients with genotype 1. Hepatology 2012; 56:367-372	We have incorporated this reference in our discussion of alternatives of how IL-28B may be used to guide treatment.
Thompson AJ, McHutchison JG. Will IL28B polymorphism remain relevant in the era of direct-acting anti-viral agents for hepatitis C virus. Hepatology 2012; 56:373-381	We have incorporated this reference in our discussion of alternatives of how IL-28B may be used to guide treatment.
Backus LL, Belperio PS, Thomas C, Cheung R, Mole LA. Week 24 and end of treatment response for direct acting antiviral (DAA)-based therapy in veterans with chronic hepatitis C. AASLD Late Breaker 30, 2012	This is an excellent and recent reference which is certain to be published in an appropriate journal. We look forward to incorporating it into future revisions of this and related work.

Comment	Response
Pearlman B, Ehleben C. Hepatitis C virus genotype 1 infection with low viral load and rapid virological response to peginterferon and ribavirin can be treated without a protease inhibitor, irrespective of IL-28B status or patient ethnicity. Hepatology 2012; 56 (4, suppl): 268A	We have incorporated this reference in our discussion of alternatives of how IL-28B may be used to guide treatment.
Thompson AJ, Shiffman ML et al. Six weeks of a NS5A inhibitor (GS-5885), protease inhibitor (GS-9451) plus peginterferon/ribavirin achieves high SVR4 rates in genotype 1 IL28B CC treatment naïve HCV patients: Interim results of a prospective, randomized trial. Hepatology 2012; 56 (4, suppl):556A	We thank the reviewer for the helpful reference on new treatments for HCV. We agree that it is an exciting time with more than 70 new treatments and combinations in various phases of clinical trials. Our recently funded HSR&D grant intends to examine these in the context of the VA.
It is unclear form this report that clinicians and patients are making treatment decision based on the IL28B result. This make extrapolation of current findings difficult.	We believe the reviewer is referring to the analysis of administrative data. Our current preliminary analysis does not directly address this question, which we agree is an important next step but which is beyond the scope of the report.
IL28B currently is a send out test. It was stated the cost was $300. However, I was told by our lab that it was only about $100. Not sure what is being used in the cost analysis.	We have clarified the text to note that we used total cost of care, including the direct cost of services and the associated indirect (overhead) cost.
p.11: 2.6% chronic hepatitis C prevalence appeared to be low for veterans. Many veterans were coded incorrectly as acute hepatitis C (070.51 instead of 070.54) if ICD-9 code is being used.	We used all ICD-9 codes for HCV infection, both acute and chronic, but only considered persons with care that was assigned this code in the study year. HCV laboratory test results were not available, but will be evaluated in the our newly approved study.
p.18: Preliminary triple therapy data of veterans was recently presented by Backus et al.	This is an excellent and recent reference which is certain to be published in an appropriate journal. We look forward to incorporating it into future revisions of this and related work.
p.21: 3-year survival rate for HCC of 70% was too high for all HCC patients- are these post-liver transplant?	The reviewer is correct. This was an error in data extraction from the VA review which cited an older article by Pawarode et al and also more updated SEER data. We have updated the note, the parameter, and the analyses. Notably this does not substantially change results over a 5 year horizon because relatively few HCCs are prevented in this period (< $1million dollar change in the estimates of total cost differences for total costs of $50-150 million).
p. 21: Did HCC treatment cost also include sorafinab which cost ~$3000/month. This is reserved for advanced HCC and might not be applicable in this analysis.	The cost of all medications and health services were included in the cost of care for persons with HCC.

Comment	Response
This report did not address the treatment experienced patients.	We have noted this in the limitations: "The modeling analysis is confined to treatment-naïve, HCV monoinfected individuals as evidence of effectiveness for those co-infected with HIV is only beginning to emerge and utilization data needed to support VA-specific analyses stratified by co-infection status are also needed. Analyses like those presented here for individuals with previous experience of HCV treatment would be important to conduct, though are complicated by a number of issues including fewer data on effectiveness, various types of treatment failures, and reasons for failure including lack of adherence to medication regimen versus non-response to appropriately taken medications."
Current model of IL28B guided therapy (figure 1) is an over simplification. See discussion by Lia and Afdhal (e.g. Fig 3 on p 371)	We appreciate the reviewer's comments. We agree that there are many ways that one could use IL-28B testing alone or with other predictive markers to optimize treatment response, side-effect profiles, and/or costs. We note that data are emerging on this important topic and have added the following sentence to the limitations: "IL-28B genotype along with other predictive markers for treatment response are an exciting new avenue. Our analysis considers one such approach, though others may also be possible. Ultimately, all such approaches attempt to optimize over treatment response, side-effects, and costs in achieving best outcomes for individual patients."
The other model would be to stratify patients based on the response during the lead-in phase. Even though majority of patients with IL28B CC had RVR, RVR is actually more important than IL28B as predictor of SVR. Patients with low viral load and achieve rapid virological response will not benefit from adding the protease inhibitor. However, this might be beyond the scope of this report.	This is an excellent point that we have noted in the report.
This report just presents the findings without any recommendations for the clinicians. The article by Lia and Afdhal actually discussed how IL-28B genotype could be used in patient management.	The goal of the report was to provide a preliminary view of current practices and a short-term (5 year) view on the impact of current practices and changes in these practices on health outcomes and costs. Informing VA clinical care guidelines with a life time cost-effectiveness analyses is a larger goal of work for which we have currently received funding from VA HSR&D.