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CLINICAL FACTORS ASSOCIATED WITH HEPATITIS C TREATMENT SELECTION IN A VETERANS AFFAIRS POPULATION

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by

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Clinical Factors Associated with Hepatitis C Treatment Selection in a Veterans Affairs Population

Abstract

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Background: Hepatitis C virus is currently the most common chronic blood borne pathogen in the United States, with only half of those infected aware of their condition. The cost for treatment is higher with Harvoni® (ledipasvir/sofosbuvir) than Viekira Pak® (ombitasvir/paritaprevir/ritonavir and dasabuvir). With finite resources available to treat patients, it is important to understand which clinical factors may influence treatment selection decisions.

Methods: The study is a 12-month medical record review within the Veterans Affairs (VA) system to evaluate significant relationships between selected clinical and sociodemographic factors and HCV treatment selection with either Harvoni® or Viekira Pak®. Clinical and demographic information was collected as well a presence of interacting medications, contraindication to components of the treatment regimen, and the treatment regimen indicated and selected.

Results: In total, 25,717 patients were extracted from the database and were compared by the use of frequency charts and logistic regression analysis with results reflective of the nationally reported numbers. There was a statistically significant difference in the prescribing pattern between the VA Northern California Health System (station 612) and the other stations nationally with Viekira Pak® prescribed more often in that station. Station 612 utilized an electronic decision tree (otherwise known as a 'quick order') during the medication ordering process. In a comparison between station 612 and the other stations within the VA a notable difference in the impact of drug-drug interactions on the prescribing patterns was found within station 612.

Conclusion: Many methods can be used to ensure optimal treatment for HCV infections. In station 612 the use of a decision tree may have assisted in avoidance of potentially modifiable factors which enabled for a higher utilization of the less expensive treatment option, Viekira Pak®, for HCV infections, thereby potentially allowing for more Veterans to be treated with finite resources.

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LIST OF ABBREVIATIONS

BMI :	Body Mass Index
CrCL :	Creatinine Clearance
CDC :	Centers for Disease Control and Prevention
DAA :	Direct Active Antiviral
DDI :	Drug-Drug Interaction
eGFR :	Estimated Glomerular Filtration Rate
ESRD :	End-Stage Liver Disease
GT :	Genotype
HCC :	Hepatocellular Carcinoma
HCV :	Hepatitis C Virus
HIV :	Human Immunodeficiency Virus
IDU :	Injection Drug Users
NAT :	Nucleic Acid Test
RNA :	Ribonucleic acid
SVR :	Sustained Virologic Response
USPSTF :	US Preventative Services Task Force
VA :	Veterans Affairs
VINCI :	Veterans Affairs Informatics and Computing Infrastructure
QALY :	Quality Adjusted Life-years

Clinical Factors Associated with Hepatitis C Treatment Selection in a Veterans Affairs Population

Background

Hepatitis C is the principal cause of death from liver disease and the leading reason for liver transplantation in the United States.[1,2] With an estimated 3-4 million individuals currently infected with the Hepatitis C Virus (HCV), the management of this disease has shifted into focus for many healthcare entities. According to the Centers for Disease Control and Prevention (CDC), 75-85% of those who are acutely infected with HCV will progress to a chronic HCV infection, with 60-70% of those individuals progressing to liver disease, and 5-20% to cirrhosis over the next 20-30 years. It is estimated that 1-5% of those that develop a chronic HCV infection will die from the consequences attributed to a long term HCV infection.[1] These estimates are expected to increase as the population ages placing greater importance on the identification and treatment of HCV-infected individuals.[3] While HCV infection is now largely curable, it is also one of the most expensive diseases to treat despite the relatively short treatment duration.[3] Therefore, cost containment and therapy optimization of HCV play a critical role for any treating entity.

It has been over twenty-five years since the identification of HCV and in recent years a surge has occurred in both the research and treatment of Hepatitis C. Cohorts at risk for an HCV infection include those who are prior or current illicit injection drug users (IDU) [account for roughly 60% of those infected], healthcare workers, those on

hemodialysis, and those who received a blood transfusion before 1992 [due to the lack of HCV screening of blood products].[1,2,4,5] It is estimated that approximately 30% of the IDU between the ages of 18-30 years old are currently infected with HCV. The infection prevalence increases to 70-90% for the older IDU population due to the needle sharing that occurred in the 1970's.[1,2,6] It is estimated that close to 3% of the US population has injected drugs at least once in their lifetime, resulting in over 6.6 million individuals potentially being exposed to HCV infection.[7] According to the United States Department of Veterans Affairs (VA), while exact numbers are not known it is expected that their patient population has a higher exposure rate to the HCV than those in the general population. Some studies suggest that 1 in 10 Vietnam Veterans returned from war with a HCV infection.[8] Although no longer considered a high risk factor, it is reported that transfusions before 1992 greatly increased the risk of exposure for this subset of the population as well.[9] With a large prevalence of exposure in the Veteran population the identification and treatment of HCV must be carefully constructed in order to ensure fiscal responsibility.

The viral lifecycle of Hepatitis C is important in recognizing and identifying those who would benefit from treatment. The virus progresses through two stages of infection, acute and chronic, with only the latter requiring and qualifying for treatment. Between 15-25% of acute infections resolve without intervention. The CDC defines a chronic HCV infection as "the presence of HCV ribonucleic acid (RNA) in the blood for at least 6 months after an acute infection".[9] For most patients, HCV slowly progresses through the stages of liver disease beginning with inflammation of the liver (hepatitis), and progressing to liver fibrosis, cirrhosis and sometimes to hepatocellular carcinoma (HCC).

Thus, identification of those infected with HCV during the early stages is extremely valuable. However, many of the early disease symptoms are nonspecific (fatigue, nausea, vomiting, loss of appetite), and therefore it may be difficult to identify those with HCV if they are unaware of their exposure.[10-12] It is estimated that only 50% of those infected are aware of their current status. The CDC and US Preventative Services Task Force (USPSTF) recommended that testing be carried out on a birth cohort determined to be at high risk. A one-time HCV RNA screening of all asymptomatic persons belonging to the 1945-1965 birth cohort as well as other persons based on exposures, behaviors, and conditions that increase the risk for HCV infection should be tested for an active HCV infection.[1,2,12] According to the 2015 census, an estimated 16% of the US population is between the ages of 55-64, with 8% (3.4 million) within that population listed as veterans.[13] According to the State of Care for Veterans with Hepatitis C 2014, as high as 9.5% of those within the VA birth cohort are infected with HCV.[8] With the sheer volume of individuals potentially at risk for an active HCV infection the treatment approach must be cautiously orchestrated in order to optimize patient outcomes.

Hepatitis C: a history. Our understanding of Hepatitis C has evolved significantly since its discovery in 1989. In recent years, at least six different genotypes that characterize certain aspects within the virus replication pathway have been identified. Variations in genotypes provide an effective target for treatment which has led to the ability to cure the disease in most individuals who are compliant with treatment. A "cure" is most commonly defined as an undetectable RNA level or sustained virologic response (SVR) at least 12 weeks after the completion of therapy. The achievement of SVR not only signifies the eradication of the HCV infection but is also associated with

numerous beneficial clinical outcomes including a lower risk of liver-related complications and death.[14-16] A 2011 study evaluated 16,864 VA patients with Genotype 1, 2 or 3 with substantial comorbidities and found a decrease in the risk for all-cause mortality in patients who achieved SVR versus those that did not; hazard ratio of 0.70 for genotype 1 ($p < 0.0001$), 0.64 for genotype 2 ($p = 0.006$) and 0.51 for genotype 3 ($p = 0.0002$).[17] Another study evaluated 530 HCV-infected patients with advanced hepatic fibrosis in Europe and Canada and found a lower all-cause mortality in those who achieved SVR. Additionally, over an average follow-up period of eight years the study found a decrease in liver-related mortality and liver transplants.[18] These types of studies support the use of SVR as a surrogate for determining Hepatitis C cure.

The first Hepatitis C treatments were approved for use by the FDA in 1991 in the form of interferon, PEGylated interferon alpha, and ribavirin combinations and resulted in an HCV cure rate of ~50%.[19,20] Early treatment was wrought with difficulties including complicated treatment methods (as most were infusions), extensive adverse side effects, and numerous drug interactions. With the introduction of the direct acting antiviral (DAA) agents in 2011, those issues have significantly improved. Although the first DAA agents [boceprevir(Victrelis®), telaprevir(Incivek®)] were given in combination with interferon and ribavirin therapy, the later DAA agents no longer required this strategy. Newer DAA agents currently include daclatasvir (Daklinza®), sofosbuvir (Sovaldi®), sofosbuvir/velpatasvir (Epclusa®), ledipasvir/sofosbuvir (Harvoni®), simeprevir (Olysio®), ombitasivir/paritaprevir/ritonavir (Technivie®), ombitasvir/paritaprevir/ritonavir with dasabuvir (Viekira Pak®), and elbasvir/grazoprevir (Zepatier®). Many others are also in the pipeline. These agents are taken orally with

fewer side effects, shorter treatment regimens, and cure rates that often surpass 90%. With the addition of nucleic acid tests (NAT) subtypes within some of the most common genotypes allow for a more targeted approach in those treatment pathways. Currently, genotype 1 HCV accounts for more than 75% of the infections in the US and has two identified subtypes (genotype 1a and genotype 1b). Only about 20-25% of those with chronic HCV have genotype 2 or 3.[9]

Current DAA therapy falls into one of four drug classes including: 1) the NS3/4A protease inhibitors (PIs) which block viral protease inhibiting RNA replication, 2) nucleoside and nucleotide NS5B polymerase inhibitors which directly interfere with RNA replication, 3) NS5A inhibitors which block the NS5A protein needed for viral replication and infection, and 4) the Non-nucleoside NS5B polymerase inhibitors which insert directly into the virus altering its ability to replicate.[21] Each chosen treatment is tailored to the viral genotype and if appropriate the subtype, as this helps predict treatment failure or cross-resistance.[22] While there has been remarkable improvement in the treatment and cure of HCV in the last 25 years, the affordability of treatment is a significant limiting factor and places excessive burden on healthcare payers and patients.

The high cost of HCV treatments creates a complicated situation for healthcare systems. While enormous effort has been dedicated to alerting the public to the necessity for HCV screening there has been little done to address the financial component of treating those that are identified. The cost of DAA agents can be a major deterrent for many seeking treatment. Typically, a standard 12-week course of therapy with a DAA agent costs between $60,000 and $100,000. While treatment costs are extremely important, cost avoidance must also be evaluated when determining feasibility of

treatment. Many patients who attain SVR not only achieve a halting of their liver disease progression, but some also experience disease regression leading to an overall decrease in the cost of care over a lifetime.[23]

To address the high demand of treatment with limited funds, the VA initially prioritized patients based on likely benefit and necessity. The VA first focused on those with advanced liver disease due to the clear benefit and downstream cost avoidance when these individuals were treated.[24,25] The disease burden of advanced liver disease can be difficult to isolate. A study projected costs to reach $6.5 billion in 2013 which would balloon to $9.1 billion in 2024. Those who develop decompensated cirrhosis were expected to contribute to 46% of that cost, with compensated cirrhosis and HCC contributing approximately 36%.[3] Another cost to consider is that associated with liver transplantation. Hepatitis C is the most common cause of liver transplant in the US and is responsible for 35-40% of liver transplantation cases in 2009.[26] Not only are transplant organs a scarce commodity but also associated with costly surgical procedure and follow-up care. In 2014, the healthcare cost associated with liver transplantation averaged nearly $740,000 per transplant.[27] With numbers such as those it is clear why treatment was initially geared toward individuals with more advanced liver disease. In recent years however, it has been determined that along with advanced forms of the disease, treatment in the early stages of liver disease is also beneficial and has been shown to provide a higher health state utility. A study conducted by the University of California, San Francisco found that while the cost of the DAA agents resulted in high initial costs for patients, there was a lower lifetime cost observed when treating all stages of liver disease, not just the advanced stages. The study found <$50,000 per quality-adjusted life years

(QALY) gained for patients treated with Harvoni® with comparable results for other DAA agents.[28] While including all stages of cirrhosis into the treatment pool is optimal for the patient population, it also increases the treatment demand to a capacity that many healthcare systems struggle to meet.

Treatment in the VA health care system. The VA is considered the largest provider of HCV treatment in the US with an average infection prevalence three times higher than the general population.[8] One benefit of working within the VA Health Care System is their coordinated, concerted effort on population health management which allows for a more focused HCV treatment approach than is often possible in the community due to the limitations of most outpatient facilities' electronic health systems. The integrated and standardized health systems streamline care and increase the access to services within their health system. One of the tools useful for disease management is the Clinical Case Registry (CCR) which can be utilized to monitor and track patients within the VA Health Care System as they receive HCV related care throughout each facility. This allows for tracking and monitoring of patients regardless of which step of the care process they are currently in. As such, the practitioner can ensure that the appropriate laboratory tests are completed, medications are picked up, and follow-up visits are maintained throughout the entire course of therapy for the HCV-infected patient. Because patient adherence and clinical monitoring are the two most important components of Hepatitis C treatment, the integrated VA Health Care System has some clear advantages. As HCV treatment is associated with such high costs it is important to control for these factors in order to validate the usage of such expensive therapies.

In fiscal year 2015, the VA health care system allocated $696 million for the utilization of newer Hepatitis C drugs.[24] The funds supported the treatment of those infected thus, fiscal responsibility was necessary to ensure treatment is available to as many veterans as possible. Since genotype 1 is the most common infecting genotype a focus was placed on its treatment.[29,30] In this study we evaluated two specific agents used to treat genotype 1 HCV infections, ledipasvir/sofosbuvir (Harvoni®), and ombitasvir/paritaprevir/ritonavir with dasabuvir (Viekira Pak®), to identify characteristics associated with the selection of either agent. The procurement cost of Harvoni® is greater than Viekira Pak®. Treatment algorithms are often utilized to ensure treatment appropriateness, consistency and fiscal responsibility and are often implemented when treatment is particularly complicated and/or expensive. The Northern California Healthcare system centered at Mather, California created an algorithm for Hepatitis C treatment which was fine-tuned to ensure optimal functionality. This study will analyze the factors associated with treatment decisions to identify possible predictors within the VA for the treatment of this disease.

Harvoni® vs. Viekira Pak®. Harvoni® and Viekira Pak® have been on the market since late 2014 and have generally resulted in an SVR above 95%.[31,32] Harvoni® contains two agents; ledipasvir (NS5A inhibitor) and sofosbuvir (HCV nucleotide analog NS5B polymerase inhibitor) and is used to treat genotype 1a/1b, 4,5 and 6. It has utility in patients that are treatment naïve, have compensated cirrhosis, or decompensated cirrhosis (necessitating either the addition of the nucleoside analogue ribavirin or extension of treatment duration to 24 weeks).[33-35] Harvoni® has been studied in patients with solid organ transplant (barring any severe drug interactions) and can also be used for a shorter

8-week course of therapy for patients monoinfected with HCV with a low viral load (<6million IU/mL). Limitations to Harvoni® use includes patients with severe renal impairment (eGFR <30mL/min/1.73m^2), end-stage renal disease (ESRD) or hemodialysis. Some important contraindicated medications in those using Harvoni® include amiodarone, anticonvulsants (carbamazepine, phenytoin, phenobarbital, oxcarbazepine) and antimycobacterials.[36,37] Viekira Pak® contains four agents (three of which are contained in one tablet with dasabuvir in a separate tablet). These agents include ombitasvir (NS5A inhibitor), paratiprevir (NS3/4A protease inhibitor), ritonavir (CYP3A inhibitor) and dasabuvir (non-nucleoside NS5B polymerase inhibitor), with ritonavir acting solely to boost the concentration of paritaprevir as it ritonavir not active against HCV. Viekira Pak® has utility in the treatment of genotype 1a/1b and can be used in patients who are treatment naïve without cirrhosis, or with compensated cirrhosis.[38-40] A limitation of Viekira Pak® includes its use in those with decompensated cirrhosis, and those co-infected with Human Immunodeficiency Virus (HIV) that are not currently treated for HIV due to the possibility of cross resistance to later HIV treatment strategies as a result of the HCV treatment. Some important contraindicated concomitant medications for those using Viekira Pak® include voriconazole and quetiapine.

Treatment strategies. There are many factors that impact treatment decisions with DAA agents in patients with HCV infection. The VA released guidance to assist with the treatment considerations of individuals with HCV. For patients that are co-infected with HIV the VA as well as the national HCV guidelines recommends treating those patients as if they were mono-infected individuals, with special consideration given only to avoid drug-drug interactions (DDI's) when necessary.[41,42] Active substance use

disorder is addressed at length in the VA Health Care System as it is increasingly common in the Veteran population. Although active substance use disorder in any form including alcohol, opioids (illicit or not), and nicotine is of concern it is not a disqualifier for patients who would otherwise be considered for treatment of their HCV infection. While abstinence is always preferred in any patient population, it is currently not a requirement for qualification and the emphasis on it as a goal prior to treatment is strongly discouraged.[42] Mental health disorders are handled in the same manner with guidance that it should only be considered when determining the capacity and willingness of a patient to adhere to the treatment regimen.[42,43] Adherence for those considered is not limited to medication adherence but also appointments including laboratory and supportive care as appropriate. In the VA Health Care System, those who are not regarded as an adherent patient to any and all aspects of HCV treatment do not qualify for treatment with a DAA agent.

Current decisions and influences. The clinical decision to use Harvoni® over Viekira Pak® has significant cost implications. There are many factors that can influence treatment management decisions and understanding those treatment predictors can lead to a more accurate approach to the disease. In general, medication management choices are influenced by five main factors; the indication, efficacy, safety, convenience, and cost. However, in the treatment of HCV with Harvoni® or Viekira Pak® many of these factors have minimal implications on this decision. The specific indications of these agents does provide some insight as Harvoni® is indicated for Genotype 1, 4, 5 and 6, is acceptable in all forms of cirrhosis as well as solid organ transplants, and can be used for a shorter treatment course (8-weeks as compared to most 12 week courses) for those mono-

infected with a viral load <6 million IU/mL.[36,37] Viekira Pak® on the other hand is only indicated for use in patients with Genotype 1, with or without compensated cirrhosis.[44,45] When comparing efficacy and safety of these two agents the results are very similar as both agents achieve a >95% cure rate and have mild side effects that are rarely a cause for discontinuation.[37,45]

Isolating the convenience of a product can be multifaceted as the term can incorporate lab monitoring, ease of product use by the patient, and ease of product dispensing by the facility. Harvoni® does have the advantage of the convenience factor as the one tablet, once daily regimen is appealing for both practitioners and patients alike. Additionally Harvoni® has fewer DDI's than Viekira Pak®, with amiodarone listed as the most troublesome unless a patient is co-infected with HIV in which treatment with Harvoni® becomes more complicated.[36,37] Viekira Pak® on the other hand requires a dosing administration of four tablets daily (two combination tablets containing ombitasvir/paritaprevir/ritonavir with one dasabuvir in the morning with food, and one dasabuvir at night with food).[44,45] DDI's are also a larger concern with Viekira Pak®, though most can be avoided by an alteration in therapy of the offending agent. Viekira Pak® has mitigated some of the issues with convenience by packaging the entire regimen into a patient friendly daily dosing card that is color coded to indicate which components and how many tablets to take. The use of this clever packaging removes much, if not all, of the concern regarding patient understanding of the more complicated regimen.

With the exception of DDI's between the two drugs, most of the other factors remain extremely similar and therefore are likely not strong predictors of treatment selection. This lends to the theory that the determining factor between which agent to

use, Harvoni® or Viekira Pak®, should largely come down to the cost of these two agents when either is indicated for use in a patient. The financial impact of treating Hepatitis C with any DAA agent is associated with tremendous expenditures for the healthcare system. With the average Harvoni® patient costing the VA Health Care System 60% more than those treated with Viekira Pak® it would seem logical for those who qualify for either agent to be placed on the less expensive therapeutic alternative. Harvoni® however remains the most commonly prescribed agent within VA.

Clinical decision trees have an important role in the healthcare setting. Not only do they promote consistency between care providers, but they also provide a clear dichotomy to guide treatment toward the appropriate choice. **Figure 1-3** illustrates the abbreviated decision tree (also known as a 'quick order') utilized by the VA station 612 for the treatment of genotype 1a/1b HCV infections. While there are areas in which a clinical decision is permitted, and some areas in which Harvoni® was preferred such as Child-Pugh grade B or C, or prior treatment with a protease inhibitor or sofosbuvir, the majority of the pathways guide the prescriber toward Viekira Pak® if clinically appropriate. The utilization of this decision tree has promoted fiscal responsibility as it guides caregivers toward the cheaper therapeutic alternative whenever clinically indicated. Internal VA reports indicated that VA Northern California Health Care System was the #1 prescriber of Viekira Pak® in the VA, even though other facilities treated a larger number of Veterans. With Harvoni® remaining highly utilized it becomes prudent to evaluate other factors that may be contributing to a decision that leads toward suboptimal financial utilization of resources.

The intent of this research is to identify characteristics that are guiding treatment to enable a better understanding of the decision to ultimately optimize the treatment of HCV. When it is clinically appropriate, treatment is guided toward the most cost-effective pathway thereby allowing the cost of HCV treatment to be minimized, increasing the potential number of treatable individuals with the finite resources available. The findings may facilitate clinician education with the goal of optimal patient outcomes and good financial stewardship.

Methods

This study is a 12-month retrospective, cross-sectional medical record review with no active patient enrollment. The study was approved by the VA investigational review board as an exempt protocol with special permission granted to access VA Informatics and Computing Infrastructure (VINCI) database which houses VA data for all sites across the country. Data was extracted using SQL query language to evaluate patient location, medication use history, laboratory data, and diagnoses.

Patients in the VA Health Care System who were initiated on either Harvoni® or Viekira Pak® for Hepatitis C after January 1, 2015 and before December 31, 2015 were included. Patients with HCV genotype 1 were included in the analysis. Those with genotype 2-6, or those with mixed genotype were excluded. Patients with genotype 1 were subdivided into genotype 1a and genotype 1b. Those who did not have subtype in laboratory results were excluded from analysis due to the nuances of treating each subtype and the ambiguity of the correct direction of prescribing. In station 612 the use of the decision tree was utilized to assist in the evaluation of HCV treatment. First the severe drug-drug interactions were acknowledged before progressing through the

decisions important for HCV treatment such as genotypes, subtypes, past treatment, cirrhosis, and renal impairment. Each level of inquiries requiring evaluation before a drug recommendation was provided.

For the analysis, patients were divided into two groups; those who received treatment with Harvoni® and those with Viekira Pak®. Clinical and demographic factors including age (or >89 years), weight, renal function, HCV genotype and subtype, HCV RNA viral load, prior treatment for HCV with sofosbuvir, protease inhibitors, PEGinterferon or ribavirin, determinants of hepatic fibrosis or cirrhosis including FIB-4 score and Child-Pugh grade, presence of interacting medication, and contraindication to components of regimen were analyzed to determine which are statistically associated with the treatment selected. Timelines for metric collections and surrogate markers are presented in **Table 1** and **Table 2** respectively. Child-Pugh scores were calculated from labs including bilirubin, INR, albumin, and evidence for ascites and hepatic encephalopathy. Child-Pugh point values were assigned to lab and diagnosis and tallied to create a raw score for each patient. The raw value was then assigned the Child-Pugh class shown in **Table 3**

Table 1: Timelines for parameters used in data collection

Metric	Method of determination – time from backbone study drug
Ribavirin added to regimen	30 days before – 60 days after first fill of study drug
Height, HCV Genotype, HCV Quantitative and qualitative labs	20 years prior
Weight, Serum Creatinine, bilirubin, eGFR, albumin, INR, AST, ALT, Platelet	2 years prior
PEGinterferon, ribavirin, sofosbuvir, simeprevir, boceprevir, telaprevir	Any time before release date
Drug-Drug interactions	Up to 1 year prior to release date

Table 2: Surrogate markers to determine diagnosis used in Child-Pugh grading

Diagnosis	Surrogate marker	Method of determination – time from backbone study drug
Hepatic encephalopathy	Rifaximin, lactulose	Between January 1, 2001 and release date
Ascites	Hydrochlorothiazide/spironolactone, spironolactone, eplerenone	Between January 1, 2001 and release date

Table 3: Liver cirrhosis point allocation (Child-Pugh score)*

Measure	1 point	2 points	3 points
Total bilirubin, mmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum Albumin, (g/dL)	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.2	>2
Ascites	None	Mild (or suppressed with medication)	<2.8
Hepatic encephalopathy	None	Grade I-II	Grade III-IV

*Class A –total points 5-6, Class B – total points 7-9, Class C – total points 10-15

Ascites was identified using diagnostic codes for ascites (ICD9 codes 789.51, 789.59 or ICD10 codes K70.11, K70.31, K71.51, R18.0, R18.8) or medications used to treat ascites including spironolactone, eplerenone in the absence of heart failure. Hepatic encephalopathy was identified using diagnostic codes for hepatic encephalopathy (ICD9 codes 323.0, 323.01, 323.4, 323.41, 323.6, 323.61, 323.62, 323.8, 323.81 ,323.9 ,348.3, 348.30,348.39, 572.2 or ICD10 codes A86, B94.1, G04.01, G04.81, G04.90, G05.3, G93.40, G93.49) or medications used to treat hepatic encephalopathy including lactulose and rifaximin. For patients with ascites or hepatic encephalopathy severity was not discerned and thus a score of 3 was assigned to those with that diagnosis in calculation of Child-Pugh grade.

Drug-drug interactions were analyzed by combining the drug interactions list from the VA Northern California Health Care System's clinical decision tree, and the package insert interaction list. Severe DDI's were categorized by including those medications listed as a contraindication specifically by the manufacturer of the drug or listed as a category D or X interaction based on drug databases such as Lexicomp® and Clinical Pharmacology®.

De-identified patient information was extracted for use in the statistical analysis. Descriptive statistics and significant ($p<0.05$) clinical factors will be reported. Inferential statistics, including Fisher's Exact, Chi Square, Independent samples t-test, and Mann-Whitney, and Kolmogorov-Smirnov Test for normality were used to test for significant differences in prescribing patterns as a function of medication use, drug-drug interactions, liver and renal function, sociodemographic information and prescribing region. Clinical factors were analyzed using a logistic regression analysis to establish

which factors predict treatment selection with Harvoni® coded as '1' and Viekira Pak® coded as '0'. For the analysis the dependent variable was the prescribing of Harvoni® vs Viekira Pak®, with demographic and clinical characteristics, medication and disease state presence as the independent explanatory variables. All significance calculations were performed with an a priori probability of making a Type 1 error set to 0.05. All statistics were performed via IBM SPSS Statistics 22 (IBM, Armonk, NY).

Results

In total 25,717 patients with HCV genotype 1 prescribed Harvoni® or Viekira Pak® were extracted from the VINCI database, of which 1,536 were eliminated as a specific subtype was not retrievable. Demographic characteristics of the study population are presented in **Table 4.** Noteworthy is important representation of African Americans, and the predominantly male Veteran population. Clinical characteristics are provided in **Table 5.** The majority were infected with genotype 1a. For the clinical indicators for Harvoni® use related to HIV co-infection, prior treatment with a protease inhibitor or sofosbuvir, or Child-Pugh class B or C, a relatively small percentage were identified in the study population (11%, 7.1%, 8.3%, respectively). Of the 2,004 patients with Child-Pugh class B or C, 1,813 were prescribed Harvoni® and 191 were prescribed Viekira Pak®. Of the 1,718 patients pretreated with protease inhibitors or sofosbuvir, 1,641 were prescribed Harvoni® and 77 were prescribed Viekira Pak®. Approximately two–thirds of the population had a significant drug- drug interaction with HCV medication. The logistic regression results for all qualifying patients is presented in **Table 6**. Of note, for all logistic regression an increased likelihood for Harvoni® prescribing is denoted by a positive correlation coefficient (B) and a negative coefficient is indicative of an increased

likelihood for Viekira Pak® prescribing. The logistic regression results identified that prescribing of Harvoni® was statistically associated with higher FIB-4 scores, HIV co-infection, presence of drug interactions and pretreatment with protease inhibitor or sofosbuvir. Child-Pugh class A and higher serum creatinine levels were associated with prescribing of Viekira Pak®.

Table 4 : Demographic Characteristics – All stations

	Number (%)
Drug	
Harvoni®	17,977 (74.3)
Viekira Pak®	6,204 (25.7)
Age (mean ±SD)	63.4 ±6.4
Sex	
Male	23,368 (96.6)
Female	813 (3.4)
Race	
White	12,680 (52.4)
Black/African American	9,546 (39.5)
Native American	240 (1.0)
Hawaiian/Pacific Islander	230 (1.0)
Asian	58 (0.2)
Declined	759 (3.1)
Unknown by patient	365 (1.5)
Not reported	303 (1.3

Table 5 : Clinical Characteristics – All stations

	Number (%)
Child-Pugh score	
Class A	22,177 (91.7)
Class B	1,350 (5.6)
Class C	654 (2.7)
BMI (mean ±SD)	28.5 ±5.3
HIV co-infection	2,661 (11.0)
Actual Body Weight CrCL (mL/min) (mean ±SD)	102.2 ±34.6
Genotype	
1a	17,179 (71.0)
1b	7,002 (29.0)
Current Ribavirin	8,992 (37.2)
Previous treatment with:	
Peg-interferon	3,965 (16.4)
Ribavirin	7,005 (29.0)
Protease inhibitor/ sofosbuvir	1,718 (7.1)
At least 1 Severe DDI	16,485 (68.2)
DDI's (mean ±SD)	
Total DDI's	
Harvoni®	0.6 ±0.7
Viekira Pak®	2.8 ±2.1
Severe DDI's (mean ±SD)	1.5 ±1.4
Harvoni®	0.5 ±0.6
Viekira Pak®	1.0 ±1.0
Non-severe DDI's (mean ±SD)	1.9 ±1.7
Harvoni®	0.1 ±0.3
Viekira Pak®	1.7 ±1.6
Potentially modifiable DDI's	
Proton Pump Inhibitors	8,798 (36.4)
Ranitidine	1,552 (6.4)
Atorvastatin	1,389 (5.7)
Simvastatin	938 (3.9)
Pravastatin	577 (2.4)
Rosuvastatin	231 (1.0)
Famotidine	95 (0.4)
Lovastatin	43 (0.2)

Table 6 : Logistic regression – All stations

Factor Analyzed	B	Sig	Exp(B)
Station 612 vs others	-1.146	**0.000**	0.318
Child Pugh Class A	-1.656	**0.000**	0.191
Child Pugh Class B	-0.633	**0.002**	0.531
Child Pugh Class C	-	-	-
Age	-0.007	**0.023**	0.993
Gender	-0.117	0.255	0.889
BMI	0.024	**0.000**	1.024
Serum Creatinine	-0.480	**0.000**	0.619
Actual Body Weight CrCL	-0.004	**0.000**	0.996
FIB4	0.083	**0.000**	1.086
APRI	-0.105	**0.001**	0.900
GENOTYPE 1a	1.047	**0.000**	2.850
GENOTYPE 1b	-	-	-
HIV	0.563	**0.000**	1.757
PrePEGinterferon	1.307	**0.000**	3.697
PreRibavirin	-1.746	**0.000**	0.174
PreTreatment	2.305	**0.000**	10.028
Total DDI's - Harvoni®	0.138	0.156	1.148
Total DDI's – Viekira Pak®	-0.042	0.471	0.959
At least 1 Severe DDI	0.142	**0.014**	1.152
# of severe DDI's - all	0.135	**0.033**	1.145
# of severe DDI's - Harvoni®	-0.003	0.984	0.997
# of severe DDI's – Viekira Pak®			
# of non-severe DDI's - all	0.144	**0.012**	1.155
Proton Pump Inhibitors	-0.429	**0.000**	0.651
Ranitidine	-0.466	**0.000**	0.628
Atorvastatin	-0.014	0.864	0.986
Simvastatin	0.120	0.214	1.127
Pravastatin	-0.479	**0.000**	0.619
Rosuvastatin	-0.799	**0.000**	0.450
Famotidine	0.420	0.249	1.521
Lovastatin	0.482	0.266	1.620

An analysis of the initial data shows a statistically significant difference in prescribing patterns of the VA Northern California Health Care System (station 612) as compared to the rest of the United States, demonstrating significantly higher rates of Viekira Pak® prescribing. This finding led to the further analysis of the patients within that station to identify what factors led to this decision. As Child-Pugh class B or C, and previous treatment with protease inhibitors (boceprevir, telaprevir, simeprevir) and sofosbuvir support treatment with Harvoni®, these patients were removed in an attempt to identify which other factors affected treatment decisions. With these patients removed (n=3,452), the total population analyzed dropped to 20,729. Demographic data and clinical characteristics for this subset are presented in **Table 7** and **Table 8**, respectively. No discernable differences between this group and the total population were noted. **Table 9** reflects logistic regression for all stations removing Child-Pugh B and C, and pretreatment with protease inhibitors and/or sofosbuvir. Of note, a drug interaction with rosuvastatin and ranitidine were statistically associated with prescribing of Viekira Pak® as is clinically indicated. Other drug interactions were not associated with expected HCV drug selection.

Table 7 : Demographic Characteristics – All stations – Filtered patients *(Child-Pugh B and C, and Pretreatment with Protease inhibitors and/or sofosbuvir removed)*

	Number (%)
Harvoni®	14,787 (71.3)
Viekira Pak®	5,942 (28.7)
Age (mean ±SD)	63.3 ±6.6
Sex	
Male	20,019 (96.6)
Female	710 (3.4)
Race	
White	10,687 (51.6)
Black/African American	8,365 (40.4)
Native American	199 (1.0)
Hawaiian/Pacific Islander	197 (1.0)
Asian	46 (0.2)
Declined	645 (3.1)
Unknown by patient	311 (1.5)
Not reported	279 (1.3)

Table 8 : Clinical Characteristics – All stations – Filtered patients *(Child-Pugh B and C, and Pretreatment with Protease inhibitors and/or sofosbuvir removed)*

	Number (%)
BMI (mean ±SD)	28.4 ±5.3
HIV	2,350 (11.3)
Actual Body Weight CrCL (mL/min) (mean ±SD)	101.5 ±33.8
Genotype	
1a	14,676 (70.8)
1b	6,053 (29.2)
Current Ribavirin	
Previous therapy with:	
PEGinterferon	2,225 (10.7)
Ribavirin	4,826 (23.3)
At least 1 Severe DDI	13,883 (67.0)
DDI's (mean ±SD)	
Total DDI's	
Harvoni®	0.5 ±0.7
Viekira Pak®	2.7 ±2.1
Severe DDI's (mean ±SD)	1.5 ±1.4
Harvoni®	0.5 ±0.6
Viekira Pak®	1.0 ±1.0
Non-severe DDI's (mean ±SD)	1.8 ±1.6
Harvoni®	0.1 ±0.2
Viekira Pak®	1.7 ±1.6
Potentially modifiable DDI's	
Proton Pump Inhibitors	7,008 (33.8)
Atorvastatin	1,294 (6.2)
Ranitidine	1,277 (6.2)
Simvastatin	877 (4.2)
Pravastatin	509 (2.5)
Rosuvastatin	203 (1.0)
Famotidine	76 (0.4)
Lovastatin	41 (0.2)

Table 9 : Logistic regression – All stations– Filtered patients *(child-Pugh B and C, and Pretreatment with Protease inhibitors and/or sofosbuvir removed)*

Factor Analyzed	B	Sig	Exp(B)
Station 612 vs others	-1.177	**0.000**	0.308
Age	-0.007	0.051	0.994
Gender	-0.142	0.182	0.868
BMI	0.023	**0.000**	1.024
Serum Creatinine	-0.407	**0.000**	0.666
Actual Body Weight CrCL	-0.004	**0.000**	0.996
FIB4	0.082	**0.000**	1.085
APRI	-0.099	**0.005**	0.906
GENOTYPE 1a	1.078	**0.000**	2.940
GENOTYPE 1b	-	-	-
HIV	0.583	**0.000**	1.792
PrePEGinterferon	1.389	**0.000**	4.010
PreRibavirin	-1.828	**0.000**	0.161
Total DDI's - Harvoni®	0.073	0.482	1.076
Total DDI's – Viekira Pak®	-0.047	0.430	0.954
At least 1 Severe DDI	0.130	**0.028**	1.139
# of severe DDI's - all	0.154	**0.019**	1.167
# of severe DDI's - Harvoni®	0.022	0.877	1.023
# of severe DDI's – Viekira Pak®	-	-	-
# of non-severe DDI's - all	0.160	**0.007**	1.173
Proton Pump Inhibitor	-0.423	**0.001**	0.655
Atorvastatin	-0.004	0.965	0.996
Ranitidine	-0.488	**0.000**	0.614
Simvastatin	0.101	0.303	1.106
Rosuvastatin	-0.843	**0.000**	0.430
Famotidine	0.457	0.234	1.580
Lovastatin	0.464	0.287	1.591

The results of the logistic regression show that there is still a statistically significant difference in the prescribing pattern for station 612 as compared to the rest of the United States. As many of the factors analyzed in the logistic regression remained the same, the focus shifts to the differences between station 612 and other stations throughout the United States. **Table 10** provides a comparison of the demographic characteristics and **Table 11** a comparison of the clinical characteristics with Chi-Square and Mann Whitney tests utilized to detect differences between these groups. No apparent clinically significant differences are noted. **Table 12** compares the logistic regression analysis results for each group. The presence of a severe drug interaction and non-severe interaction was associated with prescribing Harvoni® nationally, whereas those interactions were not associated with prescribing Harvoni® in station 612.

Table 10 : Population Characteristics – Filtered Patients – Station 612 vs Other stations *(Child-Pugh B and C, and Pretreatment with Protease inhibitors and/or sofosbuvir removed)*

	Station 612 Number (%)	Other Stations Number (%)	Significance (p<0.05)
Drug			**<0.001***
Harvoni®	198 (42.8)	14,589 (72.0)	
Viekira Pak®	265 (57.2)	5,677 (28.0)	
Age (mean ±SD)	65.4 ±6.0	63.3 ±6.6	**<0.001†**
Sex			**0.011***
Male	457 (98.7)	19,562 (96.5)	
Female	6 (1.3)	704 (3.5)	
Race			
White	236 (51.0)	10,451 (51.6)	0.799
Black/African American	172 (37.1)	8,193 (40.4)	0.155
Asian	3 (0.6)	43 (0.2)	**0.049**
Native American	11 (2.4)	188 (0.9)	**0.005***
Hawaiian/Pacific Islander	4 (0.9)	193 (1.0)	0.846
Declined	17 (3.7)	628 (3.1)	0.483
Unknown by patient	12 (2.6)	299 (1.5)	0.051
Not reported	8 (1.7)	271 (1.3)	0.471

Chi Square used to determine significance in all nominal variables

* Fisher's exact result reported

† Mann-Whitney used to determine significance in all numerical** data

**All numerical data verified by Kolmogorov-Smirnov test as not normally distributed

Table 11 : Clinical Characteristics – Filtered Patients – Station 612 vs Other stations *(child-Pugh B and C, and Pretreatment with Protease inhibitors and/or sofosbuvir removed)*

	Station 612 Number (%)	Other Stations Number (%)	Significance (p<0.05)
BMI (mean ±SD)	27.9 ±5.1	28.4 ±5.3	**0.025**†
HIV	20 (4.3)	2,330 (11.5)	**<0.001***
Actual Body Weight CrCL (mL/min) (mean ±SD)	98.6 ±34.9	33.9 ±33.8	0.100†
Genotype			
1a	328 (70.8)	14,348 (70.8)	0.984
1b	135 (29.2)	5,918 (29.2)	0.984
Previous treatment with:			
PEGinterferon	64 (13.8)	2,161 (10.7)	**0.031***
Ribavirin	150 (32.4)	4,676 (23.1)	**<0.001***
At least 1 Severe DDI	300 (64.8)	13,583 (67.0)	0.313
DDI's (mean ±SD)			
Total DDI's			
Harvoni®	0.4 ±0.6	0.5 ±0.7	**0.008**†
Viekira Pak®	2.5 ±1.8	2.7 ±2.1	**0.050**†
Severe DDI's (mean ±SD)	1.3 ±1.3	1.5 ±1.4	**0.047**†
Harvoni®	0.4 ±0.5	0.5 ±0.6	**0.023**†
Viekira Pak®	0.9 ±0.9	1.0 ±1.0	0.154†
Non-severe DDI's (mean ±SD)	1.6 ±0.9	1.8 ±1.6	0.110†
Harvoni®	0.04 ±0.2	0.1 ±0.2	0.312†
Viekira Pak®	1.5 ±1.4	1.7 ±1.6	0.148†
Potentially modifiable DDI's			
Simvastatin	29 (6.3)	848 (4.2)	**0.030***
Rosuvastatin	-	203 (1.0)	**0.016***
Atorvastatin	28 (6.0)	1,266 (6.2)	0.861
Lovastatin	1 (0.2)	40 (0.2)	0.929
Pravastatin	15 (3.2)	494 (2.4)	0.270
Ranitidine	31 (6.7)	1,246 (6.1)	0.628
Famotidine	-	76 (0.4)	0.187
Proton Pump Inhibitors	136 (29.4)	6,872 (33.9)	**0.043***

Chi Square used to determine significance in all nominal variables

* Fisher's exact result reported

† Mann-Whitney used to determine significance in all numerical** data

**All numerical data verified by Kolmogorov-Smirnov test as not normally distributed

Table 12 : Logistic Regression – Filtered Patients – Station 612 vs Other stations *(Child-Pugh B and C, and Pretreatment with Protease inhibitors and/or sofosbuvir removed)*

	Station 612			Station Other		
Factor Analyzed	B	Sig	Exp(B)	B	Sig	Exp(B)
Age	-0.004	0.862	0.996	-0.006	0.066	0.994
Gender	0.186	0.840	1.204	-0.149	0.165	0.861
BMI	0.024	0.401	1.024	0.023	**0.000**	1.023
Serum Creatinine	-0.610	0.129	0.543	-0.401	**0.000**	0.670
Actual Body Weight CrCL	-0.002	0.751	0.998	-0.004	**0.000**	0.996
FIB4	0.147	0.145	1.158	0.081	**0.000**	1.084
APRI	-0.195	0.396	0.823	-0.096	**0.007**	0.908
GENOTYPE 1a	0.875	**0.000**	2.399	1.085	**0.000**	2.959
GENOTYPE 1b	-	-	-	-	-	-
HIV	2.268	**0.009**	9.657	0.568	**0.000**	1.764
PrePEGinterferon	0.549	0.141	1.732	1.414	**0.000**	4.113
PreRBV	-0.744	**0.008**	0.475	-1.861	**0.000**	0.156
Total DDI's - Harvoni®	-0.180	0.794	0.835	0.077	0.466	1.080
Total DDI's – Viekira Pak®	-0.499	0.142	0.607	-0.033	0.592	0.968
At least 1 Severe DDI	0.456	0.200	1.578	0.113	0.060	1.120
# of severe DDI's - all	0.404	0.298	1.497	0.147	**0.028**	1.158
# of severe DDI's - Harvoni®	-1.256	0.323	0.285	0.036	0.805	1.037
# of severe DDI's – Viekira Pak®	-	-	-	-	-	-
# of non-severe DDI's - all	0.531	0.114	1.701	0.147	**0.015**	1.158
Atorvastatin	0.150	0.766	1.162	0.003	0.968	1.003
Lovastatin	20.706	1.000	982870 514.821	0.416	0.344	1.515
Simvastatin	0.950	0.067	2.585	0.083	0.405	1.087
Rosuvastatin	-	-	-	-0.857	**0.000**	0.424
Pravastatin	-2.440	**0.026**	0.087	-0.445	**0.000**	0.641
Ranitidine	0.883	0.487	2.419	-0.503	**0.000**	0.605
Famotidine	-	-	-	0.456	0.237	1.578
Proton Pump Inhibitor	1.242	0.310	3.464	-0.439	**0.001**	0.645

Discussion

One of the biggest issues for patients being considered for HCV treatment is adherence to the medication regimen as cure rate is heavily impacted by strong adherence to these agents. In the VA system, that concern is addressed with the patient before qualification for treatment is awarded. All patients are counseled heavily to the requirements for adherence to all treatment components including not only medication adherence but appointment adherence as well. Only those patients who are deemed capable and willing to make that commitment are evaluated for a course of therapy. This ability to ensure adherence allowed this study to focus on other factors that may influence decisions to treat with either agent.

There are many factors that were identified in this study that were predictable and rational. The mean age of our population was 63.4. This is expected as this falls within the targeted birth cohort population due to the increased risk of HCV infection in that group. While pill burden is often a concern for patients but more often with the geriatric population this should not have played an important role in this particular disease state as confusion with the dosing was mitigated by the manufacturer of Viekira Pak® by repackaging in a patient friendly manner. As the treatment is often only 12 weeks, the burden is minimal and therefore not likely a predictive factor to treatment. In fact, some of the regression analysis results reported increasing age association with the prescribing of Viekira Pak®.

Factors that were expected to influence prescribing due to guideline and manufacturer recommendations included pretreatment with protease inhibitors (boceprevir, telaprevir, and simeprevir) and Child-Pugh class B or C. In those patients

prescribing should be associated with prescribing Harvoni® which was observed in this study. The first logistic regression (**Table 4**) did not include patients with Child-Pugh class C unfortunately, as patients with incomplete information are excluded from this type of an analysis. This decreased the sample size for our Child-Pugh class B or C group which decreased our predictive ability for this population.

According to guidelines and the drug manufacturer, patients with creatinine clearance (CrCL) < 30 mL/min and those with ESRD should avoid Harvoni®. In this population, increasing serum creatinine levels were associated with prescribing of Viekira Pak® appropriately. Some factors however were not as rational for this study. Though neither drug manufacturer provides guidance on weight considerations, increasing BMI was consistently associated with Harvoni® treatment in our population. While a direct explanation is not clear, it is plausible that prescribers perceive that Harvoni® is more potent than Viekira Pak® (single dose Harvoni® vs multi-dose regimen with Viekira Pak®), and that it may be more effective in patients with higher BMI's.

HIV co-infection was another confounding factor in our analysis. While the diagnosis of HIV itself is not a limitation to treatment, the patient is required to accept and obtain treatment for HIV during HCV treatment to decrease the likelihood of developing cross-resistance to the HIV treatment regimens. In the VA population, only those who received concurrent HIV treatment qualify for HCV treatment and therefore the only correlation the concomitant diagnosis should play is in regards to drug interactions. That however was not consistent and did not usually correlate with the diagnosis for HIV itself. It is possible that prescribers attempted to bypass the analysis of

the DDI's by choosing the agent with fewer listed DDI's, Harvoni®. This may not be an appropriate approach and should be addressed in all stations within the VA.

Drug-drug interactions are an area in which the inclusion of a clinical pharmacy specialist may benefit the health system immensely. While it is an accurate observation that Viekira Pak® has a higher number of possible drug interactions, guidance to help mitigate some are provided. For instance, DDI's such as those with the HMG-CoA reductase inhibitors used to control cholesterol can be avoided by temporarily holding the statin therapy since the treatment typically lasts no more than 12 weeks. For those who cannot hold the medication a change to an agent that does not have the DDI can be an option as well. Considering the cost differences between Harvoni® and Viekira Pak®, the investigation into such options is important. Nationally, the presence of severe DDI or non-severe DDI was associated with Harvoni® treatment, while station 612 did not see this association. Part of the early components of the clinical decision tree for station 612 included the evaluation of significant DDI's and thus may have prompted the prescriber to contact the clinical pharmacist to discuss options. Whenever possible, the pharmacists in station 612 manage the drug interaction and optimize utilization of Viekira Pak®.

Limitations of the study. There were many limitations of this study due the nature of our study population and data extraction capabilities. One of the largest is the difficulty in the ability to accurately calculate a Child-Pugh scores in the VA Health Care System which occurred for two reasons. First, variance in the nomenclature for laboratory tests exists, along with the potential for human error when entering laboratory results into the electronic medical record. Secondly, there are challenges in determining the degree of ascites and hepatic encephalopathy required to determine the Child-Pugh

score. As such, maximum number of points were assigned to a score if evidence of the diagnosis or medications for treating ascites or encephalopathy were identified.

While great care was taken to maximize accuracy of the drug-drug interaction portion of our analysis there still remains areas of limitation. The medications identified as an interacting agent were pulled from the VINCI database if the patient was prescribed the medication up to 1 year prior to the release date of the HCV treating agent. This however does not account for agents that were prescribed but not taken by the patient, or medications that were held and/or discontinued during the treatment period. While the correlation between these agents and the HCV treating agent is still important, as the agents should not have determined treatment one way or another, this limitation does add some complication to that interpretation.

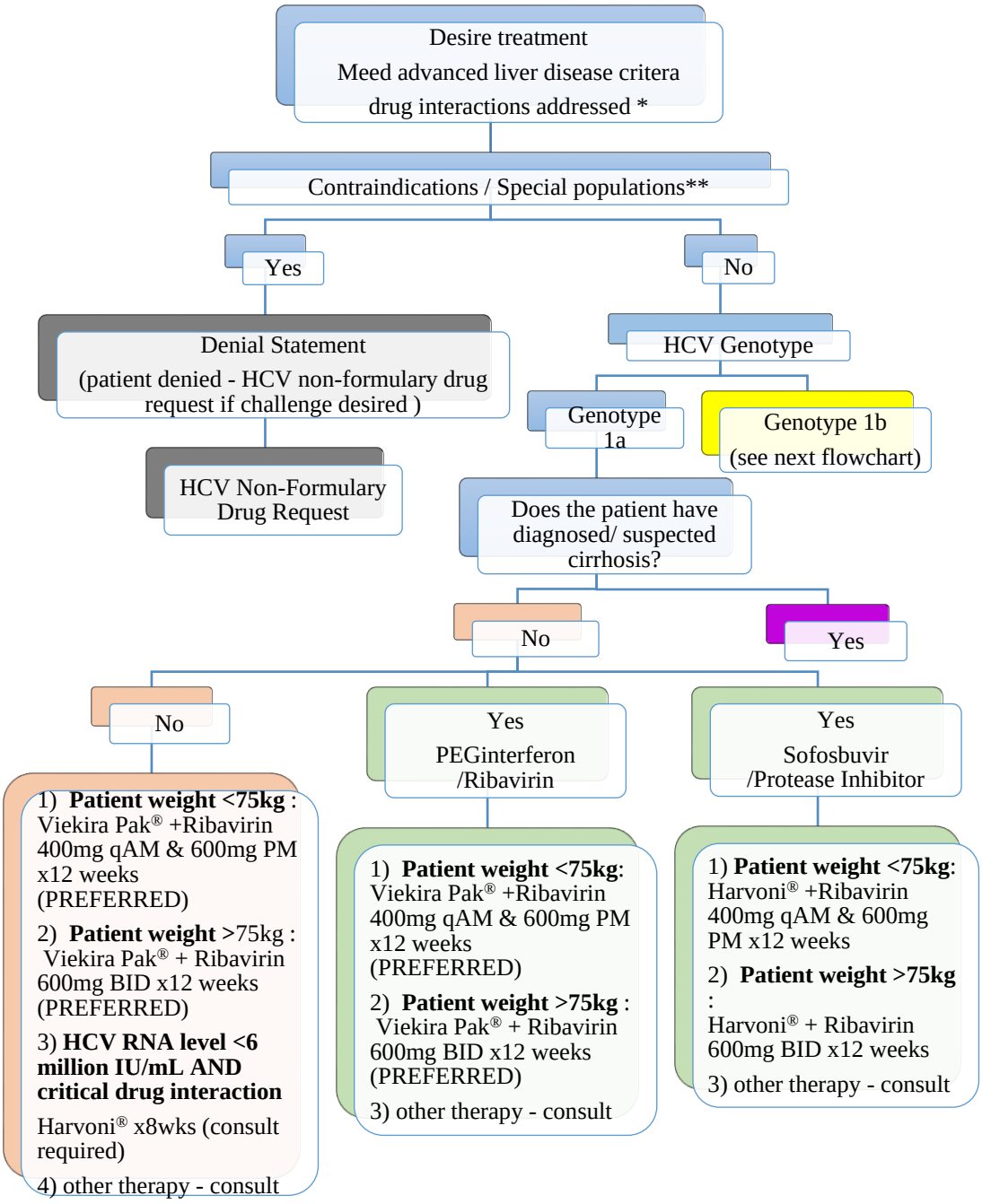
Other factors also influence prescribing, and are not measured or evaluated in this analysis. One such factor is the viral load of the patients in the study. As Harvoni® allows for an 8-week course of therapy for patients whose viral load is <6million IU/mL this could have been an area of interest to see how many of those patients, who otherwise qualified for either agent, received Harvoni®. Another factor was due to the inability of the VA to monitor and evaluate the impact of advertisements and drug sales representatives on their treatment selection (i.e.: drug bias) which is a large concern in all healthcare systems. Patient-centered advertising often has a large impact on treatment of any disease when physicians do not already have a preference for treatment in mind.[46,47] Since 2012 the Direct To Consumer (DTC) advertising budget has increase from an average of $3.2 billion to its peak in 2015 at approximately $5.3 billion. In a report listing the top twenty advertisement expenditures for 2015, Harvoni® was listed as

number seven, with Viekira Pak® not appearing on the list.[46] Instances like this could directly result in the utilization of less than optimal medication choices in order to appease patient desires. Drug representatives targeting healthcare providers also have an impact on prescribing in many health systems. Although the FDA has limited the capabilities of pharmaceutical representatives, it still has shown positive correlation between the representative and the prescribing patterns.[48]

Conclusion

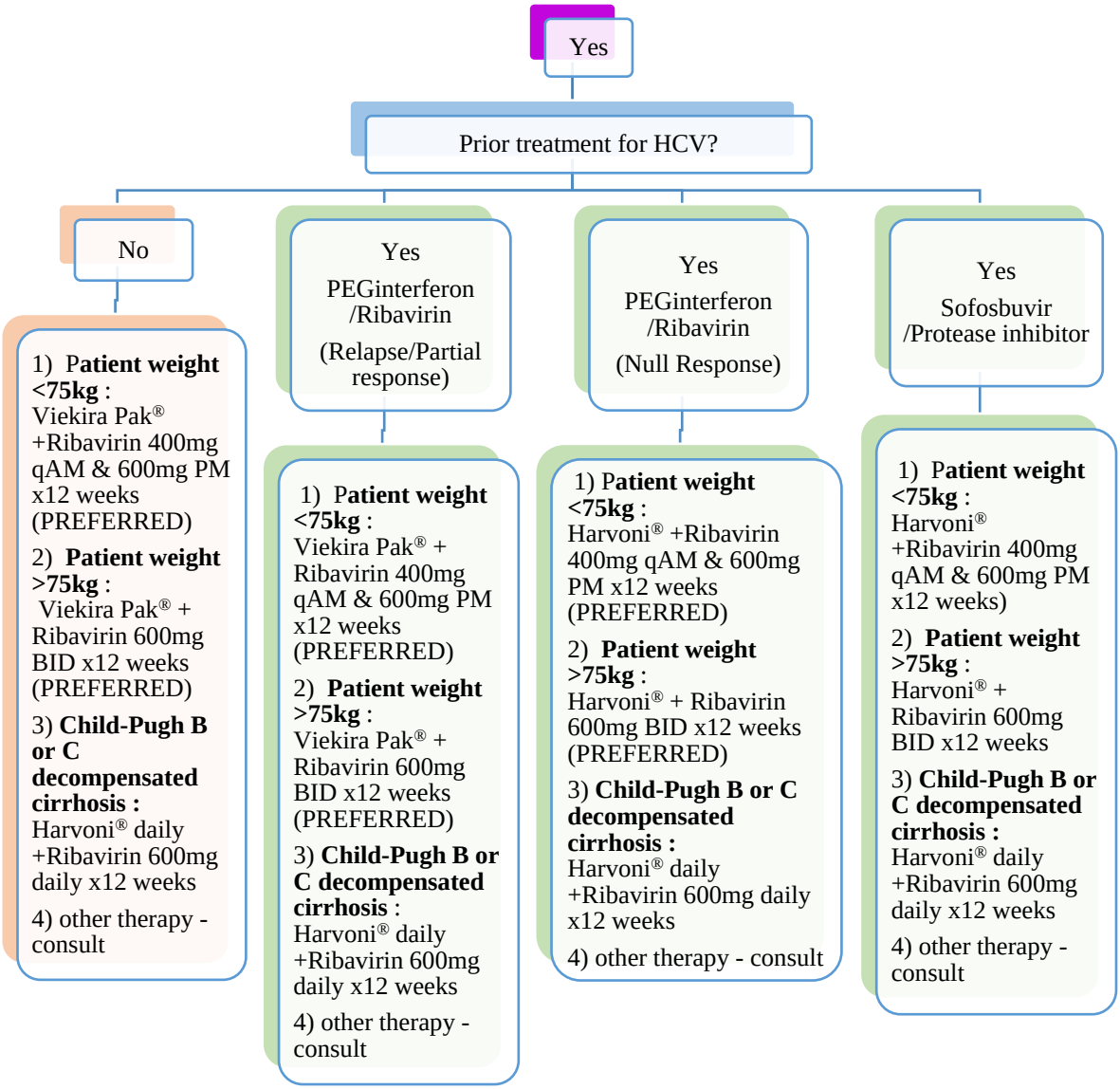
The birth cohort comprises the largest proportion of those infected with HCV and as that population ages so will the complications.[31] These complications will ultimately lead to higher healthcare costs. By treating now we incur upfront costs but a projected overall saving is expected as the avoidance of the cost of treating cirrhosis, HCC, and transplants well exceed the costs of these medications. Misconceptions in the treatment pathway such as those identified in this study are costly to the healthcare system and must be dispelled to protect the financial integrity of the institution. VA National Guidelines for treatment focused initially on patients with decompensated liver disease, warranting heavy Harvoni® usage early on. Now however, treatment of all stages of liver fibrosis are considered beneficial to both the patient and healthcare system. This unlocks the possibility to use agents such as Viekira Pak® that are less costly than Harvoni®, minimizing the financial impact of each treated patient. The fact that Viekira Pak® was prescribed to a significant degree at VA Northern California Health Care System may relate to the development of a decision tree algorithm provided to prescribers and the clinical Pharmacist support associated with its use. Their early focus on drug-drug interactions seems to have been successful in guiding treatment toward the cheaper

therapeutic option whenever it was clinically feasible. With the results of the study it can facilitate further optimization of the current decision tree/quick orders, and illustrates the impact of this type of algorithm in the appropriation of finances within the healthcare system in treating HCV infections. With the expansion of this type of algorithm the VA system could maximize the impact of their limited resources to provide care to more Veterans impacted by this disease.



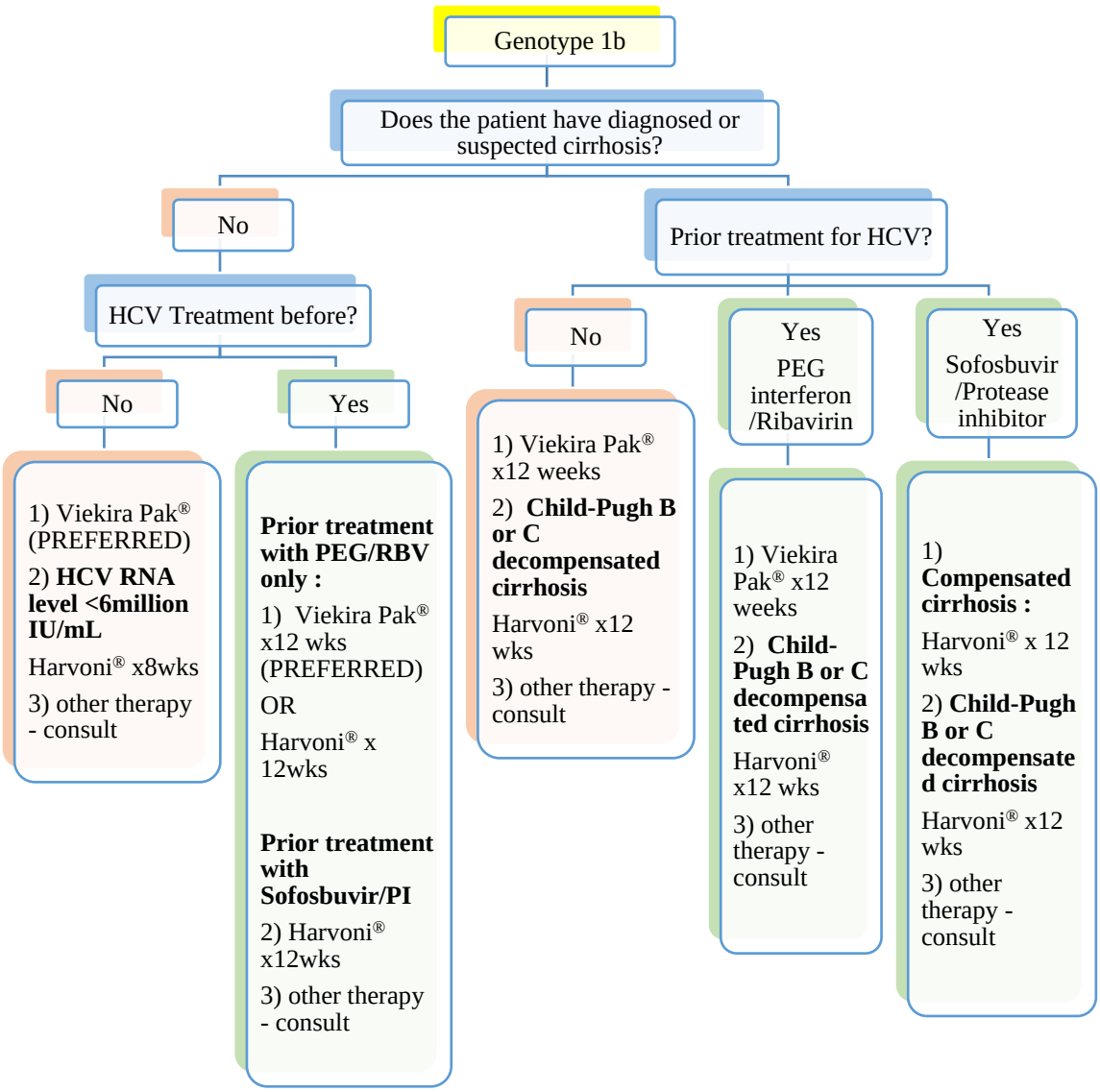
*** disclaimer – decision tree model was utilized during study period – updates may have been made outside the study window*

Figure 1 : Station 612 - HCV Genotype 1 Decision Tree – Part 1



*** disclaimer – decision tree model was utilized during study period – updates may have been made outside the study window*

Figure 2 : Station 612 - HCV Genotype 1 Decision Tree – Part 2



*** disclaimer – decision tree model was utilized during study period – updates may have been made outside the study window*

Figure 3 : Station 612 - HCV Genotype 1 Decision Tree – Part 3

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