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Assessing Prevalence of Alcohol Use and Association with Receipt of Direct-acting Antiviral Treatment and Sustained Virologic Response among Veterans with Chronic Hepatitis C at the Atlanta VA Medical Center

By

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Master of Public Health

Applied Epidemiology

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By

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B.S., University of California San Diego, 2013

Thesis Committee Chair: Jodie L. Guest, PhD, MPH

An abstract of
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Abstract

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Aims

To describe the prevalence of alcohol use in veterans with chronic Hepatitis C Virus (HCV) infection presenting for care at the Atlanta VA medical center (AVAMC) between 1/1/2015 – 11/29/2017 using alcohol biomarkers, ethyl glucuronide (EtG) and ethyl sulfate (EtS), and evaluate the association between alcohol use and receipt of direct-acting antiviral (DAA) therapy and achievement of sustained virologic response (SVR).

Short Summary

Many veterans were ineligible for interferon-based therapy because of alcohol use. DAAs are safer and more effective, lifting historical alcohol abstinence requirements from national HCV treatment guidelines. Data are still limited regarding the impact of alcohol use on virologic outcomes in the DAA era.

Methods

Prevalence of alcohol use was determined using detectable values of EtG and EtS between 1/1/2015 to 11/29/2017. To determine association between alcohol use and receipt of HCV antiviral therapy and SVR, multivariable logistic regression analysis was conducted.

Results

Of the 1764 patients tested, 34% had detectable values of EtG and EtS. For those who used alcohol during study period, the odds of receiving DAA was 0.708 (95% CI: 0.574, 0.873; p=0.0013); the odds of achieving SVR was 0.719 (95% CI: 0.515, 1.004; p=0.0525).

Conclusions

Alcohol use during the study period decreased the odds of receiving DAA but had no statistical significance on odds of achieving SVR. Overall, 85.8% of patients who received DAA therapy achieved SVR. Patients with a history of substance or alcohol use disorders should be considered for HCV antiviral therapy DAA on a case-by-case basis.

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AEPI Thesis

Assessing Prevalence of Alcohol Use and Association with Receipt of Direct-acting Antiviral Treatment and Sustained Virologic Response among Veterans with Chronic Hepatitis C at the Atlanta VA Medical Center

Chapter 1: Literature Review

Literature Review

Themes: Hepatitis C, alcohol use, EtG, EtS, HCV antiviral therapy, HCV virologic outcome, sustained virologic response, Clinical Case Registry

Hepatitis C

Hepatitis C virus (HCV) infection can be acute or chronic. Chronic HCV infection is a serious disease that affects an estimated 2.7 million people in the U.S. [1]. Acute HCV infection is usually asymptomatic and may clear spontaneously. However, about 75-85% of those with acute HCV infections will develop chronic HCV infections if infection is not cleared by 6 months. Chronic HCV is defined as having HCV RNA in one's blood for at least 6 months after acquiring HCV infection. The likelihood of developing chronic infection is variable and depends on the patients' age, sex, race, and viral immune response [2]. Chronic HCV infection is a major contributor of chronic liver diseases, increasing the risk of cirrhosis, hepatocellular carcinoma (HCC), and death [3, 4]. Around 10-15% of patients will develop cirrhosis within the first 20 years of infection. Disease progression to cirrhosis also varies, depending on the patients' consumption of alcohol, age of initial HCV infection, and other comorbidities. Those who develop cirrhosis are at higher risk of developing HCC [2]. Because liver complications from chronic HCV infection often develop after decades of infection, many HCV complications are

being seen in those who were infected in the 1960s and 1970s. By initiating treatment sooner, liver complications from chronic HCV infection progression can be prevented [5].

HCV Treatment Revolution

Identifying HCV patients is the first step toward improving health outcomes for HCV patients. HCV is diagnosed by testing for HCV antibodies and HCV RNA [6].

There is currently no vaccine available for preventing HCV, but treatment is available [6]. The goal of chronic HCV treatment is to achieve a sustained virologic response (SVR), which is when HCV RNA is undetectable at least 12 weeks after treatment completion. Achieving SVR is a marker for having cured HCV [7]. In the 1990s, pegylated interferon (PEG-IFN) with ribavirin (RBV) was the primary treatment for chronic HCV infections. PEG-IFN and RBV have a number of significant side effects that impact many organ systems including hematologic, psychiatric, cardiovascular, pulmonary, and endocrine. Many patients were ineligible for treatment due to a medical contraindication to therapy. About 28.6% of Veteran Affairs (VA) HCV patients were found to have contraindications such as anemia, bipolar disorder, and hepatic decompensation. Others suffered from adverse complications while on therapy such as depression, suicidality, hematologic, cardiovascular, thyroid abnormalities, and debilitating fatigue and nausea. Specifically, alcohol use was contraindicated with PEG-IFN and RBV administration. Due to the highly toxic and medical complexity of the regimen, very few people were even considered treatment candidates, let alone cured from treatment. The 2009 All American Association for the Study Liver Diseases (AASLD) Practice Guidelines stated that "[Current users of illicit drugs or alcohol] should be abstinent for a minimum period of 6 months [8]." In the VA clinics, where patients have high rates of psychiatric disorders and substance

abuse, it was found that 67.8% of VA patients were ineligible given the treatment criteria at the time [9].

In 2013, only 23% of HCV patients in the VA had ever received interferon-based antiviral treatment [5]. Factors that may contribute to low treatment initiation rates are: lack of awareness of treatment options, fear of side effects, financial burden, provider-patient relationship, miscommunication, and existing comorbidities [10]. Of the research that have examined what affects veterans' decision to start treatment, predictors included: nonwhite race, older age, male sex, current substance user disorder, HCV genotypes, and medical or psychiatric comorbidities. Specialist referrals and patients being seen at dedicated HCV clinics have also been strong predictors of treatment initiation [5].

Even among those who were treated with PEG-IFN and RBV, very few were cured from treatment because of low SVR rates around 30%. In 2011, the Food and Drug Administration (FDA) approved new HCV drugs known as direct-acting antivirals (DAA). Combinations of DAA were found to achieve 95% SVR rates and did not require the use of PEG-IFN [11]. In addition, treatment duration reduced to be as short as 12-24 weeks with considerably fewer adverse effects [4]. Currently, HCV can be treated using DAAs with more than 95% achieving a SVR [12]. Given the safety and efficacy of DAA therapy, nearly everyone is considered a treatment candidate and alcohol abstinence is no longer required prior to treatment. However, data are limited regarding the impact of alcohol use on virologic outcomes in the DAA era.

Geography: Atlanta VA Medical Center (AVAMC)

The Department of Veterans Affairs, Veterans Health Administration (VHA) is a federal healthcare system that provides care to eligible and enrolled U.S. veterans. VHA is the largest

single provider of HCV care in the United States. VHA's National Viral Hepatitis Program has coordinated and supported HCV care for over 15 years in developing resources for clinicians and patients, publishing policies and guidelines related to treatment and disease management, and integrating care for HCV patients [13].

Funding for HCV medication and care was made available by Congress in 2016 to solidify the VA's abilities to treat HCV-infected veterans and eradicate the disease as much as possible. This funding allowed the VA to provide HCV treatment to patients regardless of their stage of liver disease. Since then, the VA has carried out educational outreach to help veterans initiate treatment and link them to care [14].

Population: Veterans

Among veterans in the VA, chronic HCV is two to three times more prevalent compared to the general U.S. population. Many of the HCV-infected veterans were born between 1945 and 1965 and infected between 1970 and 1990 [5]. The two most common exposures associated with HCV transmission have been blood transfusions and injection drug use. Blood transfusions accounted for a large proportion of HCV cases before 1988. However, due to improved screening policies around 1990s, HCV is rarely transmitted by blood transfusions nowadays [15].

The VA estimates that 15,000 to 20,000 HCV-infected veterans are currently unwilling or unable to start or complete treatment [16]. DAA treatment usually lasts 12 weeks [17]. Cost and access to treatment, treatment eligibility, and patient-specific concerns have been shown to be barriers of treatment initiation [18]. Veterans who utilize healthcare services at the VA often suffer from poverty, with 30-40% earning an annual income of less than $10,000[19]. However, veterans who qualify for Medicaid will not pay copays for VA health care [20].

Posttraumatic Stress Disorder & Alcohol Use

Many veterans, including those who are HCV-infected, often suffer from psychiatric disorders such as depression and substance use disorders [21]. Problems of substance use is often related to posttraumatic stress disorder (PTSD), depression, pain, inability to sleep, and/or relationship problems [22]. Often, they also have other medical conditions, such as hypertension, diabetes, and other chronic illnesses [5]. These characteristics make treating VA HCV patients complicated and challenging.

Alcohol use is a concern for patients with HCV infection because studies have shown strong associations between the use of excess alcohol and progression of liver fibrosis and HCC. However, the amount of alcohol that is harmful to HCV patients and to what extent is still controversial. Thus, alcohol users should be advised to reduce or stop alcohol consumption during before or during treatment [8]. Progression to cirrhosis may be accelerated in persons who consume more than 50g of alcohol per day, although the precise quantity of alcohol associated with fibrosis progression is unknown [23].

The VA provides Substance Use Disorder (SUD) Treatment Programs. SUD includes alcohol or drug use that increases the patients' risks for adverse health outcomes. SUD treatment can include therapy and medications [24].

Ethyl Glucuronide (EtG) and Ethyl Sulfate (EtS) as Biomarkers

Self-report methods have been shown to be reasonably reliable methods for measuring alcohol consumption when study participants know that their confidentiality is protected [25, 26]. However, among alcohol abusers, alcohol use tends to be underestimated when they are not alcohol-free during the interview [27]. Additionally, there is still the limitation of recall bias and

social acceptability (e.g. on drink counts, feelings of intoxication) when it comes to self-reports [26].

Alcohol biomarkers can serve as indicators for alcohol exposure and provide insights into someone's alcohol use behavior. Traditional alcohol biomarkers are tested using blood, urine, or breath and serve as objective measures to identify recent alcohol consumption [28]. Although alcohol biomarkers are valid, accurate, and reliable [28], they should complement, and not substitute, self-report alcohol measures because they may help identify individuals with different alcohol usage [29].

To determine recent alcohol use, ethyl glucuronide (EtG) and ethyl sulfate (EtS) have been studied as useful biomarkers. Studies have found that EtG can be detected in the urine for approximately 30-110 hours and 30-70 hours for EtS [30]. Detection of EtG in urine is longer than in blood, so urine tests can help better detect problematic drinking [28]. Because EtG is highly sensitive, the use of products containing alcohol such as hand sanitizers and mouthwash can generate false positive results [31]. EtG also varies among individuals and the source of EtG often cannot be determined [28, 31]. Although the detection time for EtS is shorter, EtS and EtG have been found to be highly correlated so often these two metabolites are measured simultaneously [28].

These biomarkers can be used to monitor alcohol abstinence because of its ability to be measured at low concentrations. The appropriate cut-offs for EtG and EtS is a topic of debate. The current recommendation from the Substance Abuse and Mental Health Services Administration suggests 100–500 ng/mL for "very low" exposure to alcohol and >1,000 ng/mL for "high" exposure [31]. Other cutoffs suggested have been based on industry recommendations [30].

Although more research is needed to understand how test results may be affected by race, sex, ethnicity, medical comorbidities, and use of other medications or other substances, current research suggest EtG and EtS can be used as effective biomarkers for determining alcohol abstinence [29]. Because EtG and EtS serve as good indicators of abstinence, recovery programs, criminal justice systems, alcohol/drug specialty treatment programs, workplace wellness programs often use these two biomarkers to screen for problematic alcohol use [28].

Clinical Case Registry (CCR)

The National Hepatitis C Clinical Case Registry (CCR) uses the VHA's electronic medical record systems to create population-based data. CCR was developed to monitor trends in HCV care as well as ensure HCV-infected patients are linked to care [32]. Each VHA has local registry coordinators to validate veterans identified as HCV infected using International Classification of Diseases (ICD-9/10) codes or laboratory tests. The HCV seropositive patient is then validated using reflex, confirmatory HCV RNA test results [33]. CCR includes data on demographics, laboratory tests, clinical utilization, medical co-morbidities, and prescriptions [34].

Statement of the Problem

To understand the prevalence of alcohol use and how alcohol use impacts receipt of DAA therapy and achievement of SVR among patients with chronic HCV infection at the Atlanta VA medical center.

Purpose of the Thesis

Chronic infection with HCV causes liver inflammation, fibrosis, and can result in liver cirrhosis and liver cancer in some patients. The risks of cirrhosis, liver failure, and liver cancer are

increased in persons with HCV infection and concomitant alcohol use disorder. Among veterans, chronic HCV is three times more prevalent compared to the general U.S. population. My thesis aims to understand the prevalence of alcohol use among chronic HCV patients in the Atlanta VA hospital to better inform care management.

Aim 1: Describe the prevalence of alcohol use in veterans with chronic HCV infection presenting for care at the AVAMC between 1/1/2015 – 11/29/2017 using alcohol biomarkers, EtG and EtS.

Aim 2: Evaluate the association between alcohol use and receipt of HCV DAA therapy.

Aim 3: Evaluate the association between alcohol use and HCV virologic outcome (i.e. achievement of SVR).

Hypothesis: Patients with detectable concentrations of EtG and EtS will be less likely to receive DAA therapy. Among those with recent documented alcohol use who receive DAA therapy, they will have significantly lower achievement of SVR compared with those who have no history of alcohol use.

Chapter 2: Journal Article

Abstract

Aims

To describe the prevalence of alcohol use in veterans with chronic Hepatitis C Virus (HCV) infection presenting for care at the Atlanta VA medical center (AVAMC) between 1/1/2015 – 11/29/2017 using alcohol biomarkers, ethyl glucuronide (EtG) and ethyl sulfate (EtS), and

evaluate the association between alcohol use and receipt of direct-acting antiviral (DAA) therapy and achievement of sustained virologic response (SVR).

Short Summary

Many veterans were ineligible for interferon-based therapy because of alcohol use. DAAs are safer and more effective, lifting historical alcohol abstinence requirements from national HCV treatment guidelines. Data are still limited regarding the impact of alcohol use on virologic outcomes in the DAA era.

Methods

Prevalence of alcohol use was determined using detectable values of EtG and EtS between 1/1/2015 to 11/29/2017. To determine association between alcohol use and receipt of HCV antiviral therapy and SVR, multivariable logistic regression analysis was conducted.

Results

Of the 1764 patients tested, 34% had detectable values of EtG and EtS. For those who used alcohol during study period, the odds of receiving DAA was 0.708 (95% CI: 0.574, 0.873; p=0.0013); the odds of achieving SVR was 0.719 (95% CI: 0.515, 1.004; p=0.0525).

Conclusions

Alcohol use during the study period decreased the odds of receiving DAA but had no statistical significance on odds of achieving SVR. Overall, 85.8% of patients who received DAA therapy achieved SVR. Patients with a history of substance or alcohol use disorders should be considered for HCV antiviral therapy DAA on a case-by-case basis.

Introduction

Chronic Hepatitis C Virus (HCV) infection is a serious disease that affects an estimated 2.7 million people [1] and contributes to the development of liver cirrhosis, hepatocellular carcinoma (HCC), and deaths [3, 4]. Because liver complications from chronic HCV infection often develop after decades of infection, many HCV complications are being seen currently in those who were infected in the 1960s and 1970s. The two most common exposures associated with HCV transmission have been blood transfusions and injection drug use. Blood transfusions accounted for a large proportion of HCV cases before 1988 [15]. Many of the HCV-infected veterans were born between 1945 and 1965 and infected between 1970 and 1990 [5].

Chronic HCV infection disproportionately affects veterans. Funding for HCV medication and care was made available by Congress to solidify the Veterans Affairs' (VA) abilities to treat HCV-infected veterans and eradicate the disease as much as possible. This funding allowed the Veterans Affairs (VA) to provide HCV treatment to patients regardless of their stage of liver disease and how they acquired HCV [14].

The goal of chronic HCV treatment is to achieve a sustained virologic response (SVR), which is when HCV RNA is undetectable at least 12 weeks after treatment completion. Achieving SVR is a marker for having cured HCV [7]. In the 1990s, pegylated interferon (PEG-IFN) with ribavirin (RBV) was the primary treatment for chronic HCV infections. However, many patients were ineligible for treatment due to medical contraindications. Specifically, alcohol use was contraindicated with PEG-IFN and RBV administration. Due to the highly toxic and medical complexity of the regimen, very few people were even considered treatment candidates, let alone cured from treatment. The 2009 All American Association for the Study Liver Diseases (AASLD) Practice Guidelines states that "[Current users of illicit drugs or alcohol] should be abstinent for a minimum period of 6 months [8]." In the VA clinics, where patients have high

rates of psychiatric disorders and substance abuse, it was found that 67.8% of VA patients were ineligible given the treatment criteria at the time [9]. In 2013, only 23% of HCV patients in the VA had ever received interferon-based antiviral treatment [5].

In 2011, the Food and Drug Administration (FDA) approved new drugs known as direct-acting antivirals (DAA) [11]. Treatment duration was reduced to be as short as 12-24 weeks with considerably fewer adverse impacts [4]. Moreover, alcohol abstinence is no longer required prior to treatment. Currently, HCV can be treated using DAAs with more than 95% achieving a SVR [12]. By initiating treatment sooner, the liver complications from chronic HCV infection progression can be prevented [5]. However, data are still limited regarding the impact of alcohol use on virologic outcomes in the DAA era. Additionally, alcohol use is a concern for patients with HCV infection because of strong associations between the use of excess alcohol and progression of liver fibrosis and HCC.

Because DAA treatment and alcohol use can impact chronic HCV progression and outcomes, this study aims to describe the prevalence of alcohol use in veterans with chronic HCV infection presenting for care at the Atlanta VA Medical Center (AVAMC) between 1/1/2015 – 11/29/2017 using objective biomarkers ethyl glucuronide (EtG) and ethyl sulfate (EtS). The study also evaluates the association between alcohol use and receipt of DAA therapy and alcohol use and SVR. It is hypothesized that 1) patients with detectable concentrations of EtG and EtS will be less likely to receive DAA therapy and 2) those with history of alcohol use who receive DAA therapy will have significantly lower achievement of SVR compared with those who no evidence of alcohol use. This study differs from other studies in that alcohol use is defined using biomarkers instead of information obtained from diagnostic codes or self-report. As a result,

alcohol use is defined using EtG and EtS biomarkers. Additionally, data are still limited regarding the impact of alcohol use on virologic outcomes in the DAA era.

Methods

The VA is the largest single provider of HCV care in the U.S. The data used in this study were obtained from the Atlanta VA clinical case registry (CCR) system. The CCR connects with the VHA's electronic medical record system. Each VHA has local registry coordinators to help review medical records to validate potential HCV-infected veterans using positive antibody test results and/or diagnosis codes based on the International Classification of Diseases (ICD-9/10) codes [33]. Patients with confirmed HCV infections are then added to the CCR, where data on demographics, laboratory tests, and prescriptions are also recorded [34]. To conduct this analysis, reports using different criteria were exported and data on medication, alcohol metabolite test results, viral load test results, and demographic information such as age, sex, and race were obtained from 1/1/2015 to 11/29/2017. The datasets were merged into a single dataset for analysis.

Selection Criteria

The study aims to describe the prevalence of alcohol use in HCV-infected patients at the Atlanta Veterans Affairs Medical Center (AVAMC) who presented for care at the AVAMC from 1/1/2015 to 11/29/2017 using available alcohol metabolite testing.

Study Outcomes

To detect recent alcohol use, urine alcohol metabolite testing was performed for those presenting for routine HCV clinical care. Ethyl glucuronide (EtG) or ethyl sulfate (EtS) are alcohol

metabolites that can be detected up to 80 hours after alcohol consumption [35]. Alcohol use categories were created using the following criteria:

1) **High**: if EtG or EtS was ever greater than or equal to 10,000 ng/mL during the study period
2) **Moderate/Low**: if EtG or EtS is less than 10,000 ng/mL but not DNR (Did Not React)
3) **Abstinent**: if EtG or EtS is DNR

However, some patients underwent multiple urine alcohol metabolite tests during the study period as part of routine clinical care. Because EtS and EtG test results are good indicators for abstinence, only patients with no metabolite reaction will be considered abstinent (i.e. all tests results showing 'DNR'). If patients have any tests with values greater than DNR between 1/1/2015 to 11/29/2017, they will be considered as having used alcohol during study period. In this analysis, alcohol use categories were first created using the criteria above, then reclassified where if there are any values of 'High' and 'Moderate/Low' use among the multiple urine alcohol metabolite tests, patients were considered having recent alcohol use.

To evaluate the association between alcohol use and receipt of HCV antiviral therapy, two categories of patient were created: those who received direct-acting antivirals (DAA) and those who did not. To define those who received DAA treatment, we selected patients who were tested for alcohol metabolites and received any of the following during the study period: Daclatasvir (DCV), dasabuvir/ombitasvir/paritaprevir/ritonavir (PrOD), elbasvir/grazoprevir (EBR/GZR), glecaprevir/pibrentasvir (GLE/PIB), ledipasvir/sofosbuvir (LDV/SOF), simeprevir (SIM), sofosbuvir (SOF), sofosbuvir/velpatasvir (SOF/VEL), and sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX).

The goal of HCV treatment is to achieve a sustained virologic response (SVR), which is defined as an undetectable HCV RNA at least 12 weeks after completing DAA treatment. SVR serves as a marker for having cured HCV. One of the objectives of the study is to examine the association between alcohol use category and HCV virologic outcome (i.e. achievement of SVR). Thus, patients' virologic laboratory results were also extracted for the study time period of 1/1/2015 to 11/29/2017. Patients were considered to achieve SVR if their last test results were negative (i.e. results indicating 'Target Not Detected').

Data Cleaning

The patients' age was calculated for the last day of the study period (11/29/2017). Race was consolidated into three categories: Black or African American, White, and Other (includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, unknown by patient, declined to answer, or missing).

Dichotomous categorical variables were created for SVR. The test results from the patients' most recent laboratory result were used. If the test result indicated 'Target Not Detected' then SVR was coded as achieved. Using this method, there were seven patients who had 'COMMENT' as their result. Upon medical chart review, these patients were determined to have had lab errors relating to technical uses or had indeterminate values so they were marked as missing SVR.

The final dataset was created by merging the various datasets (See figure 1 for the logic used when combining these). The final dataset included 1876 patients. Dummy variables were created for race to conduct regression analysis.

Statistical Analysis

Data analysis was carried out using SAS. To determine the prevalence of alcohol use among AVAMC's HCV-infected veterans, frequency estimates and confidence intervals were produced using the previously defined alcohol use categories.

To determine if there is association between alcohol use and receipt of HCV antiviral therapy (treatment vs. no treatment) and SVR (achieved or not), multivariable logistic regression analysis was conducted, controlling for race and age. Because the study population was predominantly male, sex was not included as part of the analysis.

Model using receipt of HCV antiviral therapy as outcome:

$$\text{logit}P(X)=\alpha + \beta\ \text{ALC} + \gamma 1\ \text{BLACK} + \gamma 2\ \text{OTHER\_RACE} + \gamma 3\ \text{AGE}$$

Model using SVR as outcome:

$$\text{logit}P(X)=\alpha + \beta\ \text{ALC} + \gamma 1\ \text{BLACK} + \gamma 2\ \text{OTHER} + \gamma 3\ \text{AGE} + \delta 1\ \text{ALC*BLACK} + \delta 2\ \text{ALC*AGE}$$

White race = referent group

Interaction and confounding were evaluated for both models. When using HCV antiviral therapy receipt as the outcome, no interaction or confounding was seen. The model using SVR as outcome did have interaction. ALC*Black and ALC*StudyAge each had significant interaction ($p= 0.0335$ and $p=0.0206$, respectively). Because there is interaction between the variables, confounding could not be assessed.

Odds ratios (ORs) with confidence intervals were calculated. Statistical significance was determined using an $\alpha = 0.05$ for all statistical tests.

Results

Among the 1876 patients in the study, 1822 (97.1%) were male with an average of 62.9 ± 6.5 years old. The majority of patients identified as Black or African American 1300 (67.7%).

For the 1764 patients that we had alcohol metabolite test information on, all patients had more than one observation of alcohol metabolite test (57.7% had at least two observations, 18.8% had four observations, and 23.5% had more than 6 observations). In assessing the prevalence of alcohol use, 599 (34%) of the 1764 patients who were tested had at least one detectable value (i.e. Not DNR as test result) of ethyl glucuronide (EtG) and ethyl sulfate (EtS), biomarkers used to define alcohol use in this study, between 1/1/2015 to 11/29/2017 (see Table 2). In determining medication use and whether patients achieved SVR, we found that 1306 (69.6%) received DAA treatment, with a majority of patients taking Ledipasvir/Sofosbuvir (51.8%) and Elbasvir/Grazoprevir (22.5%). During the study period, 1113 out of the 1297 that had viral test results (85.8%) achieved SVR.

In the initial analysis, age was a continuous variable. Upon running the logistic regression for the SVR model, there was interaction (p=0.007). Thus, it was necessary to recode age as a categorical variable. We used the HCV Birth Cohort (52-72 years old) as one group and the rest as the other. This resulted in 1739 patients (92.7%) in the HCV Birth Cohort group.

There were 36 patients who died between 1/1/2015 to 11/29/2017. Upon further investigation, of those who died, all the patients had received DAA treatment, 26 (72.2%) had achieved SVR, 11 (30.6%) had at least one detectable alcohol metabolite test, 19 (52.8%) were Black, 17 (47.2%) were White, and the average age was 66 ± 3.2 years old (min: 60, max: 72).

Receipt of HCV Direct-acting Antiviral (DAA) Treatment

The odds of receiving DAA was 0.708 (95% CI: 0.574, 0.873; p=0.0013) for those who used alcohol during study period. This means that there is a 29.2% decrease in odds of receiving DAA among those who have recent alcohol use compared to those without during the study period. The odds of receiving DAA was 1.608 (95% CI: 1.289, 2.006; p<0.0001) for Blacks compared to Whites, meaning Blacks are 60.8% more likely to receive treatment than Whites. Variables like other races (compared to Whites) and age group did not have significant increases or decreases in odds of receiving DAA (p=0.3167 and 0.3656, respectively).

Sustained Virologic Response (SVR)

In the SVR logistic regression model, 579 observations were deleted due to missing variable (resulting in only 1297 observations used, which is 69.1% of the dataset) (see Table 2). The odds of achieving SVR was 0.719 (95% CI: 0.515, 1.004; p=0.0525) for those who used alcohol during study period. This means that there is a 28.1% decrease in odds of achieving SVR among those who have a used alcohol during study period compared to those without. However, this result is not statistically significant.

The odds of achieving SVR was 1.770 (95% CI: 1.251, 2.504; p=0.0013) for Blacks compared to Whites, meaning Blacks are 77% more likely to achieve SVR than Whites. Variables like other races (compared to Whites) and age group did not have significant increases or decreases in odds of achieving SVR (p=0.6255 and 0.4739, respectively).

Discussion

The demographics of our population are similar to the characteristics of HCV-infected persons in VA Care (2013 data). The mean age of HCV infected patients in 2013 was 59.7 [5], compared to our mean age of 62.9 with both data suggesting more than 90% of patients being older than 50

years old. In examining alcohol use, Atlanta VA patients showed a lower percentage of alcohol use compared to the greater VA population (see Table 4). However, it is important to note that the way alcohol use was calculated differs; our study used biomarkers. Prior to the availability of DAAs, alcohol use inhibited HCV patients from being eligible for treatment. In the VA's latest treatment consideration, patients with a history of substance or alcohol use disorders were recommended to be considered for DAA on a case-by-case basis [36]. This is because there is no evidence on how long patients must remain abstinent to start DAA treatment or data supporting successful treatments among patients who temporarily stop or have infrequent alcohol use.

In this study, alcohol use during the study period decreased the odds of receiving DAA. In one study, researchers found that among patients who did not receive medication, there were higher proportion of active alcohol users [37]. This echoes our finding that fewer alcohol users receive medication. This finding may be due to the fact that, historically, alcohol use complicated HCV treatment (interferon) and management. Patients may not initiate treatment because of lack of awareness on current treatment availability. Other reasons could be provider reluctance to initiate treatment for patients who use alcohol because patient may be less likely to show up for follow up visits.

This study found no statistical significance on odds of achieving SVR for those who used alcohol during study period, with 85.8% of AVAMC patients achieving SVR. Clinical trials have shown more than 95% SVR achievement rates. However, clinical trial results do not always directly translate into real-world practices because patients usually have medical comorbidities or poor treatment adherence. One study found the SVR rate to be lower by 15-20% in the patients under VA care [12], which in in agreement with this study's finding.

Another reason why this study may have observed a lower SVR achievement rate might be due to the study population selection criteria. This study included all patients who started DAA treatment with no data on treatment adherence. Lower SVR rate might also be due to factors specific to patients. Despite the lower SVR rate compared to what is shown in clinical trials, what is important is that this study found no difference in virologic cure amongst those with evidence of recent alcohol use versus not and compare this to other studies of HCV treatment in patients with alcohol use disorders.

Aligning with the VA's treatment consideration guidelines, substance use relating to alcohol should not automatically exclude patients from HCV treatment. Providers should determine whether patients can initiate DAA treatment after careful examination of patients' medical history. However, providers should encourage patients to reduce or stop alcohol use due to potential risk of non-adherence and increased risk of liver fibrosis, cirrhosis, and HCC.

There were a few limitations to this study. First, for the 1764 patients that we had alcohol metabolite test information on, all patients had more than one observation of alcohol metabolite test . As a result, alcohol use categories that were initially created were reclassified where if there are any documentation of 'High' and 'Moderate/Low' use among the multiple alcohol metabolite tests, patients were considered having alcohol use between 1/1/2015 to 11/29/2017. More sophisticated analysis could have been done if we are able to clearly define abstinent, low, medium, and high alcohol use categories and look for associations of alcohol usage with receipt of medication and SVR achievement.

In this study, objective biomarkers were used because self-report may be under-estimated due to recall bias and concerns for confidentiality and social acceptability [25, 26]. It is important to note the limitation of using EtG and EtS measures as they only detect recent use of alcohol.

Studies have found that EtG can be detected in the urine for approximately 30-110 hours and 30-70 hours for EtS [30]. Current research suggest EtG and EtS can be used as effective biomarkers for determining abstinence [29], but it cannot determine if someone has alcohol use disorder. Additionally, there can be false negatives (e.g. binge drinker could have DNR if they didn't drink within the metabolite detection timeframe) or false positives (e.g. a person who had a glass of wine the night before lab test may show a high value of alcohol metabolite). Ethnic variability in metabolism of alcohol may also play a role in metabolite detection. Thus, it is important to exercise caution when using alcohol biomarkers due to potential for mis-categorization.

Secondly, in the SVR logistic regression model, 579 observations were deleted due to missing variable (resulting in only 1297 observations used, 69.1% of the dataset). In order to be added into CCR, patients must have had a positive HCV test result, which may have been before or during our study period of 1/1/2015 to 11/29/2017. In this analysis, we had patients with no viral test data in the dataset because their first test was prior to 1/1/2015 and they were not re-tested (thus had no entry of test results) during study timeframe (1/1/2015 to 11/29/2017). This kept us from categorizing these patients as achieving SVR. However, the patients with missing viral test data included those who discontinued therapy, completed therapy but did not get follow up testing at least 12 week after treatment, or had virologic relapse or re-infection post-treatment. It would be best if we were able to separate these scenarios in our analysis; we were not able to conduct chart reviews to do so. Lastly, CCR only provided limited demographic data such as sex, race, ethnicity, and age, so the only variables included in the analysis were age and race.

Future studies should conduct survival analysis to better understand how alcohol use during treatment may affect whether patients achieve SVR within 12 weeks after finishing treatment. Researchers could also conduct sensitivity analysis using different methods of categorizing

alcohol use that may provide insight on what EtS and EtG levels of alcohol may impact treatment outcomes. Lastly, researchers should use datasets with more detailed information or conduct medical chart reviews to study how abstinence/infrequent alcohol use, amount of alcohol consumed during treatment period, and alcohol use disorder affect DAA treatment.

Chapter 3: Conclusions

We found that 34% of veterans with chronic HCV infection in the AVAMC were found to have recent alcohol use using urine alcohol metabolite testing when presenting for care during the study period. This study found that alcohol use during the study period decreased the odds of receiving DAA and had no statistical significance on odds of achieving SVR, with 85.8% of patients achieving SVR. Aligning with the VA's latest treatment consideration, patients with a history of substance or alcohol use disorders should be considered for HCV antiviral therapy DAA on a case-by-case basis. This study used biomarkers as an objective measure for recent alcohol use, so conclusion cannot be drawn for those with alcohol use disorders.

There are some advantages and disadvantages of the data and methods used in this study. First, the data downloaded from CCR was easy to obtain, but provided very limited information. The only variables that could be included in the analysis were data on medication, alcohol metabolite test results, viral load test results, and basic demographic information such as age, sex, and race. The study timeframe was determined to be from 1/1/2015 to 11/29/2017 to account for the implementation timeframe of DAA at the AVAMC to the date the data was exported from CCR. More sophisticated analysis could have been done if medical chart reviews were conducted to provide more data such as comorbidities, substance use disorders, virologic relapse, and medication adherence.

Because of the way CCR was set up, the data also had to be exported as different spreadsheets and then merged into one. This was a tricky process due to the formatting of some of the spreadsheets. For example, the data on alcohol metabolite test had the alcohol metabolite test result (positive or negative), EtG and EtS values, and 'Please Note' (to indicate to clinicians to refer to notes in medical chart) all in the same column. In this analysis, only the EtG and EtS values were kept. During the data merge, there were several issues that had to be addressed as well. For example, both spreadsheets that had information medication and viral load test results had the variable medication name. It was found that there was a discrepancy between the number of deaths and medication name recorded in these two spreadsheets. After checking for the missing data patterns in both spreadsheet, it was concluded that spreadsheet containing viral test results had more complete data. There was only one observation where a patient's medication name was not recorded in the more complete spreadsheet, so this information was obtained and added from the other spreadsheet. During the merge, demographic data was also missing in certain spreadsheets, so this data had to be merged a second time with the combined spreadsheet (See figure 1).

The longitudinal nature of the alcohol metabolite test results and viral load test results also became problematic because the study aimed to conduct regression analyses. The data had to be simplified to become simple Yes/No categories (i.e. used alcohol or not and achieved SVR or not) to fit the models. To determine SVR status, the study used the result of the last viral load test result. If the test result indicated 'Target Not Detected' then SVR was coded as achieved. However, only 69.1% of the study population had one or more recorded viral test value during the study timeframe. For patients who had been tested outside of the study timeframe and were not re-tested during the study timeframe, their SVR status could not be determined unless their

medical charts were reviewed. There were also a few instances where the virologic test results recorded 'COMMENT' which indicated that there was an error during the lab test (e.g. due to technical problems). This study was not able to further investigate into these instances.

Similarly, the alcohol metabolite test results provided information on how high the patients' alcohol metabolites were. However, each patient recorded a different number of alcohol metabolite observations based on the number of times they were tested. Results also varied greatly from one observation to another (e.g. first test indicated DNR, second test also DNR, but third test showed high alcohol metabolites). This was a major limitation in this study because the prevalence of alcohol use could not be stratified using high, medium, low, or no use, and thus regression analysis using these categories could not be conducted.

There are many ways to define and categorize alcohol use. In this study, biomarkers were used. Although biomarkers are objective measures, as opposed to subjective measures like self-report data, the only conclusions we are able to draw is that patients recently used alcohol. It does not provide insights into their long-term alcohol use or whether they suffer from alcohol abuse. A sensitivity analysis may have been helpful in comparing objective to subjective reports (i.e. comparing patients' biomarkers to their self-reported alcohol use) to ensure validity.

Future studies should make use of the longitudinal nature of the data and consider doing survival analysis to better understand how alcohol use during treatment may affect time to HCV treatment completion.

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Tables and Figures

Table 1. Patient Demographics

Number of Patients	1876
Male	1822 (97.1%)
Age	62.9 ± 6.5
Primary Race	
Black or African American	1300 (67.7%)
White	488 (26.2%)
Other	88 (4.7%)
Ethnicity	
Not Hispanic or Latino	1810 (96.5%)
Received Treatment	1306 (69.6%)
Types of Treatment*	
Ledipasvir/Sofosbuvir	677 (51.8%)
Elbasvir/Grazoprevir	294 (22.5%)
Sofosbuvir/Velpatasvir	137 (10.5%)
Other	198 (15.2%)
Achieved SVR**	1113 (85.8%)
Died during study period	36 (1.9%)

** Among the 1306 patients who received treatment.*

***N=1297 because 579 of 1876 patients had missing viral load test results; those that did not achieve SVR include those who discontinued therapy, completed therapy but did not get follow up testing at least 12 week after treatment, or had virologic relapse or re-infection post-treatment. See Table 3.*

Table 2. Number of Patients with Detectable EtG and EtS Values

Number of Patients with Alcohol Metabolite Tests	1764
Those with at least one test showing detectable values of EtS and EtG	599 (34%)
Abstinent	1165 (66%)

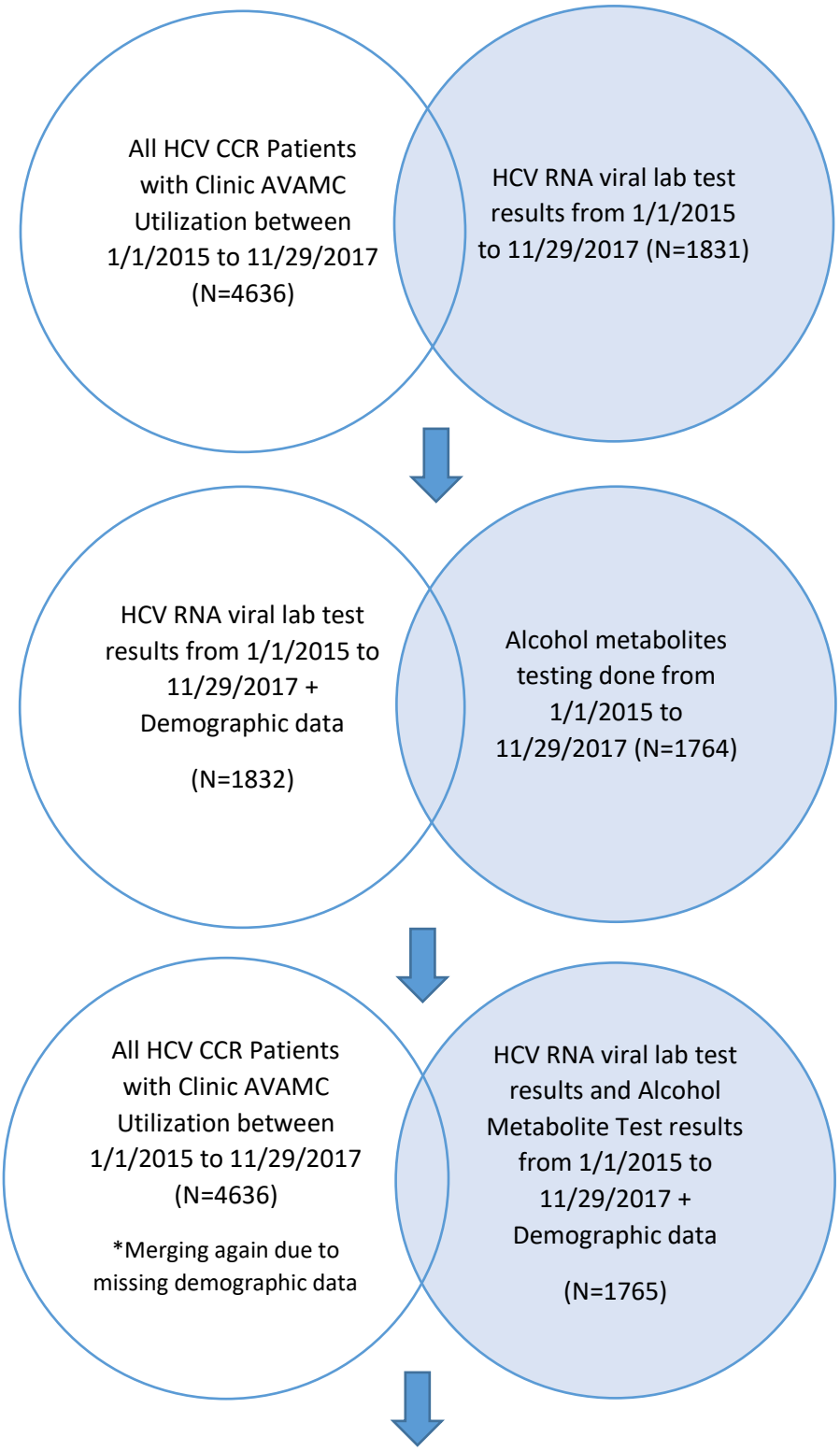
Table 3. Last Viral Test Result during Study Period

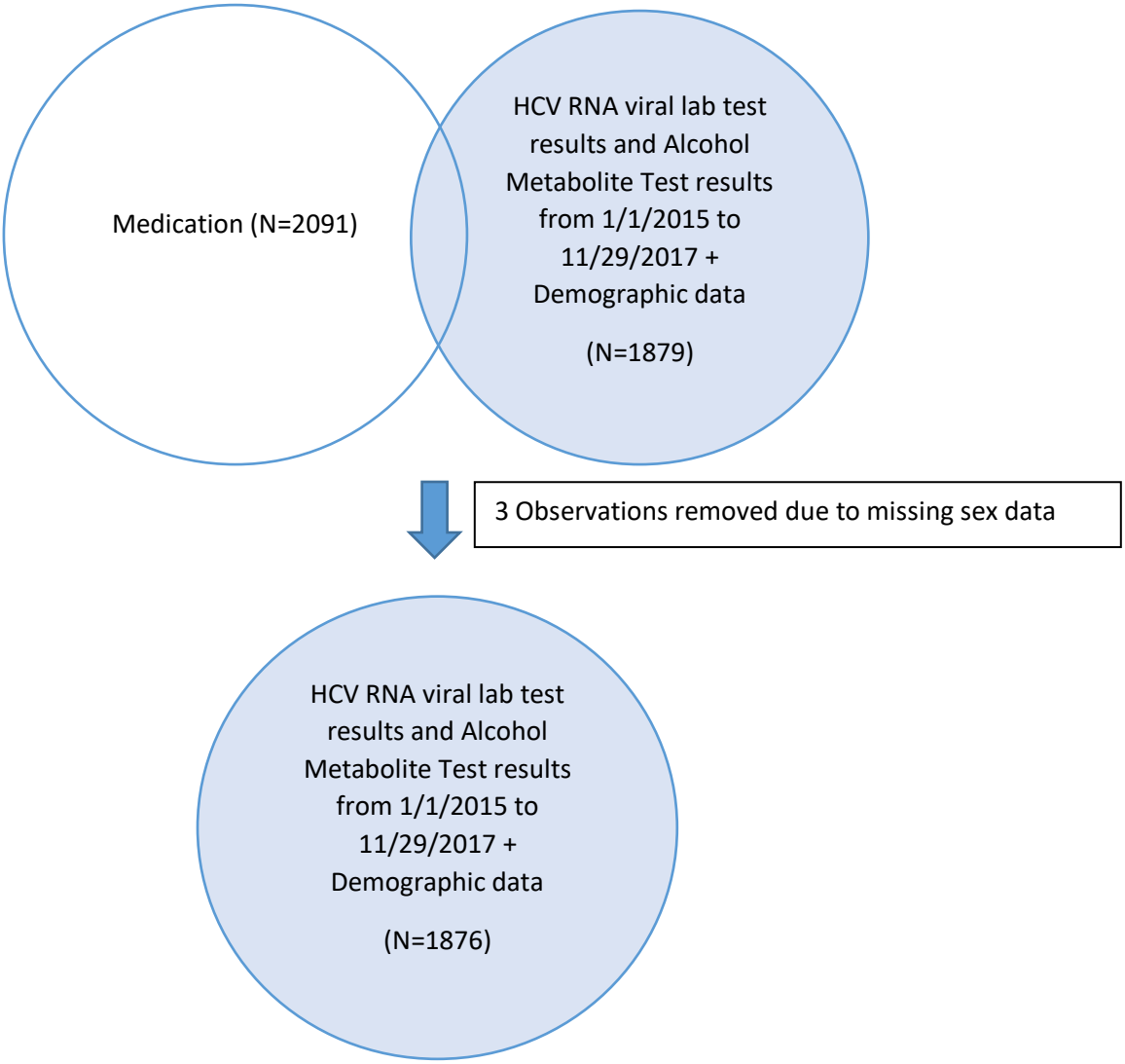
Number of Patients	1876
Target Not Detected (i.e. Achieved SVR)	1113
Had Detectable HCV virus in blood	184
Missing Viral Test Information	579

Table 3. Demographics Comparison of HCV Patients in VA Care vs. Atlanta VAMC

Characteristics	**Characteristics of HCV-Infected Persons in VA Care, 2013** [5]	**Atlanta VA**
Mean Age	59.7	62.9
Male	97%	97.1%
Race		
White	54%	26.2%
Black	34%	67.7%
Ethnicity		
Not Hispanic or Latino	89%	96.5%
Received antiviral agents	23%	69.6%
Alcohol Use	55%	34%

Figure 1. Logic for Combining Datasets




Medication (N=2091)
HCV RNA viral lab test results and Alcohol Metabolite Test results from 1/1/2015 to 11/29/2017 + Demographic data
(N=1879)
3 Observations removed due to missing sex data
HCV RNA viral lab test results and Alcohol Metabolite Test results from 1/1/2015 to 11/29/2017 + Demographic data
(N=1876)