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Alcohol use and hepatitis C virus treatment outcomes among patients receiving direct antiviral agents

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Abstract

Background: It is unclear whether alcohol use negatively impacts HCV treatment outcomes in the era of direct antiviral agents (DAAs). We aimed to evaluate the associations between current levels of drinking and treatment response among persons treated for HCV with DAAs in the national Veterans Affairs (VA) healthcare system.

Methods: We identified patients who initiated HCV DAAs over 18 months (1/1/14–6/30/15) and had documented alcohol screening with the Alcohol Use Disorders Identification Test Consumption (AUDIT-C) questionnaire within one year prior to initiating therapy. DAAs included: sofosbuvir (SOF), ledipasvir/sofosbuvir (LDV/SOF) or ombitasvir-paritaprevir-ritonavir, and dasabuvir (PRO). AUDIT-C scores were categorized as 0 (abstinence), 1–3 (low-level drinking) and 4–12 (unhealthy drinking) in men or 0, 1–2 and 3–12 in women.

Results: Among 17,487 patients who initiated DAAs, 15,151 (87%) completed AUDIT-C screening; 10,387 (68.5%) were categorized as abstinent, 3422 (22.6%) as low-level drinking and

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Contributors

George Ioannou is the guarantor of this paper.

George Ioannou: Acquisition of data, statistical analysis and interpretation of data, critical revision of the manuscript, obtained funding.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.drugalcdep.2016.10.021>.

Conflict of interest

No conflict declared

1342 (8.9%) as unhealthy drinking. There were no significant differences in sustained virologic response (SVR) rates between abstinent (SVR 91%; 95% CI: 91–92%), low-level drinking (SVR 93%; 95% CI 92–94%) or unhealthy drinking (SVR 91%; 95% 89–92) categories in univariable analysis or in multivariable logistic regression models. However, after imputing missing SVR data, unhealthy drinkers were less likely to achieve SVR in multivariable analysis (AOR 0.75, 95% CI 0.60–0.92).

Conclusion: Absolute SVR rates were uniformly high among all persons regardless of alcohol use, with only minor differences in those who report unhealthy drinking, which supports clinical guidelines that do not recommend excluding persons with alcohol use.

Keywords

Hepatitis c treatment; Direct antiviral agents; AUDIT-C

1. Introduction

Hepatitis C virus (HCV) infection is among the most common chronic viral infections in the United States, affecting approximately 3.6 million persons (Denniston et al., 2014). In the past decade it has emerged as a leading cause of death from cirrhosis and liver cancer (Ly et al., 2016), and since 2007 it has surpassed HIV as a cause of death in the USA (Ly et al., 2012). In the context of HCV, alcohol use is a major contributor to adverse health outcomes (Peters and Terrault, 2002; Schiff and Ozden, 2003). Alcohol and HCV act synergistically; studies show that risk for cirrhosis and liver cancer are substantially elevated among persons with HCV who drink heavy amounts compared to those who do not (Corrao and Arico, 1998; Donato et al., 2002; Hutchinson et al., 2005) and conversely, patients with alcohol use disorders who have HCV fare worse compared to those who do not have hepatitis C (Tsui et al., 2006). Despite these risks, HCV-infected persons in the U.S. are more likely to drink unhealthy amounts compared to uninfected persons (Armstrong et al., 2006; Taylor et al., 2016).

Given recent advances in HCV treatment with the arrival of highly efficacious directly-acting anti-viral agents (DAA), there is an opportunity to cure the vast majority of HCV-infected persons, including those with alcohol use disorders who are at the highest risk for complications. Yet persons who drink alcohol face many barriers to HCV treatment. Although current treatment guidelines do not explicitly recommend withholding treatment for persons who drink alcohol (HCV Guidance, 2016), in practice many providers and insurance companies may not offer HCV treatment to patients unless there is a period of sustained abstinence (Barua et al., 2015) and prior studies have demonstrated that persons who drink alcohol are less likely to be treated (Anand et al., 2006). In part, this could be due to concerns about poor treatment outcomes due to negative effects on adherence (Grodensky et al., 2012) or impaired immune responses jeopardizing cure (Szabo et al., 2006). Yet, evidence to suggest that alcohol use negatively impacts HCV treatment outcomes is mixed, with some studies suggesting worse outcomes (i.e., less likelihood of cure; Anand et al., 2006) and other showing no difference (Bruggmann et al., 2010; Costentin et al., 2013; Russell et al., 2012). Earlier studies were conducted prior to the existence of DAAs, in the era of interferon-based treatment when treatment courses were longer (24 to 48 weeks) and

cure rates lower. As such, lapses in adherence related to alcohol use might more strongly influence outcomes. Furthermore, alcohol might directly interfere with immune pathways critical for successful treatment with interferon (Osna et al., 2009; Ye et al., 2010), which is an immune modulator. With highly DAA-based treatments, it is unclear whether alcohol use has any impact on clinical outcomes. Data on current HCV treatment effectiveness is needed to guide clinical practice and policy.

This study examined associations between levels of drinking assessed using the Alcohol Use Disorders Identification Test Consumption (AUDIT-C) questionnaire and treatment outcomes among persons treated for Hepatitis C with DAAs in the national Veterans Health Administration (VA) healthcare system, which is the largest integrated healthcare provider for HCV-infected patients in the United States (Beste and Ioannou, 2015). Since 2004, the VA has implemented annual screening for alcohol use disorders with AUDIT-C (Bradley et al., 2006), providing a unique opportunity to evaluate associations between recent levels of drinking and treatment effectiveness among persons who were treated with DAAs.

2. Methods

2.1 Study population and data sources

Patients were included in the study sample if they initiated HCV DAA treatments during an 18-month period from January 1, 2014 to June 30, 2015, and had documented alcohol screening with the Alcohol Use Disorders Identification Test Consumption (AUDIT-C) questionnaire within one year prior to initiating antiviral therapy. January 1, 2014 was selected as the index date, as it was the month after sofosbuvir, the first DAA to be used in interferon-free regimens, was approved. National clinical and administrative data for this study were extracted from the VA's Corporate Data Warehouse, a continually-updated data repository that mirrors the VA's electronic health record (Ioannou et al., 2016; VINCI, 2016). Participants who were treated with the following direct antiviral agents (DAA) were included: sofosbuvir (SOF), ledipasvir/sofosbuvir (LDV/SOF) or ombitasvir-paritaprevir-ritonavir, and dasabuvir (PrOD). These regimens were selected because they continue to be widely used and were recommended by professional societies at the time the study was completed. These regimens were interferon-free, except for the regimen of sofosbuvir and pegylated interferon and ribavirin only for genotype-3 infected patients, which was included because it was the only interferon-containing regimen that was still recommended at the time of the study.

2.2. Primary outcome: sustained virologic response

The primary outcome of interest was sustained virologic response (SVR), defined as a viral load below the limit of quantification (i.e., undetectable) 12 or more weeks after the end of treatment. Undetectable viral load at 12 weeks has been shown to have >99% concordance with 24 week viral loads in DAA treated patients (Yoshida et al., 2015) and is considered clinically representative of cure. For patients who were missing an HCV viral load 12 weeks after treatment completion, we utilized viral load done between 4 and 12 weeks after the end of treatment to determine SVR, based on prior research suggesting a high

concordance of results for HCV viral loads drawn at 4, 12 and 24 weeks after completion of treatment (Yoshida et al., 2015).

2.3. Primary independent variables: levels of severity of alcohol use

Levels of alcohol use were derived from the 3-item Alcohol Use Disorders Identification Test (AUDIT-C) (Bush et al., 1998). The AUDIT-C is a validated screening test for identifying unhealthy alcohol use, which is used to screen all outpatients in the VA for unhealthy alcohol use annually (Bradley et al., 2006). This study included AUDIT-C data closest to HCV treatment within a year prior to HCV treatment. Because increasing AUDIT-C scores are associated with increased likelihood of alcohol-related consequences and alcohol use disorders (Rubinsky et al., 2013), AUDIT-C risk groups were defined consistent with previous studies (Bradley et al., 2003; Bush et al., 1998; Williams et al., 2014). Specifically, AUDIT-C scores of 0, 1–3, 4–12 were grouped to represent abstinence, low-level drinking, and unhealthy drinking, for men (0, 1–2, 3–12, respectively for women). While previous studies have considered low-level drinkers as the referent category, in this study non-drinkers were used as the referent category because in the setting of HCV there are no established safe levels of alcohol use and patients are counseled to abstain. In secondary analyses AUDIT-C scores were further subdivided into 0, 1–2/3, 3/4–9 and 10–12 to evaluate whether any association between alcohol use and SVR was limited to persons in the highest category of AUDIT-C scores (10–12).

2.4. Other covariates

Other covariates assessed included age, sex, race/ethnicity, current HCV treatment regimen, receipt of prior antiviral treatment, HCV genotype/subtype, HCV viral load, and medical diagnoses (cirrhosis, HCC, liver transplantation, diabetes, history of substance use disorder (not alcohol), depression, anxiety and PTSD). Data extended backwards to October 1, 1999 in order to allow determination of previous antiviral treatments, past medical history and substance use disorders. Duration of therapy was determined as the total duration of the DAA prescriptions filled. A course was considered terminated if medications were not refilled within 45 days after the final prescription was exhausted. We included information on medical and psychiatric co-morbidities based on the following diagnosis codes: diagnosis of cirrhosis (defined by ICD-9 codes for “cirrhosis with alcoholism” (571.2) or “cirrhosis no mention of alcohol” (571.5) or by the presence of decompensated cirrhosis defined by the ICD-9 codes for esophageal varices with or without bleeding (456.0–456.21), ascites (789.5), spontaneous bacterial peritonitis (567.23), hepatic encephalopathy (572.2) and hepatorenal syndrome (572.4); hepatocellular carcinoma (defined by ICD-9 code 155.0); diabetes (ICD9 codes 250.0–250.92 or prescription of diabetes medications); and liver transplantation (ICD-9 code 996.82, V42.7). We used ICD-9 codes to define depression (311.0–311.9), post-traumatic stress disorder (309.81), anxiety or panic disorder (300.0–300.9) and schizophrenia (295.0–295.9). Alcohol use disorders were identified by ICD-9 codes for alcohol abuse (305.00–305.03), dependence (303.90–303.93) and withdrawal (291.81). Substance use disorders (SUD) were defined by codes for substance abuse (305.2–305.9), dependence (304.0–304.9) or drug withdrawal (292.0). These conditions were noted only if recorded at least twice *prior to* treatment initiation in any inpatient or outpatient encounter, as in previous studies, and these ICD9-based definitions of cirrhosis and HCC

(Beste et al., 2015; Davila et al., 2011; Ioannou et al., 2013, 2007; Kramer et al., 2008,2005) as well as the other comorbidities (Backus et al., 2007; Beste et al., 2010; Davila et al.,2011; Kanwal et al., 2011; Kramer et al., 2011; Miller et al., 2004 Miller et al., 2004) have been widely used and validated in VA medical records.

2.5. Statistical analysis

Descriptive statistics were used to characterize study participants overall and by level of alcohol use, and chi-square and Student's *t*-tests were used to assess differences between groups. Unadjusted rates of SVR and their 95% confidence intervals by levels of alcohol use were calculated. Multivariate logistic regression models were used to evaluate the associations between levels of alcohol use (relative to none) and achieving SVR. The final models were adjusted for the following covariates selected *a priori* because they are known or suspected to be associated with both alcohol use and SVR: age, gender, race/ethnicity, HCV genotype/subgenotype, HCV viral load, antiviral treatment regimen, HIV, diabetes, cirrhosis, decompensated cirrhosis, HCC, liver transplantation, prior treatment, platelet count and serum bilirubin and albumin level (laboratory values reflective of presence of cirrhosis). We *a priori* hypothesized there might be effect modification based on HCV genotype, cirrhosis and HIV status and tested for the significance of multiplicative interactions between those factors and level of alcohol use on the outcome of SVR.

To address the issue of missing SVR data, we assessed all characteristics of those missing and not-missing SVR data, including the distribution of AUDIT-C categories, and we performed multiple imputations for missing SVR12 values. Missing SVR values were imputed using a logistic regression model with all patient characteristics, as well as duration of treatment. The number of imputations was varied from 10 to 200 resulting in estimates that were identical up to four significant digits. The model was determined stable and an $m = 20$ imputations were used. Data were assumed to be missing at random. This assumption was found to be reasonable using the observed data. Analyses were performed using Stata/MP version 14.1(64-bit) (StataCorp, College Station, TX).

3. Results

3.1. Characteristics of the study population

Among 17,487 persons who initiated HCV treatment with DAA therapy between January 1, 2014 and June 30, 2015,15,151 (87%) persons had completed an AUDIT-C questionnaire within a year prior to treatment initiation. Most patients had AUDIT-C scores consistent with abstinence (10,387/15,151 or 69%); 3422 (23%) were categorized as low-level drinking (AUDIT-C score 1–3 men, 1–2 women), and 1342 (9%) were categorized as drinking unhealthy amounts (AUDIT-C score 4–12 men, 3–12 women).

The characteristics of the sample overall and by level of AUDIT-C score are shown in Table 1. The sample was largely male; the majority was older and white. However, non-whites were well-represented: more than a quarter of the sample was black. More than three-quarters of the treated sample had HCV genotype 1 infection, and the antiviral treatment regimens were generally representative of the composition of genotypes. Slightly less than a

third of patients were diagnosed with cirrhosis, and much smaller percentages (generally <5%) were diagnosed with HCC or had received a liver transplant. The prevalence of a history of alcohol use disorders and substance use disorders was high in the sample overall (44% and 37% respectively). 476 patients (3% of the study sample) had documented HIV co-infection.

The distribution of factors in Table 1 was generally similar among the various levels of AUDITT-C risk, with the exception of the prevalence of alcohol use disorders, which was expectedly higher (68%) among the category of persons with unhealthy alcohol use. In addition, the proportion of individuals with cirrhosis, decompensated cirrhosis, liver cancer or diabetes was higher within the abstaining category (AUDIT-C score of “0”). The imbalance of these factors (which would be expected to predict lower likelihood of SVR) may reflect behavioral change related to disease status (i.e., “sick quitters”).

3.2. SVR rates, overall and by AUDIT-C category

Data on SVR were available in 13,742 out of 15,151 patients (91%) and are reported here and in Tables 2 and 3 and Fig. 1. Of these 13,742 patients, SVR was determined based on viral loads performed 12 or more weeks after the end of treatment in 12,901 patients, while only 841 were based on viral loads performed 4–12 weeks after the end of treatment. Rates of SVR overall and by relevant clinical categories (HCV genotype, regimen, cirrhosis and HIV) are shown in Table 2. In general, we observed favorable clinical outcomes for most patients. In the study sample, 91.7% (95% CI: 91.2–92.1) achieved SVR, with much higher SVR rates for genotype 1 (93.6%) and genotype 4 (91.0%) infected patients than for genotype 2 (87.2%) and genotype 3 (77.2%) infected patients. There were no significant differences in the proportion achieving SVR across levels of drinking based on AUDIT-C risk groups. Rates of SVR among those categorized into low-level drinking and unhealthy drinking (93.2%, 95% CI: 92.2–94.1 and 91.4%, 95% CI: 89.5–92.9, respectively) were similar to those categorized as abstaining (91.9%; 95% CI: 91.3–92.5%). There also did not appear to be clinically meaningful difference in rates of SVR by AUDITT-C categories among the various subgroups of treatment regimen, genotype, cirrhosis, and HIV status (Table 2, Fig. 1).

3.3. Association between AUDIT-C category and SVR

In the multivariable analysis adjusting for baseline patient characteristics, no significant differences were observed between low-level or unhealthy drinking and abstinent categories – the unhealthy drinkers appeared to have a lower likelihood of SVR, but this did not reach statistical significance (AOR 0.82, 95% CI 0.66–1.03) (Table 3). Also, among subgroups defined by genotype, cirrhosis status or HIV status, there was no significant association between AUDITT-C category and SVR. Interactions terms between AUDIT-C and genotype, cirrhosis and HIV status were non-significant at the $p < 0.10$ level.

When AUDIT-C values were further sub-categorized into 0, 1–3, 4–9 and 10–12 in men (or 0, 1–2, 3–9, 10–12 in women), there was no significant association between the highest alcohol category (AUDIT-C 10–12) and SVR (AOR 0.82, 95% CI 0.51–1.33) relative to the abstinent category.

3.4. Early treatment discontinuation and AUDIT-C category

Among all patients included in this study ($n = 15,151$), early discontinuation of treatment in <8 weeks was more common in persons with unhealthy drinking (6.2%), compared to persons with low-level drinking (4.8%) or abstinent (5.7%) ($p < 0.05$). Mean duration of treatment was 82.0 days in the unhealthy drinking group, 83.5 days in the low-level drinking group, and 87.8 days in the abstinent group. Among patients with available SVR data ($n = 13,742$), whose SVR results are shown in Table 2, early treatment discontinuation in <8 weeks occurred in 3.1% in unhealthy drinkers, 2.8% in low-level drinkers and 1.8% in abstinent persons.

3.5. Impact of missing SVR data and imputation for missing SVR

Data on SVR were missing in 1409 out of the 15,151 patients who received antiviral treatment (9.3%). The proportion of patients with missing SVR data was greater in the unhealthy drinkers (12.9%) than in the low-level drinkers (9.8%) and the abstinent group (8.7%). We found that patients with vs without SVR data had very similar characteristics with respect to race/ethnicity, age, HCV genotype, cirrhosis, decompensated cirrhosis, and most other baseline characteristics (Supplemental Table 1). Patients without SVR data were more likely to discontinue treatments early in <8 weeks (25%) than patients with SVR data (3%, Supplemental Table 1). However, the majority of patients without SVR data actually completed 8 or more weeks of treatment (75%) and overall patients without SVR data completed a mean of 71.8 days of treatment compared to 87.8 days in patients with SVR data. Thus, the majority of patients without SVR data were not patients who dropped out of treatment, but rather patients who were late in performing the 12-week post-treatment, HCV viral load.

Analyses with multiple imputations were performed using a logistic regression model that included duration of treatment together with all the baseline patient characteristics shown in Table 1. Those results are presented in Table 4. Comparison of observed SVR among patients with available SVR data ($n = 13,742$) to combined observed or imputed SVR among all patients who initiated antiviral treatment ($n = 14,972$) showed rates that were slightly lower overall for all AUDIT-C categories, but more so for the unhealthy drinkers – as expected since a higher proportion of them were missing SVR data. We also performed multivariate regression analyses using imputed data in the overall sample (Table 5). While the AOR for those with AUDIT-C scores in the low-level drinking category relative to those with scores of 0 remained non-significant (AOR 1.03, 95% CI 0.89–1.2), those with AUDIT-C scores in the unhealthy range were significantly less likely to achieve SVR than those with AUDIT-C scores of 0 (AOR 0.75, 95% CI 0.60–0.92).

Finally, we calculated SVR rates assuming that all patients with missing SVR data did not achieve SVR, a highly unlikely worst-case scenario (Table 4). In this analysis, the SVR rate of the patients with unhealthy alcohol use (79.1%) is even more markedly lower than the SVR rate of non-drinkers (83.5%) or low-level drinkers (83.5%), as expected since SVR data were missing more commonly in patients with unhealthy alcohol use.

4. Discussion

In this large study of over 15,000 veterans who were treated for HCV with DAA therapy who had also been screened for alcohol use with AUDIT-C within the prior year, most patients were identified as non-drinkers (69%), but a considerable proportion were low-level drinkers (23%) and even unhealthy drinkers (9%). We found that rates of cure were uniformly high, regardless of level of alcohol use (92% among those who did not drink, versus 93% among those with low-risk drinking and 91% with unhealthy alcohol use). After accounting for missing data, rates of SVR were slightly lower (91%, 92% and 89% respectively), and unhealthy drinking was associated with decreased likelihood of SVR relative to non-drinking (AOR =0.75, 95% CI 0.60–0.92). While these results suggest the possibility that, in the era of DAA treatments for HCV, unhealthy alcohol use may be associated with lower likelihood of cure, they also demonstrate that the vast majority of patients will be cured regardless of drinking status. As such, our findings support clinicians in following the current clinical guidelines, which do not recommend excluding persons who consume alcohol (HCV Guidance, 2016). Findings of sensitivity analyses, however, also support clinicians in continuing to recommend alcohol abstinence for HCV-infected patients.

Our study is among the first to explore associations between alcohol use and HCV treatment outcomes among patients who are using newer DAA therapies. Previous studies conducted during the era of interferon-based treatments showed mixed findings. In an earlier VA study by Anand et al., persons who reported recent alcohol use were more likely to discontinue treatment (40% vs 26%; p -value = 0.0002), and trended toward being less likely to attain SVR (14% vs 20%; p -value = 0.06; Anand et al., 2006). However, a subsequent study of privately insured members of an integrated health care system observed that pre-treatment heavy drinking was unrelated to SVR (Russell et al., 2012). Similarly, SVR rates were not found to be significantly different across levels of alcohol use in a study of HIV-infected persons who were treated for HCV (Bruggmann et al., 2010). Of note, we also did not observe any evidence of a significant harmful association between drinking and SVR in the small sample of persons who were co-infected with HIV. Likewise, we did not observe any differences in the impact of alcohol on treatment outcomes among persons with the harder to treat genotypes (2 and 3), and among persons with cirrhosis.

Our study has important clinical implications. Providers who treat patients for HCV should be encouraged by these results that show relatively high rates of treatment success, even among patients with unhealthy alcohol use. Our results support the current HCV treatment guidelines (HCV Guidance, 2016), which do not exclude persons who are active or even unhealthy drinkers. However, while our study suggests that the majority of patients who drink unhealthy amounts can be cured of HCV, it is important to recognize that continued alcohol use, even after HCV eradication, may put patients at risk for progression of liver disease. Moreover, findings from sensitivity analyses in the present study suggest unhealthy alcohol use may reduce the likelihood of cure. In general, persons with HCV are more likely to drink unhealthy amounts compared to uninfected persons: data from the NHANES show that HCV-infected persons are 3 times more likely to consume an average of more than 1 drink per day (35.3% vs. 13.5%; P = 0.003) and almost 8 times more likely to consume more than 3 drinks per day (19.2% vs. 2.4%; P = 0.010) (Armstrong et al., 2006). Therefore,

interventions are still needed to promote safe levels of drinking among persons with HCV to maintain a healthy liver even after eradication of HCV through treatment.

There are a number of limitations to our study. Our study is limited by the missing SVR data (9.3%). We attempted to address this limitation through the use of multiple imputation models that included duration of treatment in addition to baseline, pretreatment characteristics to impute the missing SVR data. While these results differed from the main results in suggesting that unhealthy alcohol use, relative to abstinence, could decrease the likelihood of a favorable HCV treatment outcome, the absolute difference in SVR (2%) was of arguable clinical significance. The study relies on AUDIT-C screening data to categorize alcohol use, for which there are numerous important limitations. Although the VA has been a leader in implementation of screening for alcohol use, studies have demonstrated that there have been gaps in the quality of screening, such that screening results may not reflect true levels of drinking (Bradley et al., 2011; Williams et al., 2015, 2016). Another limitation is the fact that AUDIT-C scores were not drawn immediately at the time of HCV treatment initiation, and may not reflect levels of drinking at the time of treatment. And yet, this can also be viewed as a strength: because AUDIT-C data was collected at a separate visit not tied to HCV treatment, patients may have been more willing to be truthful about their current use. An additional limitation is the nature of the study sample, which is comprised of largely male veterans: this may limit the generalizability of our findings to other patient populations that include a higher proportion of women. Finally, this study is limited by the observational study design: although we adjusted for numerous confounders, there is still possibility of residual effects from unmeasured confounders.

In summary, this study using real-world observational data on veterans who were treated with DAA for HCV we observed that nearly a third (31.5%) were found to be not abstaining from alcohol use by AUDIT-C within a year of treatment. Among those patients who had data on SVR, absolute rates of cure were high regardless of levels of alcohol use, and level of alcohol use was not associated with likelihood of cure. These results support provision of DAA treatment to all HCV patients regardless of alcohol use status. However, sensitivity analyses imputing missing data demonstrated that unhealthy drinking was associated with a significantly reduced likelihood of cure, compared to abstaining. These results leave open the possibility that unhealthy alcohol use might have a slight impact on SVR, information that could be fed back to patients during evidence-based alcohol-related interventions offered to patients with HCV who screen positive for unhealthy alcohol use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
SVR† rates achieved by DAAs in the VA nationally presented by AUDIT-C category, 2014–2015.

A. SVR rates by AUDIT-C category and HCV genotype

B. SVR rates by AUDITC category according to cirrhosis and HIV status

† SVR is calculated among 13,742 patients with available SVR data (out of 15,151 patients in this study).

Table 1

Baseline characteristics of the sample by categories of alcohol use.

	All Patients (N = 15,151)	AUDIT-C 0 No Alcohol Use (N = 10,387)	AUDIT-C 1-3 Low-Level Alcohol Use (N = 3,422)	AUDIT-C 4-12 Unhealthy Alcohol Use (N = 1,342)
Male (%)	96.7	96.7	97.4	97.1
Age, yrs mean (SD)	60.8 (6.5)	61.1 (6.4)	60.7 (6.7)	59.0 (7.1)
Race/Ethnicity (%)				
White	52.2	52.2	50.9	59.3
Black	28.9	28.9	31.3	23.1
Hispanic	5.0	5.0	5.5	4.0
Other	1.6	1.6	1.5	1.9
Declined/Missing	12.4	12.4	10.8	11.6
Treatment Experienced	29.0	32.4	23.1	18.2
Genotype (%)				
1	79.8	79.8	81.1	76.4
2	12.5	12.4	11.8	14.7
3	7.0	7.1	6.1	8.4
4	0.8	0.8	1.0	0.6
Regimen (%)				
LDV/SOF	47.3	46.5	49.5	48.6
LDV/SOF +Ribavirin	17.5	19.3	13.7	13.3
PrOD	4.3	4.13	5.1	3.9
PrOD +Ribavirin	13.6	12.9	15.6	13.9
SOF +Ribavirin	16.4	16.4	15.2	19.7
PEG+ SOF +Ribavirin	0.8	0.8	0.9	0.5
HCV RNA Viral load >6 million IU/mL (%)	18.7	18.0	20.2	2.0
Missing SVR data (%)	9.6	8.7	9.8	12.9
HIV co-infection	3.9	4.0	4.2	2.2
Cirrhosis (%)	30.0	33.2	22.7	21.9
Decompensated Cirrhosis (%)	2.8	9.7	4.5	5.5

	All Patients (N = 15,151)	AUDIT-C 0 No Alcohol Use (N = 10,387)	AUDIT-C 1–3 Low-Level Alcohol Use (N = 3422)	AUDIT-C 4–12 Unhealthy Alcohol Use (N = 1342)
Hepatocellular Carcinoma (%)	3.0	3.0	1.8	2.2
Liver Transplantation	2.2	2.9	0.5	0.5
Diabetes (%)	29.2	32.4	26.8	17.2
Alcohol Use Disorder (%)	44.1	43.1	40.8	68.4
Substance Use Disorder (%)	37.0	38.6	33.0	44.1
Depression (%)	47.4	50.3	42.9	47.2
PTSD (%)	26.8	29.0	23.7	24.1
Anxiety/Panic (%)	36.2	36.2	30.7	35.0
Laboratory Results				
Anemia [§] (%)	14.7	16.2	11.0	12.3
Platelet Count < 100 k/ μ L (%)	13.4	15.3	9.2	10.0
Creatinine > 1.1 mg/dL (%)	19.7	20.5	19.8	13.9
Bilirubin > 1.1 g/dL (%)	13.7	14.7	10.9	12.5
Albumin < 3.6g/dL (%)	20.3	22.3	15.9	16.8
INR > 1.1 (%)	22.0	23.9	17.1	18.6
FIB-4 [‡] score > 3.25 (%)	35.7	37.3	30.9	35.4

* For women: 1–2 = low level alcohol use, 3–12 = unhealthy alcohol use.

[‡] FIB-4 score (Vallet-Pichard et al., 2007) = [age x AST]/[platelets $\times$ ALT^{1/2}].

[§] Anemia is defined as a hemoglobin concentration < 13 g/dL in men or < 12 g/dL in women.

Table 2

Proportion with SVR[†] by categories of alcohol use: full sample and by HCV genotype, cirrhosis and HIV status.

	AUDIT-C SCORE			
	AH Patients % (95% CI)	0 % (95% CI)	1–3 [*] % (95% CI)	4–12 [*] % (95% CI)
AH Patients (n=13,742)	91.7 (91.2–92.1)	91.5 (90.9–92.0)	92.6 (91.6–93.5)	90.8 (89.0–92.3)
Genotype/Regimen				
Genotype 1 (n = 10,057)	93.6 (93.1–94.1)	93.4 (92.8–94.0)	94.2 (93.3–95.1)	93.0 (91.1–94.5)
LDV/SOF (n = 5974)	93.8 (93.2–94.4)	93.8 (93.1–94.5)	94.2 (92.9–95.3)	92.5 (90.0–94.4)
LDV/SOF + Ribavirin (n = 1911)	92.1 (90.9–93.2)	91.7 (90.3–93.0)	93.4 (90.3–95.5)	93.6 (87.6–96.8)
PrOD (n = 540)	95.5 (93.5–96.9)	94.9 (92.2–96.7)	96.4 (92.1–98.4)	97.7 (84.5–99.7)
PrOD + Ribavirin (n = 1632)	93.8 (92.6–94.9)	93.8 (92.3–95.0)	94.2 (91.7–95.9)	93.2 (88.0–96.2)
Genotype 2 (n = 1605)	87.2 (85.5–88.7)	87.4 (85.3–89.2)	87.4 (83.6–90.5)	85.1 (78.8–89.8)
SOF + Riba	77.2 (74.4–79.8)	76.0 (72.6–79.1)	80.6 (74.3–85.7)	78.9 (69.0–86.2)
Genotype 3 (n = 858)	79.6 (74.6–83.8)	79.2 (73.2–84.2)	80.7 (68.0–89.2)	80.0 (60.8–91.2)
LDV/SOF + RIBA (n = 270)	88.8 (81.1–93.6)	88.0 (78.2–93.7)	89.3 (69.9–96.7)	**
SOF + PEG + RIBA (n = 104)	73.5 (69.5–77.1)	71.7 (66.9–76.1)	78.2 (68.9–85.3)	76.8 (63.6–86.3)
SOF + RIBA (n = 484)	91.0 (83.9–95.1)	92.0 (83.0–96.4)	89.3 (69.9–96.7)	87.5 (31.9–99.1)
Genotype 4 (n = 104)	93.2 (89.9–96.4)	93.3 (89.9–96.4)	93.6 (89.9–96.7)	91.8 (87.6–96.1)
LDV/SOF or PrOD ± RIBA				
No Cirrhosis (n = 8920)				

	AUDIT-C SCORE			
	AH Patients % (95% CI)	0 % (95% CI)	1–3 [*] % (95% CI)	4–12 [*] % (95% CI)
Cirrhosis (n = 3704)	(92.7–93.7) 87.9	(92.7–93.9) 87.7	(92.5–94.5) 89.1	(89.8–93.4) 87.1
No HIV (n = 12,148)	(86.8–88.9) 91.6	(86.5–88.8) 91.4	(86.5–91.3) 92.6	(82.4–90.7) 90.6
HIV (n = 476)	(91.1–92.1) 92.8	(90.8–91.9) 93.1	(91.7–93.5) 91.0	(88.8–92.1) 96.3
Treatment Naïve (n = 9683)	(90.2–94.7) 92.1	(90.1–95.3) 92	(84.7–94.8) 93	(75.4–99.5) 90.8
Treatment Experienced (n = 4059)	(91.6–92.7) 90.5	(91.3–92.7) 90.3	(91.9–93.9) 91.3	(88.8–92.5) 90.7
	(89.5–91.4)	(89.2–91.3)	(89.1–93.2)	(85.9–93.9)

^{*} For women: 1–2=low level alcohol use, 3–12=unhealthy alcohol use.

^{**} Insufficient number of observations.

[†] SVR is calculated among 13,742 patients with available SVR data (out of 15,151 patients in this study).

Table 3

Adjusted* Odds Ratios for SVR associated with categories of alcohol use among patients treated with DAAs for HCV, overall and by genotype, cirrhosis and HIV status.

		AOR (95% CI)		
	AUDIT-C 0	AUDIT-C 1–3	AUDIT-C 4–12	
All patients	1	0.99 (0.85–1.17)	0.82(0.66–1.03)	
Genotype				
1	1	1.02 (0.84–1.24)	0.83 (0.63–1.10)	
2	1	0.87 (0.43–1.15)	0.70 (0.43–1.15)	
3	1	1.20 (0.78–1.85)	1.05 (0.59–1.86)	
4	N/A	N/A	N/A	
No Cirrhosis	1	1.00 (0.83–1.22)	0.77 (0.59–1.01)	
Cirrhosis	1	1.01 (0.76–1.34)	0.97 (0.64–1.47)	
No HIV	1	1.01 (0.86–1.19)	0.81 (0.65–1.02)	
HIV	1	0.77 (0.36–1.68)	1.31 (0.16–10.9)	

* Adjusted for regimen, genotype, age, race/ethnicity, sex, baseline HCV viral load, cirrhosis, decompensated cirrhosis, HCC, HIV, diabetes, liver transplantation, treatment experienced/naïve, platelet count and serum bilirubin and albumin level.

Table 4

Comparison of observed SVR among patients with available SVR data (n= 13,472) and combined observed or imputed SVR among all patients who initiated antiviral treatment (n= 14,972*).

	Observed SVR % (95% CI) n= 13,742	Observed SVR or Imputed SVR ^a for patients missing SVR data, % (95% CI) n= 14,972	SVR assuming all patients with missing SVR data did not achieve SVR, % (95% CI) N = 15,151
All Patients	91.7(91.2–92.1)	90.5 (90.0–91.0)	83.1 (82.5–83.7)
AUDIT-C GROUPS			
0	91.5 (90.9–92.0)	90.4(89.8–91.0)	83.5 (82.8–84.2)
1–3	92.6(91.7–93.5)	91.5 (90.5–92.5)	83.5 (82.2–84.7)
4–12	90.8 (89.1–92.4)	88.5 (86.6–90.4)	79.1 (76.9–81.2)
Genotype 1			
0	93.4 (92.9–94.0)	92.5 (91.9–93.1)	85.6 (84.9–86.4)
1–3	94.2(93.3–95.1)	93.3 (92.3–94.3)	85.4(84.1–86.7)
4–12	93.0 (91.4–94.7)	91.4 (89.6–93.3)	82.0 (79.6–84.3)
Genotype 2			
0	87.4 (85.4–89.3)	85.7 (83.7–87.8)	78.5 (76.1–80.6)
1–3	87.4 (84.0–90.9)	85.7 (82.0–89.3)	77.3(72.9–81.1)
4–12	85.1 (79.7–90.6)	80.7 (74.7–86.8)	72.6 (65.9–78.4)
Genotype 3			
0	76.0 (72.7–79.3)	74.4(71.1–77.7)	68.1 (64.7–71.4)
1–3	80.6 (74.9–86.4)	78.3(72.5–84.1)	71.4 (64.9–77.2)
4–12	78.9 (70.3–87.5)	74.9 (66.0–83.8)	63.4 (54.0–71.9)
Genotype 4			
0	92.0 (85.7–98.3)	91.2 (84.6–97.8)	87.3(77.8–93.1)
1–3	89.3 (77.1–100.0)	89.3 (77.2–100.0)	75.8 (57.4–87.9)
4–12	<i>b</i>	<i>b</i>	<i>b</i>

^aImputed by multiple imputation using a logistic regression model that included duration of treatment together with all the baseline patient characteristics shown in Table 1. The number of patients is slightly less than 15,151 due to missing data in the characteristics used to impute SVR.

^bUnable to calculate due to insufficient number of outcomes.

Percentage achieving SVR, and adjusted^a Odds Ratios for SVR associated with levels of drinking, among patients with observed SVR data only compared to observed plus imputed data.

Table 5

	SVR (95% CI) Observed only ^{**}	SVR (95% CI) Observed plus imputed [†]	AOR (95% CI) Observed SVR only ^{**}	AOR (95% CI) Observed plus imputed [†]
0	91.5 (90.9–92.0)	90.4(89.8–91.0)	1	1
1–3	92.6 (91.6–93.5)	91.5(90.5–92.5)	0.99(0.85–1.17)	1.00 (0.86–1.17)
4–12	90.8 (89.0–92.3)	88.5 (86.6–90.4)	0.82(0.66–1.03)	0.75 (0.60–0.92)

^a Adjusted for regimen, genotype, age, race/ethnicity, sex, baseline HCV viral load, cirrhosis, decompensated cirrhosis, HCC, HIV, diabetes, liver transplantation, treatment experienced/naïve, platelet count and serum bilirubin and albumin level.

^{**} N = 13,742.

[†] N = 14,972.