



Original Investigation | Gastroenterology and Hepatology

Alcohol Use and Sustained Virologic Response to Hepatitis C Virus Direct-Acting Antiviral Therapy

Emily J. Cartwright, MD; Chloe Pierret, MSc; Caroline Minassian, PhD; Denise A. Esserman, PhD; Janet P. Tate, ScD; Matthew B. Goetz, MD; Debika Bhattacharya, MD; David A. Fiellin, MD; Amy C. Justice, MD, PhD; Vincent Lo Re III, MD, MSCE; Christopher T. Rentsch, PhD

Abstract

IMPORTANCE Some payers and clinicians require alcohol abstinence to receive direct-acting antiviral (DAA) therapy for chronic hepatitis C virus (HCV) infection.

OBJECTIVE To evaluate whether alcohol use at DAA treatment initiation is associated with decreased likelihood of sustained virologic response (SVR).

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used electronic health records from the US Department of Veterans Affairs (VA), the largest integrated national health care system that provides unrestricted access to HCV treatment. Participants included all patients born between 1945 and 1965 who were dispensed DAA therapy between January 1, 2014, and June 30, 2018. Data analysis was completed in November 2020 with updated sensitivity analyses performed in 2023.

EXPOSURE Alcohol use categories were generated using responses to the Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) questionnaire and *International Classification of Diseases, Ninth Revision* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* diagnoses for alcohol use disorder (AUD): abstinent without history of AUD, abstinent with history of AUD, lower-risk consumption, moderate-risk consumption, and high-risk consumption or AUD.

MAIN OUTCOMES AND MEASURES The primary outcome was SVR, which was defined as undetectable HCV RNA for 12 weeks or longer after completion of DAA therapy. Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% CIs of SVR associated with alcohol category.

RESULTS Among 69 229 patients who initiated DAA therapy (mean [SD] age, 62.6 [4.5] years; 67 150 men [97.0%]; 34 655 non-Hispanic White individuals [50.1%]; 28 094 non-Hispanic Black individuals [40.6%]; 58 477 individuals [84.5%] with HCV genotype 1), 65 355 (94.4%) achieved SVR. A total of 32 290 individuals (46.6%) were abstinent without AUD, 9192 (13.3%) were abstinent with AUD, 13 415 (19.4%) had lower-risk consumption, 3117 (4.5%) had moderate-risk consumption, and 11 215 (16.2%) had high-risk consumption or AUD. After adjustment for potential confounding variables, there was no difference in SVR across alcohol use categories, even for patients with high-risk consumption or AUD (OR, 0.95; 95% CI, 0.85-1.07). There was no evidence of interaction by stage of hepatic fibrosis measured by fibrosis-4 score (P for interaction = .30).

(continued)

Key Points

Question Is alcohol use associated with achieving a sustained virologic response (SVR) when treating hepatitis C virus (HCV) infection with direct-acting antiviral (DAA) therapy?

Findings In this cohort study of 69 229 adults with HCV infection, there was no difference in SVR across alcohol use categories, even for patients with high-risk consumption or alcohol use disorder, after adjusting for potential confounding variables.

Meaning These findings suggest that restricting access to DAA therapy on the basis of alcohol use creates an unnecessary barrier for patients and challenges HCV elimination goals.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Abstract (continued)

CONCLUSIONS AND RELEVANCE In this cohort study, alcohol use and AUD were not associated with lower odds of SVR. Restricting access to DAA therapy according to alcohol use creates an unnecessary barrier to patients and challenges HCV elimination goals.

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Introduction

Previously, chronic hepatitis C virus (HCV) infection was treated with interferon-based regimens, a poorly tolerated therapy. In the interferon era, patients with active alcohol use in the previous year were more likely to discontinue interferon-based HCV treatment; consequently, many clinicians were reluctant to treat those with recent alcohol use.¹ However, for patients who successfully completed interferon-based therapy, comparable rates of sustained virologic response (SVR) were achieved regardless of reported alcohol use.¹⁻⁴ In 2009, the American Association for the Study of Liver Diseases (AASLD) treatment guidelines stated that candidates for HCV treatment should be abstinent from alcohol for a minimum of 6 months before initiating treatment.⁵

With the advent of safe and highly effective direct-acting antiviral (DAA) therapy for HCV, the impact of alcohol use on achieving SVR is less clear. Clinical trials⁶⁻¹¹ examining DAA safety and efficacy excluded participants who had clinically relevant alcohol use or reported high-risk alcohol consumption within the prior 12 months, as defined by Alcohol Use Disorder Identification Test–Consumption (AUDIT-C) scores of 8 or more. Empirical data on the effectiveness of DAAs in persons with current unhealthy alcohol use has been limited to an observational study¹² examining SVR in a cohort of 17 487 US Veterans who initiated DAA therapy between 2014 and mid-2015. The study found that most persons across all alcohol use categories achieved SVR (>91%), and no association between alcohol use and SVR was observed in all primary analyses. However, that study used patients who reported abstinence from alcohol as the referent group, which may be prone to biased results owing to this being a heterogeneous group known to include persons who consumed alcohol previously and quit because of alcohol-related or other health problems (ie, *sick quitters*).¹³

Current AASLD/Infectious Diseases Society of American (IDSA) HCV treatment guidelines advise that patients with HCV avoid excess alcohol use but do not recommend restricting access to DAA therapy on the basis of alcohol intake, regardless of any level of consumption.¹⁴ Similarly, the Department of Veterans Affairs (VA)—the largest provider of HCV care in the US—does not recommend withholding DAA therapy from patients with alcohol use disorder (AUD). DAA therapy is available to patients with HCV infection at no or substantially reduced cost to the individual in the VA system.^{15,16} Despite these recommendations, some clinicians continue to delay or withhold HCV therapy from patients who consume alcohol.¹⁷⁻²⁰ Furthermore, some payers include alcohol abstinence as a requirement for reimbursement of DAA therapy for HCV.^{21,22} To provide updated, empirical data on the effect of alcohol use on cure of HCV infection, we used national VA electronic health record data to examine the association of alcohol use categories with SVR.

Methods

Study Design and Data Source

We conducted a retrospective cohort study using electronic health record data from the VA. The VA comprises more than 1200 points of health care mostly in the US, including hospitals, medical centers, and community outpatient clinics, from which all care is recorded in a central data repository, with daily uploads into the VA Corporate Data Warehouse. The VA Corporate Data Warehouse includes information on demographics, outpatient and inpatient encounters, *International Classification of Diseases, Ninth Revision* and *International Statistical Classification of*

Diseases and Related Health Problems, Tenth Revision diagnostic codes, smoking and alcohol use, pharmacy dispensing records, laboratory measures, vital signs, and death. This study was approved by the institutional review boards of Yale University and VA Connecticut Healthcare System. It has been granted a waiver of informed consent because the data were anonymous, in accordance with 45 CFR §46, and is compliant with the Health Insurance Portability and Accountability Act. This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline and the Reporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) statements.

Study Population

We extracted data from the 1945 to 1965 VA Birth Cohort, which includes all individuals born between 1945 and 1965 who had at least 1 VA encounter on or after October 1, 1999. This birth cohort was chosen because people born between 1945 and 1965 are known to have a 6-fold higher prevalence of HCV infection compared with all other age groups.²³ In addition, the Centers for Disease Control and Prevention and the US Preventive Services Task Force recommended onetime HCV screening for these individuals during the time of study.^{24,25} We included all patients who initiated interferon-free DAA therapy between January 1, 2014, and June 30, 2018. The index date was defined as the day the patient was dispensed their first DAA regimen. We have previously demonstrated that DAA therapies and date of initiation are accurately recorded in VA electronic health record data.²⁶

Alcohol Category

Our primary exposure variable combined information on alcohol consumption (using the AUDIT-C) and AUD diagnoses ascertained in the 18 months before the index date. For those with more than 1 AUDIT-C measure in the ascertainment window, the value closest to the index date was chosen. The AUDIT-C is an externally validated 3-item questionnaire that assesses alcohol consumption and has been required annually in the VA since 2007.²⁷⁻³⁰ We classified patients as having AUD by the presence of at least 1 inpatient or outpatient diagnostic code, including *International Classification of Diseases, Ninth Revision* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes 303.*, 305.0*, F10.1*, or F10.2*.

Consistent with a recent study on DAA initiation in the VA,²⁰ we classified patients into 5 mutually exclusive groups on the basis of AUDIT-C score and AUD diagnoses: (1) abstinent without AUD (AUDIT-C score of 0 and absence of AUD diagnosis); (2) abstinent with AUD (AUDIT-C score of 0 and presence of AUD diagnosis); (3) lower-risk consumption (AUDIT-C score of 1-3 and absence of AUD diagnosis); (4) moderate-risk consumption (AUDIT-C score of 4-7 and absence of AUD diagnosis); and (5) high-risk consumption or AUD (AUDIT-C score of ≥ 8 or presence of AUD diagnosis with nonzero AUDIT-C score). Similar to Haque et al,²⁰ we used lower-risk consumption as the referent group in all analyses.

Outcome

The primary outcome was SVR, defined by undetectable HCV RNA 12 weeks or longer and less than 6 months after completion of DAA therapy. HCV RNA measurements through December 31, 2018, were extracted for analysis. If there were multiple HCV RNA measurements available, the latest result was chosen. For patients with no measurements 12 weeks or more after completion of DAA therapy, we selected the latest result available in the 4 to 11 weeks after completion of DAA therapy. Previous studies^{31,32} have demonstrated high concordance between SVR defined at 4, 12, and 24 weeks after treatment.

Covariates

Figure 1 depicts the study design and details on exposure and covariate ascertainment windows. Covariates included age in years, sex (male vs female), race and ethnicity (Hispanic, non-Hispanic

Black, non-Hispanic White, other [ie, American Indian, Asian, multiracial, and Pacific Islander], or missing as identified in the electronic health record), rural or urban residence type, body mass index, smoking status, HIV coinfection, Charlson Comorbidity Index score, liver-related variables (ie, HCV genotype, hepatitis B coinfection, fibrosis 4 [FIB-4] score, hepatic decompensation, or liver cancer), and other HCV treatment-related variables (ie, previous receipt of non-DAA therapy for HCV infection, year of DAA therapy initiation, and DAA regimen type). Data on race and ethnicity were included because of known associations with DAA medication receipt and SVR outcomes.

Statistical Analysis

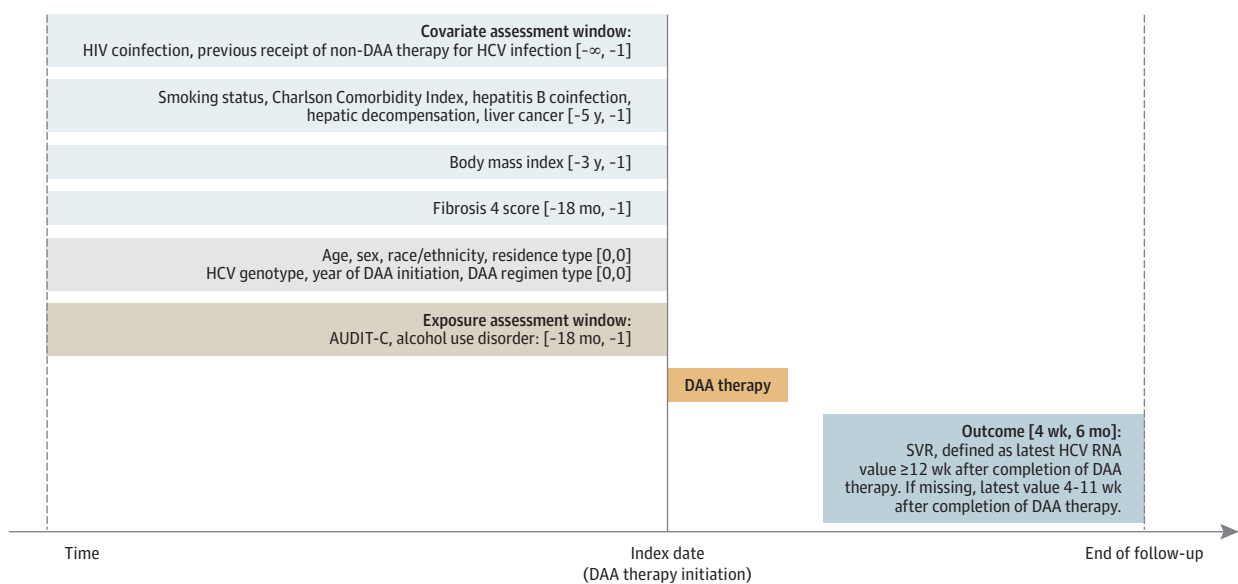
Data analysis was completed in November 2020 with updated sensitivity analyses performed in 2023. We calculated absolute standardized mean differences (SMDs) to identify differences in the covariate distribution between patients with and without AUDIT-C or HCV RNA results to define SVR. We considered SMD less than 0.2 as balanced.³³

After excluding those with missing alcohol and HCV RNA results, an additional 7339 participants (9.6%) had missing data for any of the other covariates (ie, 6.9% missing FIB-4, 1.4% missing HCV genotype, 1.1% missing smoking status, and 0.8% missing body mass index). Our primary analyses were performed on complete cases because the overall level of missingness among covariates was less than 10%, and a large proportion of missingness was likely to be missing not at random. A complete case analysis will be unbiased if, conditional on model covariates, missingness is independent of the outcome,³⁴ which we demonstrate is the case in our data.

We used logistic regression to estimate odds ratios (ORs) and 95% CIs for the association of alcohol category with SVR, adjusting for demographics, clinical characteristics, liver-related variables, and other HCV treatment-related variables. We then assessed possible interaction by specifying a cross-product term in the fully adjusted model between alcohol category and FIB-4 score because FIB-4 scores greater than 3.25 are associated with advanced liver fibrosis or cirrhosis and risk of liver cancer, which may be associated with a lower likelihood of SVR.^{35,36} Statistical significance was set at 2-sided $P < .05$. Analyses were performed using Stata statistical software version 17.0 (StataCorp).

In sensitivity analyses, we compared estimates from the fully adjusted model in the primary analysis to models including patients with missing outcome data using 3 assumptions: (1) multiple imputation (10 imputations) of the outcome with imputation model included all extracted covariates;

Figure 1. Study Diagram



AUDIT-C indicates Alcohol Use Disorder Identification Test-Consumption; DAA, direct-acting antiviral; HCV, hepatitis C virus; and SVR, sustained virologic response.

(2) all patients with missing outcome data were assumed to have achieved SVR; and (3) all patients with missing outcome data were assumed to not have achieved SVR. Although multiple imputation may not be appropriate because it assumes data to define SVR were missing at random,³⁷ we included this sensitivity analysis to compare our findings with those of previous studies that applied multiple imputation. We extended the outcome ascertainment window to include HCV RNA measurements up to 12 months after completion of DAA therapy. We reclassified women with AUDIT-C score of 3 and no AUD as having moderate-risk consumption.

Results

Cohort Description

Among 94 388 patients who initiated DAA therapy between January 1, 2014, and June 30, 2018 (Figure 2), 3763 (4.0%) had missing AUDIT-C score and 22 323 (24.6%) had no HCV RNA laboratory values to define SVR within 12 weeks to 6 months after DAA completion. Among those with missing HCV RNA laboratory values in this window, 8266 (37.0%) had measurements in the 4 to 11 weeks after completion of DAA therapy; thus, 14 057 patients had no information to define SVR in primary analyses. Compared with patients with AUDIT-C values, Charlson Comorbidity Index scores were lower in patients without AUDIT-C values (SMD = 0.29), but the distribution of other covariates was similar (all SMD <0.2; most SMD <0.1) (eTable 1 in Supplement 1). Distributions were also similar for those with and without HCV RNA laboratory values, including no observed differences by alcohol category (eTable 2 in Supplement 1).

Of the 69 229 patients included in the primary analyses (mean [SD] age, 62.6 [4.5] years), 67 150 (97.0%) were men, 34 655 (50.1%) were non-Hispanic White, 28 094 (40.6%) were non-Hispanic Black, and 46 220 (66.8%) were current smokers at DAA initiation (Table 1). Most patients (58 477 patients [84.5%]) had HCV genotype 1, 15.4% (10 632 patients) had previous receipt of non-DAA therapy for HCV infection, 3.2% (2217 patients) had HIV coinfection, and 1.9% (1308 patients) had HBV coinfection. Approximately one-half of patients (35 032 patients [50.6%]) had FIB-4 scores between 1.45 and 3.25, whereas 16 103 patients (23.3%) had scores less than 1.45, and

Figure 2. Patient Flow Diagram

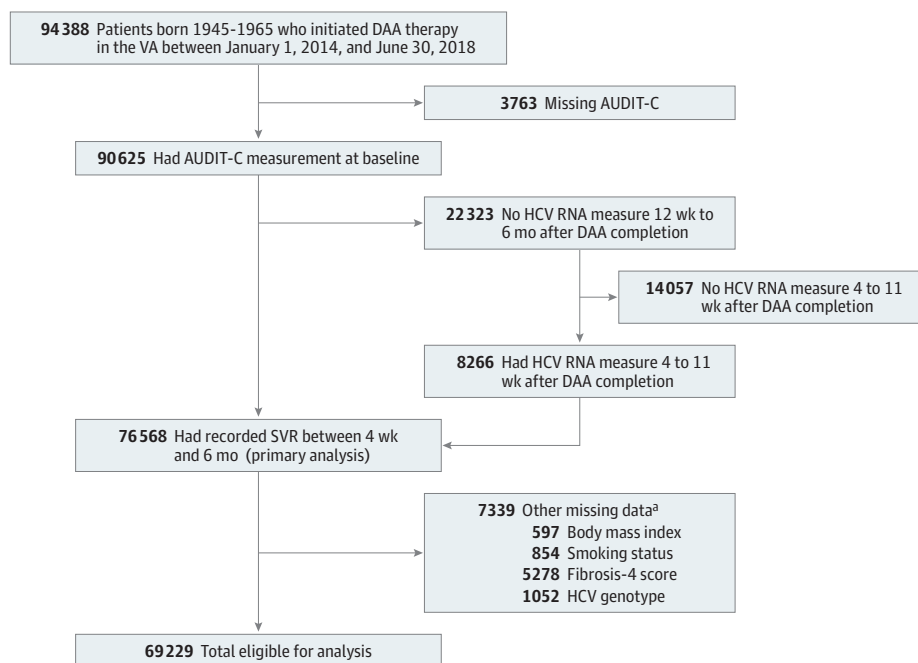


Table 1. Characteristics of Patients Who Initiated DAA Therapy by Alcohol Consumption Category

| Characteristic | Patients, No. (%) (N = 69 229) | | | | |
|---|--------------------------------|---------------------|-------------------------|--------------------------|-------------------------------|
| | Abstinent | | Consumption | | |
| | Without AUD (n = 32 290) | With AUD (n = 9192) | Lower risk (n = 13 415) | Moderate risk (n = 3117) | High risk or AUD (n = 11 215) |
| Demographic characteristics | | | | | |
| Age, median (IQR), y | 63.3 (59.9-66.4) | 61.6 (58.4-65.0) | 63.0 (59.7-66.1) | 63.0 (59.8-66.1) | 61.8 (58.6-65.2) |
| 48-54 | 1440 (4.5) | 725 (7.9) | 662 (4.9) | 143 (4.6) | 793 (7.1) |
| 55-59 | 6787 (21.0) | 2635 (28.7) | 2982 (22.2) | 688 (22.1) | 3212 (28.6) |
| 60-64 | 12 418 (38.5) | 3497 (38.0) | 5233 (39.0) | 1248 (40.0) | 4290 (38.3) |
| 65-73 | 11 645 (36.1) | 2335 (25.4) | 4538 (33.8) | 1038 (33.3) | 2920 (26.0) |
| Sex | | | | | |
| Women | 1074 (3.3) | 251 (2.7) | 474 (3.5) | 49 (1.6) | 231 (2.1) |
| Men | 31 216 (96.7) | 8941 (97.3) | 12 941 (96.5) | 3068 (98.4) | 10 984 (97.9) |
| Race and ethnicity | | | | | |
| Hispanic | 1649 (5.1) | 450 (4.9) | 638 (4.8) | 112 (3.6) | 506 (4.5) |
| Non-Hispanic Black | 12 702 (39.3) | 3738 (40.7) | 5608 (41.8) | 1117 (35.8) | 4929 (44.0) |
| Non-Hispanic White | 16 403 (50.8) | 4666 (50.8) | 6535 (48.7) | 1723 (55.3) | 5327 (47.5) |
| Other or missing ^a | 1536 (4.8) | 338 (3.7) | 633 (4.7) | 165 (5.3) | 453 (4.0) |
| Residence type | | | | | |
| Rural | 8815 (27.3) | 2099 (22.8) | 3516 (26.2) | 964 (30.9) | 2695 (24.0) |
| Urban | 23 475 (72.7) | 7093 (77.2) | 9899 (73.8) | 2153 (69.1) | 8520 (76.0) |
| Clinical characteristics | | | | | |
| Body mass index^b | | | | | |
| Underweight (<18.5) | 467 (1.4) | 126 (1.4) | 208 (1.6) | 58 (1.9) | 243 (2.2) |
| Normal (18.5-24.9) | 8482 (26.3) | 2601 (28.3) | 3783 (28.2) | 1084 (34.8) | 3952 (35.2) |
| Overweight (25.0-29.9) | 12 244 (37.9) | 3515 (38.2) | 5232 (39.0) | 1186 (38.0) | 4208 (37.5) |
| Obese (≥30.0) | 11 097 (34.4) | 2950 (32.1) | 4192 (31.2) | 789 (25.3) | 2812 (25.1) |
| Smoking status | | | | | |
| Never | 5117 (15.8) | 795 (8.6) | 1840 (13.7) | 323 (10.4) | 779 (6.9) |
| Current | 18 686 (57.9) | 7053 (76.7) | 8831 (65.8) | 2305 (73.9) | 9345 (83.3) |
| Former | 8487 (26.3) | 1344 (14.6) | 2744 (20.5) | 489 (15.7) | 1091 (9.7) |
| HIV coinfection | 1072 (3.3) | 318 (3.5) | 409 (3.0) | 74 (2.4) | 344 (3.1) |
| Charlson Comorbidity Index score | | | | | |
| 1 | 12 107 (37.5) | 3322 (36.1) | 6031 (45.0) | 1578 (50.6) | 4883 (43.5) |
| 2 | 8230 (25.5) | 2394 (26.0) | 3398 (25.3) | 834 (26.8) | 2976 (26.5) |
| 3 | 3273 (10.1) | 879 (9.6) | 1284 (9.6) | 265 (8.5) | 1072 (9.6) |
| 4 | 3313 (10.3) | 913 (9.9) | 1098 (8.2) | 195 (6.3) | 921 (8.2) |
| ≥5 | 5367 (16.6) | 1684 (18.3) | 1604 (12.0) | 245 (7.9) | 1363 (12.2) |
| Liver-related variables | | | | | |
| HCV genotype | | | | | |
| 1 | 27 342 (84.7) | 7727 (84.1) | 11 358 (84.7) | 2584 (82.9) | 9466 (84.4) |
| 2 | 2889 (8.9) | 824 (9.0) | 1242 (9.3) | 354 (11.4) | 1023 (9.1) |
| 3 | 1739 (5.4) | 560 (6.1) | 663 (4.9) | 153 (4.9) | 610 (5.4) |
| 4, 5, or 6 | 320 (1.0) | 81 (0.9) | 152 (1.1) | 26 (0.8) | 116 (1.0) |
| Hepatitis B coinfection | 581 (1.8) | 253 (2.8) | 185 (1.4) | 43 (1.4) | 246 (2.2) |
| Fibrosis-4 score | | | | | |
| <1.45 | 7402 (22.9) | 2162 (23.5) | 3400 (25.3) | 712 (22.8) | 2427 (21.6) |
| 1.45-3.25 | 16 489 (51.1) | 4353 (47.4) | 7137 (53.2) | 1641 (52.6) | 5412 (48.3) |
| >3.25 | 8399 (26.0) | 2677 (29.1) | 2878 (21.5) | 764 (24.5) | 3376 (30.1) |
| Hepatic decompensation | 1091 (3.4) | 640 (7.0) | 117 (0.9) | 14 (0.4) | 346 (3.1) |
| Liver cancer | 786 (2.4) | 363 (3.9) | 154 (1.1) | 34 (1.1) | 200 (1.8) |

(continued)

Table 1. Characteristics of Patients Who Initiated DAA Therapy by Alcohol Consumption Category (continued)

| Characteristic | Patients, No. (%) (N = 69 229) | | | | |
|---|--|------------------------|----------------------------|-----------------------------|----------------------------------|
| | Abstinent Without AUD (n = 32 290) | With AUD (n = 9192) | Consumption | | |
| | | | Lower risk (n = 13 415) | Moderate risk (n = 3117) | High risk or AUD (n = 11 215) |
| Treatment-related characteristics | | | | | |
| Previous non-DAA therapy for HCV infection | 6021 (18.6) | 1551 (16.9) | 1635 (12.2) | 298 (9.6) | 1127 (10.0) |
| Year of DAA therapy initiation | | | | | |
| 2014 | 3298 (10.2) | 978 (10.6) | 760 (5.7) | 116 (3.7) | 466 (4.2) |
| 2015 | 9995 (31.0) | 3111 (33.8) | 3556 (26.5) | 584 (18.7) | 2623 (23.4) |
| 2016 | 11 574 (35.8) | 3325 (36.2) | 5204 (38.8) | 1271 (40.8) | 4502 (40.1) |
| 2017 | 5932 (18.4) | 1400 (15.2) | 3099 (23.1) | 923 (29.6) | 2826 (25.2) |
| 2018 | 1491 (4.6) | 378 (4.1) | 796 (5.9) | 223 (7.2) | 798 (7.1) |
| DAA regimen type | | | | | |
| Sofosbuvir and ledipasvir | 18 526 (57.4) | 5569 (60.6) | 7954 (59.3) | 1867 (59.9) | 6805 (60.7) |
| Elbasvir and grazoprevir | 3387 (10.5) | 729 (7.9) | 1484 (11.1) | 361 (11.6) | 1234 (11.0) |
| Sofosbuvir and velpatasvir with or without voxilaprevir | 2270 (7.0) | 592 (6.4) | 1085 (8.1) | 341 (10.9) | 1000 (8.9) |
| Glecaprevir and pibrentasvir | 972 (3.0) | 234 (2.5) | 552 (4.1) | 127 (4.1) | 506 (4.5) |
| Paritaprevir, ritonavir, and ombitasvir with or without dasabuvir | 2747 (8.5) | 697 (7.6) | 1084 (8.1) | 199 (6.4) | 725 (6.5) |
| Sofosbuvir and daclatasvir | 389 (1.2) | 121 (1.3) | 148 (1.1) | 28 (0.9) | 124 (1.1) |
| Simeprevir and sofosbuvir | 1410 (4.4) | 427 (4.6) | 295 (2.2) | 29 (0.9) | 205 (1.8) |
| Sofosbuvir and ribavirin | 2589 (8.0) | 823 (9.0) | 813 (6.1) | 165 (5.3) | 616 (5.5) |

Abbreviations: AUD, alcohol use disorder; DAA, direct-acting antiviral; HCV, hepatitis C virus.

^a Other includes American Indian, Asian, multiracial, and Pacific Islander.

^b Body mass index is calculated as weight in kilograms divided by height in meters squared.

18 094 patients (26.1%) had scores greater than 3.25 at DAA initiation. Sofosbuvir and ledipasvir (58.8%) was the most frequently prescribed DAA regimen.

Alcohol Category and SVR

There was considerable variation in the alcohol category: 32 290 patients (46.6%) were abstinent without AUD, 9192 patients (13.3%) were abstinent with AUD, 13 415 patients (19.4%) had lower-risk consumption, 3117 patients (4.5%) had moderate-risk consumption, and 11 215 patients (16.2%) had high-risk consumption or AUD. Overall, 65 355 (94.4%) of all DAA-initiating patients achieved SVR, with 58 651 SVR outcomes measured 12 weeks to 6 months after DAA completion, and 6704 at 4 to 12 weeks after DAA completion.

In an unadjusted model, patients who were abstinent without AUD history (OR, 0.89 [95% CI, 0.81-0.97]) and those who were abstinent with AUD history (OR, 0.71 [95% CI, 0.64-0.80]) had lower odds of achieving SVR compared with patients who reported lower-risk consumption (Table 2). However, in the fully adjusted model, we found no evidence that any alcohol category was significantly associated with decreased odds of SVR (OR, 1.09 [95% CI, 0.99-1.20] for abstinent without AUD history; OR, 0.92 [95% CI, 0.82-1.04] for abstinent with AUD history; OR, 0.96 [95% CI, 0.80-1.15] for moderate-risk consumption; and OR, 0.95 [95% CI, 0.85-1.07] for high-risk consumption or AUD) (Table 2). In addition, we found no evidence that the association of alcohol category with the odds of SVR differed by baseline stage of hepatic fibrosis measured by FIB-4 less than or equal to 3.25 vs greater than 3.25 (*P* for interaction = .30) (Table 2).

Sensitivity Analyses

Findings persisted after including patients with missing data using multiple imputation (lowest adjusted OR, 0.90 [95% CI, 0.80-1.02] for patients who were abstinent with AUD history) and assuming all patients with missing outcome data achieved SVR (lowest adjusted OR, 0.94 [95% CI,

0.84-1.06] for patients who were abstinent with AUD history) (Table 3). In an analysis assuming the highly unlikely scenario that all patients with missing outcome data did not achieve SVR, we observed that patients who were abstinent with AUD history (adjusted OR, 0.92 [95% CI, 0.86-0.98]) and those with high-risk consumption or AUD (adjusted OR, 0.88 [95% CI, 0.83-0.93]) had lower odds of SVR compared with patients who reported lower-risk consumption. Conclusions from the primary analysis held after extending the outcome ascertainment window from 6 to 12 months. Results were nearly identical after reclassifying women with AUDIT-C score of 3 and no AUD as moderate risk consumption.

Discussion

In this nationwide cohort study of chronically HCV-infected adults born between 1945 and 1965 who initiated DAA therapy between 2014 and 2018 in the largest provider of HCV care in the US, we found no evidence that any level of alcohol use was associated with decreased odds of achieving SVR. This finding did not differ by baseline stage of hepatic fibrosis. Moreover, 94.4% of all patients achieved SVR in this clinical practice setting of an older population with multiple comorbidities who are typically underrepresented in clinical trials. Furthermore, some patients were treated with older DAA regimens including sofosbuvir and ribavirin, which are less well tolerated and are associated with a lower percentage of patients achieving SVR. Taken together, our findings support providing DAA therapy without regard to reported alcohol consumption or AUD.

Our results support the current AASLD/IDSA recommendations that current or prior alcohol use is not a contraindication to HCV DAA therapy. However, a recent analysis of administrative claims and encounters in the US found that only 23% of Medicaid, 28% of Medicare, and 35% of private

Table 2. Associations of Alcohol Category With Sustained Virologic Response

| Variable | OR (95% CI) ^a All patients with exposure and outcome data (n = 76 568), unadjusted | Complete case analysis (n = 69 229) | | | |
|--------------------|--|-------------------------------------|------------------|----------------------------------|--------------------|
| | | Unadjusted | Fully adjusted | By fibrosis-4 score ^b | |
| | | | | ≤3.25 (n = 51 135) | >3.25 (n = 18 094) |
| Abstinent | | | | | |
| Without AUD | 0.88 (0.80-0.95) | 0.89 (0.81-0.97) | 1.09 (0.99-1.20) | 1.11 (0.99-1.25) | 1.08 (0.92-1.27) |
| With AUD | 0.70 (0.63-0.78) | 0.71 (0.64-0.80) | 0.92 (0.82-1.04) | 0.96 (0.82-1.11) | 0.88 (0.72-1.06) |
| Consumption | | | | | |
| Lower risk | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Moderate risk | 1.03 (0.87-1.22) | 1.04 (0.86-1.24) | 0.96 (0.80-1.15) | 1.00 (0.79-1.26) | 0.87 (0.64-1.19) |
| High risk or AUD | 0.91 (0.81-1.01) | 0.92 (0.82-1.03) | 0.95 (0.85-1.07) | 0.91 (0.79-1.06) | 1.02 (0.82-1.21) |

Abbreviations: AUD, alcohol use disorder; OR, odds ratio.

^a Fully adjusted model included age, sex, race and ethnicity, residence type, body mass index, smoking status, HIV coinfection, Charlson Comorbidity Index score, liver-related variables (ie, hepatitis C virus [HCV] genotype, hepatitis B coinfection, fibrosis-4 score, hepatic decompensation, and liver cancer), and other HCV treatment-related variables (ie, previous receipt of non-direct-acting antiviral [DAA] therapy for HCV infection, year of DAA therapy initiation, and DAA regimen type).

^b P value for interaction = .30.

Table 3. Sensitivity Analyses

| Variable | Adjusted OR (95% CI) ^a | | | | |
|--------------------|-----------------------------------|---|---|---|---|
| | Primary analysis (n = 69 229) | Multiple imputation of missing SVR (n = 81 703) | Missing SVR, assumed to be cured (n = 81 703) | Missing SVR, assumed to be not cured (n = 81 703) | Extending outcome ascertainment window (n = 73 956) |
| Abstinent | | | | | |
| Without AUD | 1.09 (0.99-1.20) | 1.08 (0.97-1.20) | 1.09 (0.99-1.20) | 1.00 (0.96-1.05) | 1.08 (0.96-1.20) |
| With AUD | 0.92 (0.82-1.04) | 0.90 (0.80-1.02) | 0.94 (0.84-1.06) | 0.92 (0.86-0.98) | 0.95 (0.83-1.09) |
| Consumption | | | | | |
| Lower risk | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Moderate risk | 0.96 (0.80-1.15) | 0.95 (0.76-1.19) | 0.95 (0.79-1.15) | 1.03 (0.94-1.13) | 0.98 (0.78-1.22) |
| High risk or AUD | 0.95 (0.85-1.07) | 0.95 (0.84-1.08) | 0.98 (0.87-1.11) | 0.88 (0.83-0.93) | 0.96 (0.84-1.10) |

Abbreviations: AUD, alcohol use disorder; OR, odds ratio; SVR, sustained virologic response.

^a Fully adjusted model included age, sex, race and ethnicity, residence type, body mass index, smoking status, HIV coinfection, Charlson Comorbidity Index score, liver-related variables (ie, hepatitis C virus [HCV] genotype, hepatitis B coinfection, fibrosis-4 score, hepatic decompensation, and liver cancer), and other HCV treatment-related variables (ie, previous receipt of non-direct-acting antiviral [DAA] therapy for HCV infection, year of DAA therapy initiation, and DAA regimen type).

insurance recipients initiated DAA treatment within 1 year of HCV diagnosis.³⁸ Furthermore, that analysis found that Medicaid recipients were less likely to initiate DAA treatment if they resided in a state with Medicaid treatment restrictions including alcohol abstinence. Even though the VA has not required alcohol abstinence before DAA treatment, preexisting alcohol use still impacts who initiates DAA therapy. Haque et al²⁰ found that individuals in the 1945 to 1965 VA Birth Cohort with current AUD and those who were abstinent with an AUD history were significantly less likely to receive DAA treatment compared with patients with lower-risk drinking. Although alcohol use has a dose-dependent association with incident cirrhosis and is associated with increased risk of hepatocellular carcinoma in those with chronic HCV infection, curative HCV treatment has been shown to significantly reduce the risk of cirrhosis and hepatocellular carcinoma in those with chronic hepatitis C.³⁹⁻⁴¹ The VA does offer substance use disorder treatment, and any veteran can be referred and assessed for treatment, which may include inpatient, intensive outpatient, university model, or residential treatment programs. Some VA facilities partnered with residential substance use disorder program to integrate HCV treatment.⁴² Our findings suggest that clinicians and policy makers should encourage HCV treatment in those with unhealthy alcohol consumption or AUD, rather than creating barriers to HCV treatment. Given the high rates of SVR across all alcohol use categories, there is no indication for payers to require alcohol abstinence before reimbursement of DAA therapy for HCV infection.

Although numerous studies from the interferon era examined alcohol use and SVR,¹⁻⁴ there are few such studies in the DAA era. Tsui et al¹² examined alcohol use and SVR in the VA including the first 18 months of the DAA era. Although the authors found no difference in SVR across alcohol use categories in all primary analyses, after imputing missing HCV RNA values for 9% of their cohort, they observed a significantly lower likelihood of SVR among those reporting unhealthy alcohol use. However, Tsui et al¹² also demonstrated that those with unhealthy alcohol use (defined as AUDIT-C score ≥ 4) were more likely to have missing HCV RNA values, and, therefore, the assumptions required for multiple imputation may have been violated.³⁷ Furthermore, Tsui et al¹² used patients reporting abstinence as the referent group; however, this is a heterogeneous group comprising very few lifetime abstainers, and the majority quit drinking after experiencing alcohol-related or health problems.¹³ To avoid misclassification, we used lower-risk consumption as the referent group and distinguished patients reporting abstinence by whether they had received a diagnosis of AUD. In sensitivity analyses assuming everyone with missing outcome data did not achieve SVR, persons with high-risk consumption or AUD had 12% decreased odds of achieving SVR (adjusted OR, 0.88) in multivariable analysis. We know in clinical practice that not every missing SVR value is a treatment failure, and, in fact, many persons are found to have SVR when reengaged in care⁴³; therefore, we express caution in interpreting this single association.

Strengths and Limitations

This study has many strengths, including the availability of detailed, longitudinal, electronic health record data on a diverse nationwide cohort of HCV-infected patients initiating DAA therapy and findings that were robust to multiple sensitivity analyses. Importantly, the VA has been more successful than most health care systems in the US in diagnosing and treating HCV infection given its unified electronic health record, nationalized health care system, and prioritization of HCV.⁴⁴ The VA has far exceeded other health care systems^{38,45-49} by treating nearly 85% of patients with known chronic HCV infection in VA care.^{16,50,51}

We also recognize possible limitations. First, as a result of the observational nature of the study, a degree of uncertainty persists owing to the potential for residual confounding. Second, we assessed HCV RNA measurements in the 6-month period following the end of DAA treatment to define SVR, which may have resulted in potential misclassification of some patients who may have experienced viral relapse; however, this has been shown to be an extremely rare event.⁵² Some patients may also have had their first evidence of SVR recorded beyond that window of measurement, which we would have classified as a missing outcome, although extending the

ascertainment window to 12 months did not change our results. Third, alcohol use measurement may have been influenced by both patient-level and practitioner-level factors,⁵³⁻⁵⁶ including underreporting level of alcohol use because of social desirability bias,⁵⁷ which may have resulted in misclassification of some patients with high-risk consumption at lower levels of consumption. Furthermore, we categorized patients with AUD separately and used patients with lower-risk consumption as the referent category, which minimized the potential of misclassification of sick quitters.¹³ Fourth, we performed a complete case analysis, which will be unbiased if, conditional on model covariates, missingness is independent of the outcome.³⁴ To that end, we demonstrated that missing outcome data were not associated with any covariate used in the model, suggesting complete case analysis was appropriate. However, we also performed multiple sensitivity analyses, all of which were consistent with our findings from our complete case analysis. Fifth, our study leveraged available data on patients born between 1945 and 1965; therefore, our findings may not generalize to patients born before 1945 or after 1965. Sixth, although individuals in VA care represent a diversity of backgrounds, women represented a small proportion of individuals in the cohort. However, given the current payer restrictions requiring alcohol abstinence before initiating DAA therapy, the ability to study the association of alcohol use with HCV treatment outcomes, including SVR, may be limited in other US health care settings.

Conclusions

In conclusion, achieving SVR has been shown to be associated with reduced risk of post-SVR outcomes, including hepatocellular carcinoma, liver-related mortality, and all-cause mortality. Our findings suggest that DAA therapy should be provided and reimbursed despite alcohol consumption or history of AUD. Restricting access to DAA therapy according to alcohol consumption or AUD creates an unnecessary barrier to patients accessing DAA therapy and challenges HCV elimination goals.

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Corresponding Authors: Emily J. Cartwright, MD, Atlanta Veterans Affairs Medical Center, 1670 Clairmont Rd NE, Decatur, GA 30033 (emily.cartwright@va.gov); Christopher T. Rentsch, PhD, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK (christopher.rentsch@lshtm.ac.uk).

Author Affiliations: Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia (Cartwright); Atlanta Veterans Affairs Medical Center, Decatur, Georgia (Cartwright); Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, United Kingdom (Pierret, Minassian, Rentsch); Veterans Affairs Connecticut Healthcare System, US Department of Veterans Affairs, West Haven (Esserman, Tate, Justice, Rentsch); Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut (Tate, Fiellin, Justice, Rentsch); Department of Internal Medicine, David Geffen School of Medicine, University of California, Los Angeles (Goetz, Bhattacharya); Veterans Affairs Greater Los Angeles Health Care System, US Department of Veterans Affairs, Los Angeles, California (Goetz, Bhattacharya); Yale Program in Addiction Medicine, Yale School of Medicine, New Haven, Connecticut (Fiellin, Justice); Yale School of Public Health, New Haven, Connecticut (Fiellin, Justice); Division of Infectious Diseases, Department of Medicine and Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Lo Re).

Author Contributions: Ms Pierret and Dr Rentsch had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Cartwright, Pierret, Esserman, Tate, Fiellin, Justice, Lo Re, Rentsch.

Acquisition, analysis, or interpretation of data: Cartwright, Pierret, Minassian, Esserman, Tate, Goetz, Bhattacharya, Fiellin, Justice, Rentsch.

Drafting of the manuscript: Cartwright, Pierret, Lo Re, Rentsch.

Critical review of the manuscript for important intellectual content: Pierret, Minassian, Esserman, Tate, Goetz, Bhattacharya, Fiellin, Justice, Lo Re, Rentsch.

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SUPPLEMENT 1.

eTable 1. Covariate Distribution Between Those With and Without Primary Exposure Data

eTable 2. Covariate Distribution Between Those With and Without Outcome Data

SUPPLEMENT 2.

Data Sharing Statement