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A Randomized Controlled Trial of an Integrated Alcohol Reduction Intervention in Patients With Hepatitis C Infection

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BACKGROUND AND AIMS: Hepatitis C virus (HCV) and alcohol use are patient risk factors for accelerated fibrosis progression, yet few randomized controlled trials have tested clinic-based alcohol interventions.

APPROACH AND RESULTS: A total of 181 patients with HCV and qualifying alcohol screener scores at three liver center settings were randomly assigned to the following: (1) medical provider–delivered Screening, Brief Intervention, and Referral to Treatment (SBIRT), including motivational interviewing counseling and referral out for alcohol treatment (SBIRT-only), or (2) SBIRT plus 6 months of integrated colocated alcohol therapy (SBIRT + Alcohol Treatment). The timeline followback method was used to assess alcohol use at baseline and 3, 6, and 12 months. Coprimary outcomes were alcohol abstinence at 6 months and heavy drinking days between 6 and 12 months. Secondary outcomes included grams of alcohol consumed per week at 6 months. Mean therapy hours across 6 months were 8.8 for SBIRT-only and 10.1 for SBIRT + Alcohol Treatment participants. The proportion of participants exhibiting full alcohol abstinence increased from baseline to 3, 6, and 12 months in both treatment arms, but no significant differences were found between arms (baseline to 6 months, 7.1% to 20.5% for SBIRT-only; 4.2% to 23.3% for SBIRT + Alcohol Treatment; P = 0.70). Proportions of participants with any heavy drinking days decreased in both groups at 6 months but did not significantly differ between the SBIRT-only (87.5% to 26.7%) and SBIRT + Alcohol Treatment (85.7% to 42.1%) arms (P = 0.30). Although both arms reduced average grams of alcohol consumed per week from baseline to 6 and 12 months, between-treatment effects were not significant.

CONCLUSIONS: Patients with current or prior HCV infection will engage in alcohol treatment when encouraged by liver medical providers. Liver clinics should consider implementing provider-delivered SBIRT and tailored alcohol treatment referrals as part of the standard of care. (Hepatology 2020;71:1894-1909).

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; CI, confidence interval; DAA, direct acting antiviral; EMR, electronic medical record; GI, gastroenterology; HCV, hepatitis C virus; IRB, Institutional Review Board; SBIRT, Screening, Brief Intervention, and Referral to Treatment; UNC, University of North Carolina; VA, Veterans Affairs.

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Affecting an estimated 71 million people worldwide,[1] chronic hepatitis C virus (HCV) infection can lead to fibrosis, cirrhosis, and life-shortening complications of portal hypertension and hepatocellular carcinoma.[2] Alcohol use in the setting of HCV infection is associated with increased rates of fibrosis progression, liver-related mortality, and overall mortality.[3]

Compared with people without HCV, people with HCV infection living in the United States are estimated to be excessive drinkers 1.3 times more often.[4] Consequently, guidelines recommend abstinence from alcohol and clinical interventions to facilitate alcohol cessation in patients with active infection.[5,6] Even after HCV cure with therapy, patients with cirrhosis remain at higher risk for fibrosis progression and hepatocellular carcinoma; these patients are particularly cautioned against excessive alcohol use.[5,6]

Screening, Brief Intervention, and Referral to Treatment (SBIRT) is an evidence-based alcohol reduction practice. This 5- to 10-minute intervention includes an alcohol screener followed by dialogue with patients to elicit their thoughts about their alcohol use. SBIRT follows the principles of motivational interviewing, "a person-centered, goal-oriented method of communication for eliciting and strengthening intrinsic motivation for positive change" and has a strong evidence base.[7,8] Systematic reviews[9,10] and meta-analyses of randomized clinical trials[9] show the effectiveness of SBIRT in reducing hazardous drinking in patients presenting in primary care and other settings. Across 32 controlled studies, SBIRT was more effective than no counseling and often as effective as more extensive treatment.[10] The U.S. Preventative Services Task Force recommends behavioral counseling interventions for primary care patients with risky or harmful alcohol use.[11] Although SBIRT has been adopted to address risky alcohol use in various health care settings,[12], randomized controlled trials of SBIRT delivered in hepatology clinics have not been conducted.

The main treatment arm of this trial encompasses a colocated integrated care model addressing both HCV and alcohol use. Integrated care can be conceptualized on a continuum from services being coordinated (information shared across settings) to services being colocated (both services delivered at one location) to services being integrated (merged medical and behavioral health components in one treatment plan).[13] This trial builds on the experience of our pilot study with colocated and integrated HCV and alcohol treatment components, including individual and group therapy; participants experienced alcohol abstinence rates of 21% at baseline versus 44% at 6 months.[14]

For a comparison group, we choose SBIRT instead of the standard of care because indications in 2014 were that SBIRT would become widely implemented in liver clinics and thus become the standard of care. In addition, because SBIRT is less resource-intensive, we wanted to know if integrated HCV-alcohol treatment was superior to SBIRT or not. The primary aim

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of the current study was to compare, among patients with ongoing alcohol use with current or prior chronic HCV, the efficacy of provider-delivered SBIRT versus provider-delivered SBIRT plus colocated, integrated HCV- alcohol treatment in hepatology clinics. The two coprimary outcomes were alcohol abstinence and relapse.

Participants and Methods

DESIGN OVERVIEW

This unblinded, randomized, pragmatic trial enrolled patients with current or prior chronic HCV who drank alcohol. Participants were randomly assigned to either SBIRT-only (i.e., the SBIRT model that includes a patient-administered alcohol screener, medical provider–delivered brief intervention using motivational interviewing counseling, and referral to outside alcohol treatment) or SBIRT + Alcohol Treatment (i.e., SBIRT plus up to 6 months of integrated colocated individual and/or group therapy that provided motivational, cognitive, and behavioral strategies to reduce alcohol consumption).

Trial design details have been published[15] and registered at ClinicalTrials.gov (NCT02176980). The study received *a priori* approval by the Duke Medical Center Institutional Review Board (IRB), the University of North Carolina (UNC) Medical Center IRB, and the Durham Veterans Administration (VA) IRB and was also overseen by an independent data and safety monitoring board. Protocols conformed to the ethical guidelines of the 1975 Declaration of Helsinki. All participants provided written informed consent.

SETTING AND PARTICIPANTS

Participants were recruited between October 2014 and September 2017 from three diverse liver center settings. The Duke University Health System included several academically affiliated gastroenterology (GI), hepatology, and infectious diseases (ID) clinics based on the campus and in the community of Durham, North Carolina. The UNC Medical Center at Chapel Hill included academically affiliated public liver clinics based on the campus and an off-site clinic in Chapel Hill, North Carolina. Finally, the Durham VA Medical Center included the GI, liver, ID-GI, and HCV treatment management clinics.

Inclusion criteria required previously confirmed chronic HCV, irrespective of HCV treatment status (before, during, or after direct-acting antiviral [DAA] therapy); an Alcohol Use Disorders Identification Test (AUDIT)[16] score of ≥4 for women or ≥8 for men; at least one alcoholic drink in the past 60 days; age 18 years or older; ability to understand and speak English; not currently engaged in effective substance abuse treatment; willing to be involved in the study for 12 months; and able to access transportation to attend at least one individual therapy session. Patients with active psychosis, as determined by referring medical providers, were excluded.

RANDOMIZATION

After enrollment and baseline data collection, within each site, each participant was randomly assigned, through a randomization sequence generated by independent statisticians, to SBIRT-only or SBIRT + Alcohol Treatment on a 1:1 basis, stratified by AUDIT score (<20; ≥20). An AUDIT score of 20 or greater indicates likely alcohol dependence.[17] At the VA site only, randomization was also stratified by sex because fewer patients were women. The randomization schema was programmed into survey software; individual assignments were concealed from study staff until the intervention was assigned.

INTERVENTIONS

SBIRT

Provider-patient conversations about alcohol were already the standard of care at the three sites. For the study, we structured this conversation using SBIRT. HCV patients completed a self-reported AUDIT survey[16] on clinic visit and then saw medical providers (HCV specialists with medical, physician assistant, and nurse practitioner degrees) trained in SBIRT, who provided counseling based on patients' AUDIT answers. Medical providers were encouraged to conduct SBIRT during every visit for patients who indicated current alcohol use, whether or not they were enrolled in the study or had previously received

SBIRT. SBIRT was especially encouraged for scores (≥8 for men and ≥4 for women) that met the recommendation of the National Institute of Alcohol Abuse and Alcoholism guide.[18] Patients received SBIRT before being approached by their medical provider about study participation. This brief intervention aspect of SBIRT consisted of talking with patients for 5 to 10 minutes about their thoughts on their alcohol use using the principles of motivational interviewing.[7,8] Before the study, all medical providers attended a 2-hour educational session about the FRAMES steps: giving Feedback on how the patient's alcohol use may affect their current and future health; stating that it is the patient's Responsibility to change behavior; Advising the patient to stop drinking due to medical concerns; offering a Menu of options for cutting down on drinking; expressing Empathy; and reinforcing the patient's Self-efficacy to change.[19]

SBIRT-Only Group

Following SBIRT and study consent, participants randomly assigned to the SBIRT-only group were referred by study staff for alcohol treatment that was tailored to their individual needs based on insurance status, geographic location, and transportation resources. Example referral sites included university-affiliated outpatient programs, short-term or long-term residential detoxification/addiction treatment, and Alcoholics Anonymous or Narcotics Anonymous alone or in conjunction with other treatments.

SBIRT + Alcohol Treatment Group

Following SBIRT and study consent, participants randomly assigned to the integrated HCV-alcohol treatment were contacted by their site's addiction therapist. The integrated treatment differed slightly by site. At Duke, an addiction therapist was colocated in the clinics; at the VA, one addiction therapist from within the VA system was available; and at UNC, a therapist was located across the street from the UNC liver clinic. The addiction therapist and medical provider communicated through on-site contact and shared notes through the electronic medical record (EMR). To standardize implementation across sites and providers, a 24-session, manual-based treatment with content on HCV and alcohol use was developed. The addiction therapist offered up to a total of 36 individual and group therapy sessions spaced according to addiction therapist recommendations and participant preference. Therapists used principles of cognitive behavioral therapy,[20] motivational enhancement therapy,[8] and substance abuse treatment, applicable to both alcohol and substance use. The session content integrated HCV and alcohol issues into alcohol treatment, liver health, and personal domains, with didactic content and homework in the manual. Therapy began with three core sessions for increasing knowledge about HCV, alcohol, and liver health; enhancing motivation to decrease alcohol use; developing multiple skills for decreasing alcohol use; implementing alcohol reduction behaviors and meaningful activities; and improving health and well-being practices. Additional sessions consisted of content (e.g., sleep) jointly chosen for relevance by the participant and addiction therapist. Therapy emphasized alcohol reduction but also addressed substance use when present. All sessions were audio-recorded, and quality assurance was conducted on all initial sessions for each therapist, followed by a random subset of therapy sessions throughout the study.

Although in-person individual therapy was encouraged, because of the pragmatic nature of the study, telephone therapy was also offered and commonly used to increase retention. Group therapy was offered at the Duke site only. Psychiatric treatment was offered by a study psychiatrist to participants who requested a consultation or when recommended by the addiction therapist. The study psychiatrist provided services for the duration of their 6-month participation in the SBIRT + Alcohol Treatment arm in the liver clinic setting and documented encounters in the shared EMR. Tailored treatment recommendations consisted of prescribing medications for anxiety, depression, or alcohol relapse prevention, as appropriate.

We hypothesized that the SBIRT + Alcohol Treatment participants would do significantly better than SBIRT-only participants on all primary and secondary outcomes.

OUTCOMES AND FOLLOW-UP

Primary Outcomes

The coprimary study outcomes were as follows: (1) alcohol abstinence, defined as the proportion of participants with no alcohol consumed during the 30 days in

the sixth month after baseline, and (2) alcohol relapse, defined as the proportion of participants with any heavy drinking days (i.e., five or more drinks for men and four or more drinks for women) occurring in the 7 to 12 months after enrollment among participants with full abstinence at the sixth month.[21]

The timeline followback, a reliable and validated interview measure for alcohol use outcomes, was used to assess primary outcomes.[22] Compared with data from blood tests and reports from friends and family members, the self-reported timeline followback method has been shown to be more complete over time and to result in higher reported amounts of alcohol use.[23] In addition, to encourage accurate reporting, staff collected urine samples at in-person interviews and informed participants that the sample would be tested for alcohol and substance use. Study staff were trained on the timeline followback by one of the measure's original developers. Participants were asked to recall the type and amount of alcohol consumed per day for the past 90 or 180 days, assisted by identifying special dates on calendars and creating patterns of drinking. Staff recorded responses on paper and conducted double data entry for this primary-outcomes measure.

Secondary Outcomes

Using the timeline followback, our secondary alcohol outcomes included (1) grams of alcohol consumed per week at 6 months, (2) grams of alcohol consumed per week at 12 months, (3) the number of heavy drinking days in the 6-month period after enrollment, and (4) the number of alcohol-abstinent days at 12 months. Additionally, self-reported and urine-tested substance use data were analyzed.

Follow-Up

We conducted interviews at baseline and at 3, 6, and 12 months. For participants assigned to the SBIRT + Alcohol Treatment arm, 6 months marked the end of their treatment period.

DESCRIPTIVE MEASURES

Depressive symptoms were measured using the Patient Health Questionnaire-8, which consists of eight items assessing symptoms during the past 2 weeks.[24] Scores range from 0 to 24. Based on validation studies, depression was defined as a score ≥10.[25] Anxiety symptoms were measured using the Generalized Anxiety Disorder-7, which consists of seven items assessing symptoms during the past 2 weeks.[26] Scores range from 0 to 21 with anxiety defined as a score ≥8.[27]

We abstracted participant medical records for liver status. Participants were considered to have compensated cirrhosis if they had no history of complications of portal hypertension but were confirmed to have liver biopsy results consistent with cirrhosis, transient elastography scores greater than 12.5 kPa, or Fibrosis-4 scores greater than 3.25. Decompensated cirrhosis was defined as having a history of ascites, variceal hemorrhage, or hepatic encephalopathy.

STATISTICAL ANALYSIS

As reported, in our prestudy power analysis for dependent drinkers at 6 months we assumed a 39% abstinence rate for the SBIRT + Alcohol Treatment group and a 10% abstinence rate for the SBIRT-only group.[15] For those with harmful drinking, we assumed a 57% versus 25% abstinence rate for the respective groups. Between 6 and 12 months, we expected heavy drinking days in the SBIRT-only group to decrease by 29% and expected heavy drinking days in the SBIRT + Alcohol Treatment group to decrease by 42%. We sought 230 patients. The final sample size of 181 patients provided approximately 90% power to test the coprimary hypotheses.[15]

Analysis was intent-to-treat; that is, it included all participants as randomly assigned. *A priori* demographic and disease characteristics were compared between treatment intervention arms using the Student *t* test (continuous variables) or chi-squared test (categorical variables). Descriptive statistics were computed for all outcomes by treatment intervention arm, at each time point in the overall sample and within specific participant subgroups of interest (i.e., at baseline, heavy drinkers, nonheavy/light drinkers, participants with and without cirrhosis). Mean numbers of abstinent days and heavy drinking days were plotted over time by treatment arm.

To examine the two binary outcomes of (1) full abstinence from alcohol during month 6 and (2) any heavy drinking days during months 7 through 12 after

baseline, among the participants who fully abstained during month 6, we applied a robust Poisson regression model using a natural log link function and robust variance estimator. Model variables included the time point in the course of the study (baseline and 3, 6, and 12 months after baseline), baseline date, treatment intervention arm (SBIRT-only or SBIRT + Alcohol Treatment), baseline AUDIT score group (<20; ≥20), treatment site (Duke, UNC, or VA), and any demographic or disease characteristics that significantly differed between treatment arms despite the randomization. Population-averaged effects were specified for repeated observations. Using the parameter estimates from each model, differences between 1 month before baseline and month 6 after baseline for full abstinence, and between 3 months before baseline and months 7 to 12 after baseline for any heavy drinking days, were compared between treatment intervention arms.

Additionally, using the same model variables as in the Poisson regression, we used a generalized least squares regression model to examine continuous outcomes: (1) the number of heavy drinking days among the participants who fully abstained during month 6, (2) the grams of alcohol consumed, and (3) the number of heavy drinking days. In all models, population-averaged effects were specified for repeated observations. Using the parameter estimates from each model, differences in the number of heavy drinking days between 3 months before baseline and months 7 to 12 after baseline were compared between treatment arms; differences in grams of alcohol consumed and number of heavy drinking days between 1 month before baseline and month 6 after baseline were compared between treatment arms. For each regression model, only observations with complete data for the outcome and independent variables were included. Subgroup analyses were considered exploratory; we did not control for multiplicity in these analyses.

All statistical analyses were conducted in Stata version 15.1.[28]

Results

The study Consolidated Standards Of Reporting Trials flow diagram is provided in Fig. 1. Between October 2014 and September 2017, 181 patients were randomly assigned, with 95 being assigned to SBIRT + Alcohol Treatment and 86 being assigned to SBIRT-only. Interview data at 6 months were available for 86 of 95 (90.5%) SBIRT + Alcohol Treatment participants and 79 of 86 (91.8%) SBIRT-only participants. SBIRT-only participants experienced seven adverse events, and SBIRT + Alcohol Treatment participants also experienced seven adverse events, defined as hospitalization and death. No adverse events could be specifically traced to either SBIRT-only or SBIRT + Alcohol Treatment.

PRIMARY OUTCOMES

Tables 1 and 2 depict the baseline participant demographic and disease characteristics. At the Duke site, 109 participants were randomly assigned; at UNC, 53 were randomly assigned; and at the VA, 19 were randomly assigned. Factors were well balanced between treatment arms with the exception of race-ethnicity, which differed significantly across three levels ($P = 0.003$), so that the statistical models included it as a covariate.

Results for full abstinence during month 6 by intervention are shown in Table 3. The proportion of participants exhibiting full alcohol abstinence increased from baseline to months 3, 6, and 12 in both treatment arms. No significant differences were found between treatment arms for full abstinence in the sixth month versus baseline (7.1% to 20.5%, SBIRT-only baseline and month 6; 4.2% to 23.3%, SBIRT + Alcohol Treatment baseline and month 6; estimated coefficient for the 6-month intervention effect, 0.65 [95% confidence interval {CI}, −0.65, 1.96], $P = 0.33$).

Table 4 presents the proportion of participants with any heavy drinking days and the number of heavy drinking days per month, among participants who fully abstained in the sixth month (n = 37), by time period and treatment arm. No significant differences were found. Proportions of participants with any heavy drinking days decreased from 85.7% over 3 months before baseline to 42.1% over months 7 to 12 after baseline in the SBIRT + Alcohol Treatment arm and decreased from 87.5% to 26.7% in the SBIRT-only arm (estimated coefficient for the intervention effect [95% CI], 0.5 [−0.5, 1.4]; $P = 0.33$). The mean number of heavy drinking days decreased from 6.8 (SD = 7.0) to 1.1 (SD = 1.2) in the SBIRT + Alcohol Treatment arm and from 8.1 (SD = 10.9) to 1.3 (SD = 1.8) in the SBIRT-only arm ($P = 0.68$).

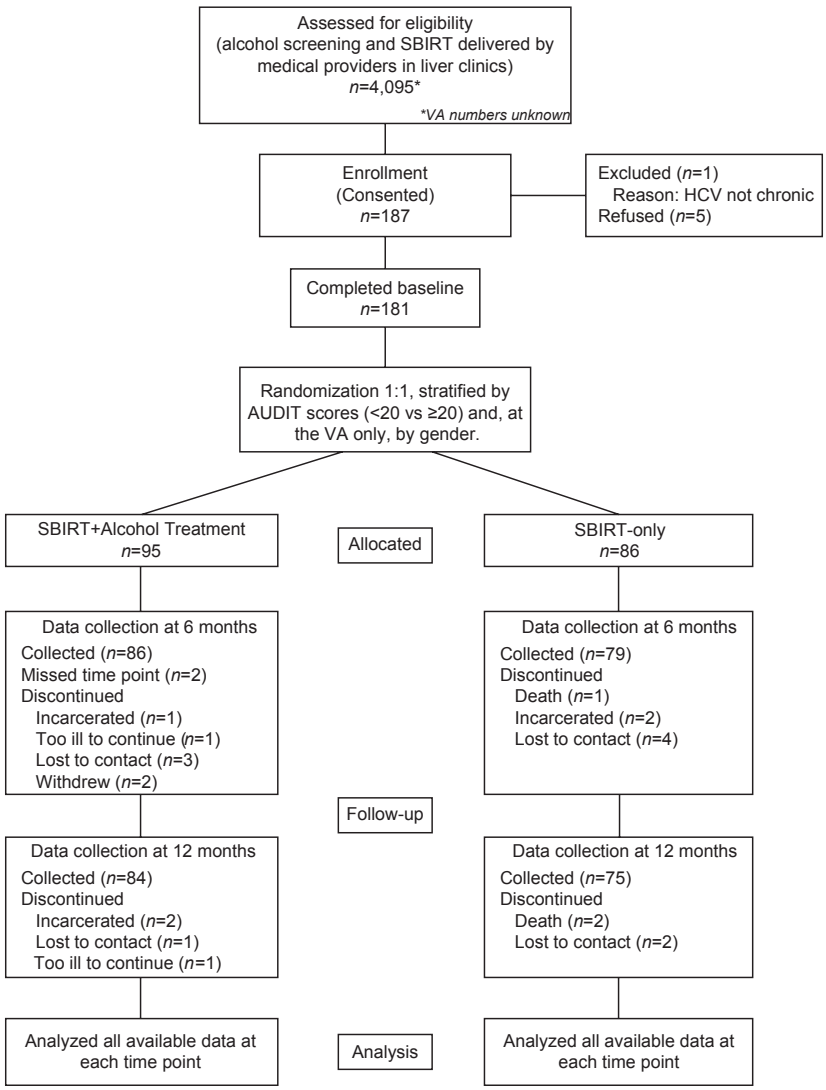

FIG. 1. Hep ART study participant flowchart. Abbreviation: Hep ART, Hepatitis C–Alcohol Reduction Treatment.

SUBGROUP ANALYSES OF PRIMARY OUTCOMES

No significant intervention effects were found for full abstinence among any of the participant subgroups analyzed: heavy alcohol users, light alcohol users, participants with cirrhosis, and participants without cirrhosis (Table 3).

SECONDARY OUTCOMES

Both arms exhibited significantly fewer grams of alcohol consumed per week from baseline to months 6 and 12. On average, SBIRT-only participants consumed 186 g/week (SD = 165) at baseline and 94 g/week (SD = 123) in month 6. SBIRT + Alcohol Treatment participants consumed 206 g/week (SD = 243) at baseline and 134 g/week (SD = 246) in month 6. Results were similar at 12 months. No significant between-treatment effects were observed (6-month intervention effect estimated coefficient, 22.1 g/week [95% CI, −32.7, 76.9], $P = 0.43$; 12-month intervention effect estimated coefficient, 27.7 g/week [95% CI: −25.7, 81.1], $P = 0.31$).

Figure 2 illustrates the mean numbers of heavy drinking days at baseline and in months 3, 6, and 12 for the full sample and among participant subgroups. Among all participants, both treatment

TABLE 1. Demographics of Participants (n = 181) at Baseline by Treatment Arm

Characteristics	SBIRT + Alcohol Treatment (n = 95) % (n) or M (SD)	SBIRT Only (n = 86) % (n) or M (SD)	Total % (n) or M (SD)
Age (years)	55.0 (9.6)	54.8 (9.5)	54.9 (9.5)
Sex			
Female	28.4% (27)	29.1% (25)	28.7% (52)
Male	71.6% (68)	70.9% (61)	71.3% (129)
Married/cohabitating	27.5% (25)	33.7% (28)	30.5% (53)
Race and ethnicity			
Black, non-Hispanic	70.5% (67)	46.5% (40)	59.1% (107)
White, non-Hispanic	24.2% (23)	38.4% (33)	30.9% (56)
Other (including biracial/multiracial)	5.3% (5)	15.1% (13)	9.9% (18)
Education			
High school or below	58.9% (56)	59.3% (51)	59.1% (107)
Some college or associate degree	30.5% (29)	32.6% (28)	31.5% (57)
Bachelor's degree or above	10.5% (10)	8.1% (7)	9.4% (17)
Employment			
Full-time	26.3% (25)	30.2% (26)	28.2% (51)
Part-time	13.7% (13)	9.3% (8)	11.6% (21)
Unemployed	14.7% (14)	23.3% (20)	18.8% (34)
Disabled	36.8% (35)	31.4% (27)	34.3% (62)
Other	8.4% (8)	5.8% (5)	7.2% (13)
Individual monthly income in dollars	1,665 (2,552)	1,476 (1,573)	1,575 (2,143)
Housing			
Own or rent apartment, room, or house	69.5% (66)	73.3% (63)	71.3% (129)
Someone else's apartment, room, or house	21.1% (20)	17.4% (15)	19.3% (35)
Shelter, street, or outdoors	6.3% (6)	4.7% (4)	5.5% (10)
Other	3.2% (3)	4.7% (4)	3.9% (7)
Health insurance status			
Private	32.6% (31)	30.2% (26)	31.5% (57)
Government: Medicare, Medicaid, etc.	45.3% (43)	41.9% (36)	43.6% (79)
Other public: VA, etc.	8.4% (8)	11.6% (10)	9.9% (18)
Local charity care plan	2.1% (2)	2.3% (2)	2.2% (4)
None	11.6% (11)	14.0% (12)	12.7% (23)
Study site			
Duke	57.9% (55)	62.8% (54)	60.2% (109)
UNC	28.4% (27)	30.2% (26)	29.3% (53)
VA	13.7% (13)	7.0% (6)	10.5% (19)

Data are missing for 7 participants for marital status and 1 participant for income in dollars; this latter participant reported that his monthly income fell between $500 and $1,000.

arms improved over time by similar amounts (1.8 heavy drinking days in the past month, 95% CI, −1.5, 5.1, $P = 0.29$ for 6-month intervention effect). Among participants with heavy alcohol use at baseline (binge drinking for 5 or more days during past 30 days; n = 99), the SBIRT-only participants improved more than the SBIRT + Alcohol Treatment participants from baseline to month 6 (4.2 heavy drinking days in the past month, 95% CI, −0.6, 9.0, $P = 0.09$ without adjustment for multiple comparisons).

Figure 3 illustrates numbers of days abstinent at baseline and in months 3, 6, and 12. Significant differences between arms were not found at any follow-up

TABLE 2. Disease Characteristics of Participants at Baseline

Characteristics	SBIRT + Alcohol Treatment (n = 95)	SBIRT Only (n = 86)	Total
Time since HCV diagnosis (years)	8.1 (8.7)	7.3 (7.8)	7.7 (8.3)
HCV treatment status			
Naïve (including before treatment)	80.0% (76)	80.2% (69)	80.1% (145)
Experienced	20.0% (19)	19.8% (17)	19.9% (36)
Presence of cirrhosis			
No cirrhosis	67.4% (64)	68.6% (59)	68.0% (123)
Compensated cirrhosis	31.6% (30)	29.1% (25)	30.4% (55)
Decompensated cirrhosis	1.1% (1)	2.3% (2)	1.7% (3)
AUDIT ≥ 20	17.9% (17)	16.3% (14)	17.1% (31)
Alcohol use disorder*			
None/mild	11.6% (11)	7.0% (6)	9.4% (17)
Moderate	20.0% (19)	24.4% (21)	22.1% (40)
Severe	68.4% (65)	68.6% (59)	68.5% (124)
Number of binge drinking days in the past month†			
5+ days, i.e., heavy alcohol use	55.8% (53)	55.3% (47)	55.6% (100)
0-4 days, i.e., lighter alcohol use	44.2% (42)	44.7% (38)	44.4% (80)
Any illegal drug use in past 30 days			
Marijuana	52.6% (50)	42.4% (36)	47.8% (86)
Other drugs‡	34.7% (33)	24.4% (21)	29.8% (54)
Presence of HIV	8.4% (8)	3.5% (3)	6.1% (11)
Depression symptoms			
Depression symptoms severity mean score (PHQ8)	8.0 (5.4)	7.5 (5.4)	7.8 (5.4)
Presence of depression (PHQ8 ≥ 10)	36.8% (35)	37.2% (32)	37.0% (67)
Anxiety symptoms			
Anxiety symptoms severity mean score (GAD7)	7.3 (5.3)	7.7 (6.1)	7.5 (5.7)
Presence of anxiety (GAD7 ≥ 10)	30.9% (29)	38.4% (33)	34.4% (62)
Presence of anxiety and/or depression	42.6% (40)	47.7% (41)	45.0% (81)
Transport time to and from clinic (minutes)	81 (66)	86 (74)	84 (70)

Data were missing in 3 participants for (self-reported) time since HCV diagnosis, in 1 participant for binge drinking, in 1 participant for marijuana use, in 1 participant for anxiety, and in 1 participant for transport time to and from the clinic. HCV diagnosis year was missing for 10 participants in their EMRs; therefore, their self-reported year of diagnosis was used for analysis.
*Alcohol use disorder was not assessed clinically but was based on responses to structured research interview questions.
†Assessment of binge drinking was based on structured timeline followback research interview questions. A binge drinking day equaled five or more standard drinks for men and four or more standard drinks for women.
‡Other drugs include cocaine, heroin, nonprescription methadone, and opioids and sedatives in amounts greater than prescribed.
Abbreviations: GAD7, Generalized Anxiety Disorder 7-Item Scale; HIV, human immunodeficiency virus; PHQ8, Patient Health Questionnaire 8-Item Depression Scale.

time point versus baseline, for the full sample or among subgroups.

Table 5 depicts alcohol therapy and service use for both treatment arms. SBIRT-only participants reported a mean of 8.8 (SD, 31.5) alcohol therapy hours over 6 months after baseline, compared with a mean of 10.1 (SD, 14.9) hours of study-provided clinic-based alcohol and nonstudy alcohol therapies for SBIRT + Alcohol Treatment participants.

Supporting Table S1 depicts urine-tested substance use outcomes. No significant differences were found over time or between treatment arms.

Discussion

SBIRT and other evidence-based alcohol reduction interventions have been developed and disseminated in various health care settings to address harmful alcohol use. However, randomized controlled trials of alcohol interventions delivered in hepatology clinics with patients at risk for liver disease progression have not been conducted.[12] Although we hypothesized that participants in the more intensive 6-month SBIRT plus integrated alcohol treatment condition would have better alcohol outcomes than patients who received

TABLE 3. Percentages of Participants With Full Abstinence for 30 Days by Intervention

% (n/N)	30 Days Before BL	30 Days Comprising the Third Month After BL	30 Days Comprising the Sixth Month After BL (Primary Outcome)	30 Days Comprising the Twelfth Month After BL
The entire sample (n = 181)	n = 180	n = 164	n = 164	n = 154
SBIRT only	7.1% (6/85)	19.0% (15/79)	20.5% (16/78)	26.4% (19/72)
SBIRT + Alcohol Treatment	4.2% (4/95)	21.2% (18/85)	23.3% (20/86)	25.6% (21/82)
6-month intervention effect, coef (95% CI); *P*			0.65 (–0.65, 1.96); *P* = 0.327	
Males (n = 129)	n = 128	n = 116	n = 116	n = 106
SBIRT only	6.7% (4/60)	19.3% (11/57)	19.3% (11/57)	27.5% (14/51)
SBIRT + Alcohol Treatment	4.4% (3/68)	18.6% (11/59)	16.9% (10/59)	25.5% (14/55)
6-month intervention effect, coef (95% CI); *P*			0.33 (–1.24, 1.89); *P* = 0.680	
Females (n = 52)	n = 52	n = 48	n = 48	n = 48
SBIRT only	8.0% (2/25)	18.2% (4/22)	23.8% (5/21)	23.8% (5/21)
SBIRT + Alcohol Treatment	3.7% (1/27)	26.9% (7/26)	37.0% (10/27)	25.9% (7/27)
6-month intervention effect, coef (95% CI); *P*			1.30 (–1.18, 3.78); *P* = 0.305	
Black, single-racial, non-Hispanic (n = 107)	n = 107	n = 99	n = 101	n = 97
SBIRT only	7.5% (3/40)	13.2% (5/38)	21.1% (8/38)	25.0% (9/36)
SBIRT + Alcohol Treatment	4.5% (3/67)	18.0% (11/61)	25.4% (16/63)	26.2% (16/61)
6-month intervention effect, coef (95% CI); *P*			0.73 (–0.87, 2.33); *P* = 0.372	
Other races (including white, biracial, and multiracial) and/or Hispanic (n = 74)	n = 73	n = 65	n = 63	n = 57
SBIRT only	6.7% (3/45)	24.4% (10/41)	20.0% (8/40)	27.8% (10/36)
SBIRT + Alcohol Treatment	3.6% (1/28)	29.2% (7/24)	17.4% (4/23)	23.8% (5/21)
6-month intervention effect, coef (95% CI); *P*			0.50 (–2.08, 3.09); *P* = 0.702	
Heavy alcohol users at BL (n = 100)	n = 100	n = 92	n = 94	n = 87
SBIRT only	0.0% (0/47)	13.3% (6/45)	10.9% (5/46)	21.4% (9/42)
SBIRT + Alcohol Treatment	0.0% (0/53)	12.8% (6/47)	14.6% (7/48)	11.1% (5/45)
Intervention effect model does not converge			0.00 (0.00, 0.00); *P* < 0.001	
Lighter alcohol users at BL (n = 80)	n = 80	n = 71	n = 69	n = 66
SBIRT only	15.8% (6/38)	27.3% (9/33)	35.5% (11/31)	34.5% (10/29)
SBIRT + Alcohol Treatment	9.5% (4/42)	31.6% (12/38)	34.2% (13/38)	43.2% (16/37)
6-month intervention effect, coef (95% CI); *P*			0.49 (–0.83, 1.82); *P* = 0.464	
Severe alcohol use disorder at BL (n = 124)	n = 123	n = 111	n = 110	n = 106
SBIRT only	6.9% (4/58)	14.8% (8/54)	19.2% (10/52)	26.5% (13/49)
SBIRT + Alcohol Treatment	4.6% (3/65)	21.1% (12/57)	15.5% (9/58)	14.0% (8/57)
6-month intervention effect, coef (95% CI); *P*			0.22 (–1.35, 1.79); *P* = 0.780	
Moderate, mild, or no alcohol user disorder at BL (n = 57)	n = 57	n = 53	n = 54	n = 48

TABLE 3. *Continued*

% (n/N)	30 Days Before BL	30 Days Comprising the Third Month After BL	30 Days Comprising the Sixth Month After BL (Primary Outcome)	30 Days Comprising the Twelfth Month After BL
SBIRT only	7.4% (2/27)	28.0% (7/25)	23.1% (6/26)	26.1% (6/23)
SBIRT + Alcohol Treatment	3.3% (1/30)	21.4% (6/28)	39.3% (11/28)	52.0% (13/25)
6-month intervention effect, coef (95% CI); *P*			1.07 (–1.44, 3.59); *P* = 0.402	
Presence of cirrhosis at BL (n = 58)	n = 57	n = 54	n = 53	n = 49
SBIRT only	7.7% (2/26)	16.0% (4/25)	16.7% (4/24)	31.8% (7/22)
SBIRT + Alcohol Treatment	6.5% (2/31)	20.7% (6/29)	24.1% (7/29)	25.9% (7/27)
6-month intervention effect, coef (95% CI); *P*			0.47 (–1.53, 2.46); *P* = 0.647	
No cirrhosis present at BL (n = 123)	n = 123	n = 110	n = 111	n = 105
SBIRT only	6.8% (4/59)	20.4% (11/54)	22.2% (12/54)	24.0% (12/50)
SBIRT + Alcohol Treatment	3.1% (2/64)	21.4% (12/56)	22.8% (13/57)	25.5% (14/55)
6-month intervention effect, coef (95% CI); *P*			0.84 (–0.95, 2.62); *P* = 0.357	

Abbreviations: BL, baseline; coef, coefficient.

TABLE 4. Drinking Relapse Among Participants Who Fully Abstained During the 30 Days Comprising the Sixth Month After Baseline

Characteristics	3 Months Before BL	Months 7-12 After BL
Any heavy drinking days, % (n/N)		
SBIRT only (n = 16)	87.5% (14/16)	26.7% (4/15)
SBIRT + alcohol treatment (n = 21)	85.7% (18/21)	42.1% (8/19)
Intervention effect, coef (95% CI); *p*	0.47 (–0.48, 1.43); *P* = 0.328	
Number of heavy drinking days per month, mean (SD), median		
SBIRT only (n = 16)	8.1 (10.9), 3.7	1.3 (1.8), 0.6
SBIRT + alcohol treatment (n = 21)	6.8 (7.0), 3.7	1.1 (1.2), 0.6
Intervention effect, coef (95% CI); *P*	1.1 (–4.0, 6.1); *P* = 0.681	

Heavy drinking day = five or more standard drinks for men or four or more standard drinks for women on a day.
Abbreviations: BL, baseline; coef, coefficient.

only provider-delivered SBIRT, this randomized controlled trial showed that patients randomly assigned to either intervention had improved alcohol outcomes with no significant between-group differences.

Although 44% of HCV-infected participants achieved alcohol abstinence at 6 months in our pilot study[14] and 36% percent achieved alcohol abstinence in an integrated care study by Dieperink et al.,[29] only 23% achieved this in the SBIRT + Alcohol Treatment arm. Moreover, we had anticipated that 10% of SBIRT-only participants would achieve alcohol abstinence at 6 months[15] but observed that 21% were abstinent at 6 months. For reasons discussed below, the SBIRT plus intensive alcohol treatment arm underperformed, and the provider-delivered SBIRT-only arm outperformed expectations.

Contributing to the lack of between-group differences may have been the absence of a true "treatment-as-usual" group. Participants in the SBIRT-only arm all received medical provider–delivered brief alcohol counseling, and some acted on alcohol treatment referrals. Based on other studies,[30] we had not expected many SBIRT-only participants to follow through on alcohol treatment referrals, yet 12% reported participating in four or more, and 6% reported participating in one to three, external alcohol counseling sessions. In contrast, 60% of SBIRT + Alcohol Treatment participants reported engaging in four or more alcohol treatment sessions (see Table 6), making the similar outcomes between arms all the more

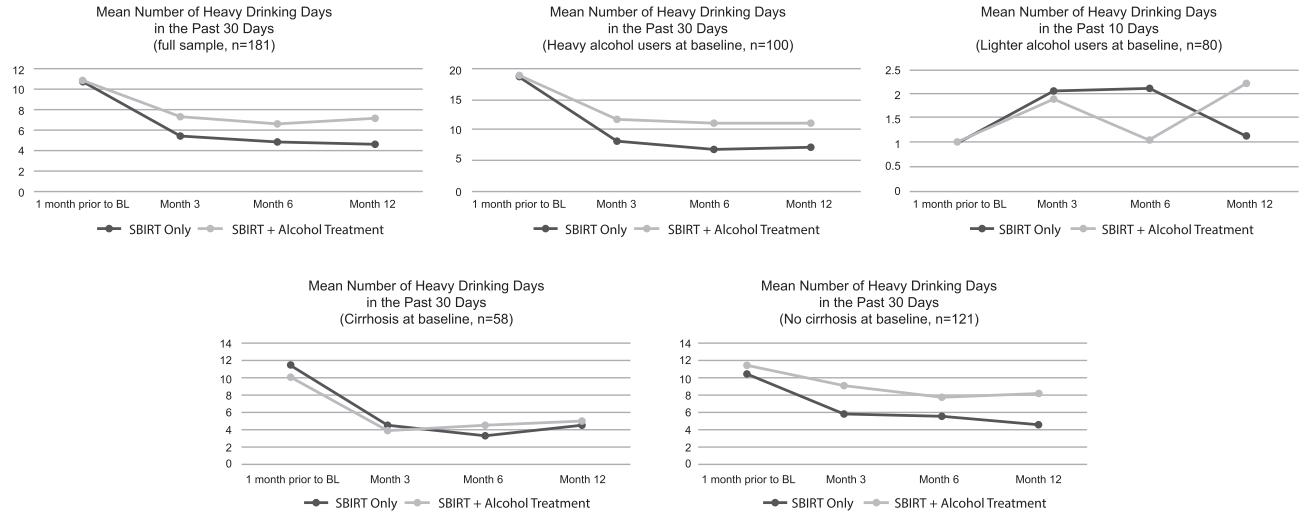

FIG. 2. Number of heavy drinking days.

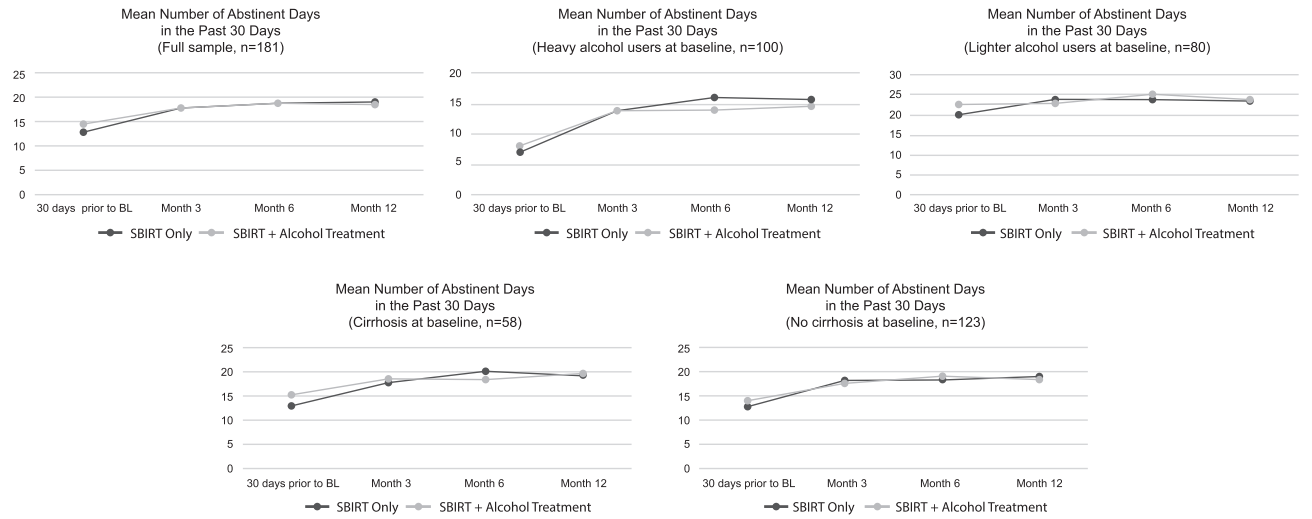

FIG. 3. Number of alcohol abstinence days.

noteworthy. Follow-through on referrals by SBIRT-only participants may have been due to the involvement of research staff in making alcohol treatment referrals, or it may have been that SBIRT-trained medical providers beginning their patient encounters with an emphasis on alcohol reduction, combined with the patients having HCV, effectively motivated follow-through. In addition, it is possible that both groups benefited from the study's data collection components, which included a detailed assessment of alcohol use and drinking motives at baseline as well as at two time points before the final study endpoint. The authors of previous studies have opined that data collection procedures and frequent interactions with research staff can have inadvertent positive effects on study outcomes.[31]

This study's findings suggest implications for integrated alcohol care in liver clinics. Few integrated HCV-alcohol treatment models have been tested in patients with liver disease.[32] A systematic literature review found only five behavioral studies targeting alcohol reduction among patients with HCV.[33] Published HCV-alcohol integrated treatments have mainly focused on people who inject drugs recruited

TABLE 5. Study Alcohol Treatment Offered to Participants in the SBIRT + Alcohol Treatment Arm and Nonstudy Alcohol Treatment Used by the 181 Study Participants Between Baseline and 6 Months Follow-Up

Characteristics	# Sessions, Mean (SD), Median	# Total Hours, Mean (SD), Median	Participation in 4+ Sessions, % (n/N)	Participation in 1-3 Sessions, % (n/N)	Nonparticipation, % (n/N)
Hep ART study–provided alcohol treatment, individual and group sessions colocated in liver clinics					
SBIRT + Alcohol Treatment arm	7.2 (7.2), 5	7.2 (9.0), 4	55.8% (53/95)	32.6% (31/95)	11.6% (11/95)
Individual sessions	5.8 (5.2), 4	5.0 (4.8), 3.6	54.7% (52/95)	33.7% (32/95)	11.6% (11/95)
Group sessions	1.4 (3.8), 0	2.2 (6.1), 0	13.7% (13/95)	3.2% (3/95)	83.2% (79/95)
Non–Hep ART study alcohol treatment, individual and group sessions*					
SBIRT-only arm	2.8 (8.5), 0	8.8 (31.5), 0	12.2% (10/82)	6.1% (5/82)	81.7% (67/82)
SBIRT + Alcohol Treatment arm	1.3 (5.6), 0	2.7 (11.3), 0	6.7% (6/90)	3.3% (3/90)	90.0% (81/90)
Hep ART and non–Hep ART alcohol treatment*					
SBIRT-only arm	2.8 (8.5), 0	8.8 (31.5), 0	12.2% (10/82)	6.1% (5/82)	81.7% (67/82)
SBIRT + Alcohol Treatment arm	8.7 (9.8), 6.5	10.1 (14.9), 4.7	60.0% (54/90)	28.9% (26/90)	11.1% (10/90)

*Excluding sessions required for receiving medication that keeps participant away from heroin.
Abbreviation: Hep ART, Hepatitis C–Alcohol Reduction Treatment.

TABLE 6. Alcohol Services Other Than Alcohol Treatment Used by the 181 Study Participants Between Baseline and 6 Months Follow-Up

AA, NA, and Support Groups	Any Participation, % (n/N)	# Sessions Among the Participants, Mean (SD), Median
SBIRT only	22.0% (18/82)	27.4 (28.8), 17
SBIRT + Alcohol Treatment	23.1% (21/91)	10.6 (11.2), 6
Residential alcohol treatment	**Any participation, % (n/N)**	**# days among the participants, mean (SD), median**
SBIRT only	2.5% (2/81)	16.5 (16.3), 16.5
SBIRT + Alcohol Treatment	1.1% (1/90)	7.0 (0.0), 7
Alcohol detox treatment	**Any participation, % (n/N)**	**# days among the participants, mean (SD), median**
SBIRT only	7.4% (6/81)	4.2 (1.7), 4
SBIRT + Alcohol Treatment	5.6% (5/90)	6.6 (3.8), 7

Abbreviations: AA, alcoholics anonymous; NA, narcotics anonymous.

from needle exchange settings[34] or on patients with severe alcohol use disorders.[35] Two studies tested integrated care for patients with less severe alcohol use. Although limited by nonrandomized study designs, the findings indicated increased initiation of HCV antiviral therapy and reduced or abstinent alcohol consumption.[29,36] In a retrospective study, in patients who drank heavily while experiencing chronic HCV and undergoing HCV treatment, SBIRT plus additional 30-minute cognitive behavioral sessions (average, 4.5) with a colocated psychiatric nurse specialist was associated with significant drinking reductions and alcohol abstinence.[29] Another study that tested four sessions of motivational enhancement therapy delivered by psychologists to patients with HCV and alcohol use disorder found more days of alcohol abstinence in the treatment group.[37] These studies and our pilot study were conducted before the current era of widely available DAA treatments for HCV.

Before the DAA era, alcohol abstinence was recommended during HCV treatment with interferon regimens because of concerns about lower response rates and increased adverse events with ongoing alcohol use. In contrast, DAA regimens are well-tolerated with high response rates. During our earlier pilot, many payers restricted DAAs to those with no alcohol use, which may have motivated higher abstinence.[38] Although alcohol reduction with a goal of abstinence is still recommended to patients with coexisting HCV infection, alcohol use is not considered a contraindication to antiviral therapy. As a result, patients in recent years may be less motivated to decrease their alcohol use. The current study is important in that it shows that patients with current or prior HCV infection will engage in alcohol treatment when encouraged by liver medical providers, even in the DAA era. Our trial demonstrates the value of integrating alcohol use disorder interventions into hepatitis care and could serve as a model for incorporating other alcohol treatments,

including psychosocial, behavioral, and pharmacological treatments, to provide patient-centered holistic approaches to these comorbid diseases. The current study's findings highlight that liver clinic medical providers' provision of alcohol screening and discussion is feasible and acceptable to patients; patient-provider discussions about alcohol remain relevant to liver health even after HCV cure.

The current study provides insights about integrated care in subspecialty clinics. First, at two university-based liver clinics, patients were willing to enroll and engage in clinic-based alcohol treatment. Addiction therapists at all clinics offered telephone therapy, which turned out to be the predominant delivery mode at the public university–based liver clinic. At the VA site, it was more difficult to enroll patients for several possible reasons, including ongoing engagement in alcohol or mental health treatment conveniently offered at the same VA location (although not in the liver clinics specifically). In addition, a larger number of patients with HCV in VA care had received DAA therapy by the time we started recruiting in the VA in 2016, leading to fewer patients with HCV attending the clinic. For all sites, it was difficult to recruit 8 patients simultaneously to deliver group therapy. Virtual visit options for group therapy should be explored in future research.

This study's findings further suggest important implications for implementation of SBIRT as part of routine care in liver clinics. Recent recommendations support the use of SBIRT as a model for integrated care of patients with chronic liver disease and substance use and mental health problems.[39] Large research projects with substantial funding have effectively implemented SBIRT in medical practices, but the evidence that SBIRT can be implemented in clinics with little external funding remains limited.[40]

The current design and findings suggest that medical provider–delivered SBIRT in liver clinics may be feasible and effective, even in liver clinics with little external funding to provide SBIRT. Specifically, we organized a 2-hour, annual training for the medical providers in each liver clinic and engaged an SBIRT trainer to provide didactic content and facilitate role-plays. We used National Institute of Alcohol Abuse and Alcoholism–developed handouts for SBIRT that were shared with clinic providers. Beyond training, some clinic resources were necessary to sustain SBIRT. These included the receptionist handing out the AUDIT screener to patients and medical providers engaging in brief alcohol counseling with patients. The referral out for alcohol treatment required 10 to 20 minutes. Although our study team conducted these referrals, in the absence of research funding and staff, someone in the liver clinic would need to take responsibility for arranging for referral for specialty addiction care. In a word of caution, for patients with alcohol-induced liver disease, more intensive treatments than those studied here may be needed.

This study has several limitations. The study lacked a treatment-as-usual control group and substituted an SBIRT-based enhanced-treatment-as-usual intervention. Because both treatment groups improved, and in the absence of a pure treatment-as-usual control group, it is not possible to tease apart the effects of medical provider attention during study referral or the detailed alcohol assessments during data collection. Similarly, data collection or research staff attention may have served as an alcohol intervention.

In addition, by design we enrolled patients with various alcohol use levels because of its deleterious effect on hepatitis C progression. At baseline, over 30% had less than a severe alcohol use disorder. If a higher percentage had severe alcohol use disorder, it is possible that we would have seen greater differences between treatment arms, given that SBIRT does not work as well for people with more severe alcohol use.[41] Furthermore, the integrated care intervention was not fully implemented as intended. Only one site ever provided group alcohol therapy, which can be a highly effective treatment.[42] Also, because of limited space in the liver clinic, one site required participants to cross a street to a nearby but less familiar setting, which may have been perceived as being similar to a referral. Furthermore, SBIRT-only participants participated in a similar number of alcohol treatment hours as SBIRT + Alcohol Treatment participants. Researchers of future studies of integrated care in liver clinics may want to introduce accountability or contingency management techniques to improve session compliance. Finally, few VA patients enrolled (n = 19). Recruitment from three diverse liver clinics enhances generalizability, which is nevertheless limited by our geographic location in central North Carolina.

In conclusion, the results of this randomized trial indicate that alcohol use outcomes can be improved in liver clinic patients with current or prior HCV

when receiving either provider-delivered SBIRT or 6 months of integrated HCV-alcohol counseling, combined with study enrollment and detailed alcohol use data collection. Future research can better determine the benefits of SBIRT provision to patients with HCV by testing it against a no-enhancement standard-of-care group. Given the moderate degree of resources required to implement SBIRT, paired with the potential harm of alcohol use for patients with current and prior HCV, liver clinics should consider implementing provider-delivered SBIRT and alcohol-treatment-referral practices as part of the standard of care.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.31058/suppinfo.