Medication Non-adherence in a Prospective, Multi-center Cohort Treated with Hepatitis C Direct-Acting Antivirals

Marina Serper, MD¹, Donna M. Evon, PhD², Paul W. Stewart, PhD³, Anna S. Lok, MD⁴, Jipcy Amador, MS³, Bryce B. Reeve, PhD⁵, Carol E. Golin, MD⁶, Michael W. Fried, MD², K. Rajender Reddy, MD¹, Richard K. Sterling, MD⁷, Souvik Sarkar, MD⁸, Adrian M. Di Bisceglie, MD⁹, Joseph K. Lim, MD¹⁰, David R. Nelson, MD¹¹, and Nancy Reau, MD¹²

¹Division of Gastroenterology and Hepatology, Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA; ²Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina, Chapel Hill, NC, USA; ³Department of Biostatistics, University of North Carolina, Chapel Hill, NC, USA; ⁴Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA; ⁵Department of Population Health Sciences, Duke University, Durham, NC, USA; ⁶Division of General Medicine and Clinical Epidemiology, Department of Medicine, Department of Health Behaviors, University of North Carolina, Chapel Hill, NC, USA; ⁷Division of Gastroenterology, Hepatology & Nutrition, Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA, USA; ⁸Division of Gastroenterology and Hepatology, Department of Medicine, University of California at Davis, Davis, CA, USA; ⁹Division of Gastroenterology and Hepatology, Department of Internal Medicine, Saint Louis University, St. Louis, MO, USA; ¹⁰Yale Liver Center and Section of Digestive Diseases, Yale University, New Haven, CT, USA; ¹¹Division of Gastroenterology, Hepatology & Nutrition, Department of Medicine, University of Florida, Gainesville, FL, USA; ¹²Department of Internal Medicine, Section of Hepatology, Rush University, Chicago, IL, USA.

BACKGROUND: The prevalence and risk factors for non-adherence to direct-acting antivirals (DAAs) for chronic hepatitis C virus (HCV) in clinical practice settings are under-studied.

OBJECTIVES: (1) To quantify DAA non-adherence in the total cohort and among subgroups with and without mental health conditions, alcohol use, and substance use, and (2) to investigate patient- and treatment-level risk factor non-adherence.

DESIGN: Prospective, observational cohort study.

PARTICIPANTS: A total of 1562 patients receiving DAAs between January 2016 and October 2017 at 11 US medical centers including academic and community practices.

MAIN MEASURES: Self-reported medication non-adherence, defined as any missed doses in the past 7 days, surveyed early (T2: at 4 ± 2 weeks) and late in treatment (T3: 2–3 weeks prior to end of treatment). Non-adherence to post-treatment follow-up visits was defined as absence of lab results after DAA therapy completion.

KEY RESULTS: Of 1447 patients, 162 (11%) reported non-adherence at T2 or T3. Medical records indicated 262 (17%) of the 1562 participants had not returned for post-treatment visits. At baseline, 37% of patients reported mental health conditions, 15% reported alcohol use, and 23% reported using substances in the previous year. Baseline characteristics associated with DAA non-adherence included alcohol use (OR 1.96), younger age (< 35 years vs. > 55 years: OR 3.40), non-white race (OR >

2.26), and DAA treatment cohort, but not substance use or mental health condition. Non-adherence to follow-up exhibited association with younger age and a higher baseline overall symptom burden. Among 1287 patients with evaluable sustained virologic response (SVR) data, 53 patients (4%) did not achieve SVR. The bivariate correlation between adherence and SVR was negligible ($r = 0.01$).

CONCLUSIONS: DAA non-adherence was low and SVR rates were high. Mental health conditions, substance use, and alcohol use should not disqualify patients from DAA therapy. Patients with alcohol use disorder before DAA therapy initiation may benefit from targeted on-treatment support.

KEY WORDS: adherence; liver disease; alcohol use; substance use.

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INTRODUCTION

Medication non-adherence to hepatitis C (HCV) therapy was investigated during pegylated interferon regimens and associated with side effects and lower sustained virologic response (SVR).¹ In the era of all-oral direct-acting antivirals (DAAs), regimens have been simplified and side effects are less severe, thereby making universal access to HCV treatment and viral elimination a realistic goal.^{2,3} Nonetheless, third-party payers vary with regard to approving DAA therapy for disenfranchised populations^{4,5} and most state Medicaid programs continue to have alcohol and/or illicit substance abstinence requirements prior to HCV therapy approval.⁶

The literature on DAA adherence among people who use substances mostly comes from DAA registration trials^{7–9}; however, even in the largest pooled analysis, patients with significant

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drug abuse (except cannabinoids) in the prior 12 months were excluded.⁸ Real-world adherence data are currently emerging among DAA-treated patients engaged in opioid substitution treatment (OST) and have shown acceptable SVRs.^{10–12} Despite these data, considerable gaps exist regarding the prevalence of DAA non-adherence in patients treated in real-world settings as well as the impact of mental health and substance use on adherence.¹¹ Filling these gaps is particularly important as providers and payers may have concerns about psychosocial risk factors for non-adherence and ability to achieve SVR.¹³

The Patient-Reported Outcomes Project (PROP-UP) is a large prospective, multi-center study of patient-reported outcomes in a real-world HCV-infected US cohort treated with DAAs. The specific aims of the current analysis were to (1) quantify the prevalence of DAA non-adherence in the total cohort and in the subgroups with and without mental health conditions, alcohol use, and substance use at baseline; (2) understand the most common patient-reported reasons for non-adherence; (3) investigate the associations between patient- and treatment-level factors with medication non-adherence; and (4) explore the relationship between patient factors and non-adherence to clinical follow-up.

METHODS

Study Design

A total of 1601 patients were enrolled across 11 subspecialty gastroenterology/hepatology practices, 9 academic and 2 community-based. Full protocol details have previously been described.¹⁴ From January 2016 to October 2017, patients prescribed any of five DAA regimens with and without ribavirin (RBV) were eligible. Data were collected directly from participants before treatment at baseline (T1), around treatment week 4 $\pm$ 2 weeks (T2), late in treatment (2–3 weeks prior to end of treatment, T3), and 12 weeks post-treatment (T4). At each time point, participants responded to several patient-reported outcome (PRO) instruments and medication adherence surveys at T2 and T3. Sites obtained local Institutional Review Board (IRB) approval and all participants provided informed consent.

Participants

Subgroups with Mental Health Conditions, Alcohol Use, and Substance Use. Participants responded to questions related to psychiatric history and substance and alcohol use. Participants were classified as having mental health conditions if they reported taking medications for psychiatric conditions at enrollment or had ever been psychiatrically hospitalized. Substance and alcohol use questions were adapted from the validated Substance Abuse and Mental Illness Symptoms Screener (SAMISS) and included frequency and amount of alcohol consumption and use of non-prescription street drugs and misuse of prescription medication.^{15, 16} Current alcohol use was defined as ≥ 5 on the SAMISS.^{17, 18} Substance use

was classified as any self-reported use of prescription drugs to get high or use of non-prescription street drugs in the last year.

Study Outcomes

Voils' Medication Adherence Survey. The Voils' Medication Adherence Survey (VMAS) is an adherence questionnaire shown to be valid and reliable for HCV. It includes 3 self-reported items ("I missed my medicine"; "I skipped a dose of my medicine"; "I did not take a dose of my medicine") that measure the extent of adherence in the past 7 days using a 5-point Likert scale (from "none of the time" to "every time").^{19, 20} Patients were categorized as adherent if answering "none of the time" to all 3 items; otherwise, they were categorized as non-adherent. The primary outcome was combined non-adherence at T2 and/or T3. The VMAS also assessed *reasons* for non-adherence.

Non-adherence to Clinical Follow-up. This secondary non-adherence measure was defined as absence of lab results, including HCV RNA, ≥ 10 weeks after DAA therapy completion, and after multiple attempts by clinicians to schedule follow-up visits.

Sustained Virologic Response. Sustained virologic response (SVR) status was ascertained from patients' electronic health records (EHR) and was defined as an undetectable HCV RNA at ≥ 10 weeks after treatment completion.

Covariates

Patient Characteristics and Clinical Data. Self-reported demographics, education, employment, and income were obtained at baseline. Low socioeconomic status (SES) was defined as having $\leq$ high school education and self-reported annual income $\leq$ \$40,000. Clinical data were extracted from EHRs at sites. Cirrhosis was ascertained using imaging, laboratory data, and expert clinician adjudication.

Overall Symptom Burden. A comprehensive list of 32 symptoms common to many health conditions was assessed using the Memorial Symptom Assessment Scale (MSAS) at baseline.^{21, 22} A total MSAS (TMSAS) score was calculated from the average of all 32 symptoms and ranged from 0 (absence of symptom) to 4 (severe, frequent and distressing).^{21, 23}

On-treatment Side Effects. Three common DAA side effects and potential risk factors for non-adherence (fatigue, nausea, headache) were measured as change from baseline to treatment week 4 window using the Patient-Reported Outcomes Measurement Information System® (PROMIS®) instruments and the Headache Impact Test (HIT-6).^{23–26}

Statistical Analysis

All statistical estimates were computed along with corresponding 95% confidence intervals to indicate precision. Overall and subgroup-specific estimation of rates of non-adherence and SVR relied on tabulation of percentages of patients. For aims 3 and 4, multivariable logistic regression was used for both confirmatory analyses via logistic regression models specified a priori and in the investigation of potential associations and risk factors. For a priori models, logistic methods included use of Firth's penalized likelihood approach. Covariate adjustment was used to attenuate biases due to potentially confounding factors. For the primary model of predictors of medication non-adherence, selected variables were age, sex, race, alcohol use, substance use, mental health condition, number of medical comorbidities, and DAA treatment cohort. This a priori selection was based on subgroups of primary interest (alcohol, substance use, mental health), age, race and sex, and interest in DAA treatment cohorts and number of baseline health comorbidities. For investigation of non-adherence risk factors, we used a cross-validation strategy based on data splitting and randomization to two groups. Sample 1 ($n = 700$) generated a set of candidate predictor variables derived from stepwise variable selection algorithms. Sample 2 ($n = 862$) was used to test and potentially validate the candidate models. Candidate variables using sample 2 were considered "validated" if $p < 0.01$. The candidate predictor variables for model building based on sample 1 included (1) sociodemographics; (2) clinical and treatment-related variables; and (3) mental health, alcohol, and substance use variables.

Analyses were performed using SAS System software version 9.4 (SAS Institute, Cary, NC). PROMIS T scores were computed using R software (R Foundation for Statistical Computing) and RStudio (RStudio Inc.).

RESULTS

Patient and Treatment Characteristics

Of the 1601 patients enrolled in PROP-UP, 1562 self-reported medication adherence during either the T2 or T3 assessment window. Among the 1513 patients with medication adherence data at T2, 65 (4%) were non-adherent, and among the 1476 patients with medication adherence data at T3, 119 (8%) were non-adherent. A total of 1447 patients provided either T2 and/or T3 medication adherence data; of these, 162 (11%) were non-adherent at either T2 and/or T3, and 88 (6%) changed from adherent to non-adherent status from T2 to T3. Among those 1447, 37% had mental health condition, 15% reported current alcohol use, and 23% reported prescription or non-prescription drug use in the last year.

Table 1 shows baseline patient characteristics stratified by non-adherence at T2 and/or T3 ($n = 162$) and adherence ($n =$

1285). The two strata exhibited notable differences in patient characteristics for age, sex, race, income, treatment cohort, and alcohol use (22% vs. 14%). The non-adherent patients exhibited a higher proportion of female patients (52% vs. 43%), black patients (43% vs. 31%), and patients with an annual income less than \$40,000 (83% vs. 73%).

In Figure 1a, the proportions of patients who were non-adherent during T2 (early treatment) and T3 (late treatment) are characterized by mental health history, alcohol use, and substance use. At T2, the rate of non-adherence for patients with mental health conditions, substance use, and alcohol use was 5–6% and similar to patients without these characteristics (4%). Overall, non-adherence doubled at T3 from 4 to 8% and was similar for participants with and without mental health conditions and those with or without substance use. At T3, the non-adherence rate was twice as high among patients with alcohol use compared to those without (14% vs. 7%).

Figure 1b shows non-adherence stratified by additional patient and treatment characteristics: demographics, treatment duration, RBV use, TMSAS scores, and health comorbidities. At T2, the non-adherence rate was 7% in black patients and 3% in whites; otherwise, no clinically important differences were noted among any other characteristics. Compared to T2, at T3, non-adherence increased by 14% among patients younger than 35, 9% in the "other" race category and among patients with elevated baseline creatinine of (2 mg/dL), and 6% among patients who had higher baseline symptom burden (scores ≥ 1 on the TMSAS).

Among non-adherent patients at T2 and/or T3, the most common reasons for non-adherence were forgetfulness (54%), being out of a routine (47%), and being too late with the medication dose (33%) (Fig. 2).

Predictors of Medication Non-adherence

The multivariable model for non-adherence (Table 2) exhibited little or no association between non-adherence and substance use (OR 1.20 [95% CI 0.81, 1.78]) and mental health conditions (OR 1.02 [95% CI 0.71, 1.47]). In contrast, associations were evident for alcohol use (OR 1.96 [95% CI 1.27, 3.01]) and for age, race, number of health comorbidities, and DAA cohort. Compared to patients treated with SOF/LED, two other treatment cohorts exhibited higher rates of non-adherence: OBV/PTV/r + DSV (OR 2.04 [95% CI 1.27–3.27]) and GRZ/ELB (OR 2.80 [95% CI 1.44–5.46]). Cirrhosis, treatment experience, and RBV were not selected in the multivariable models.

Exploration of Differences Among DAA Treatment Cohorts

We explored differences in non-adherence among DAA treatment cohorts in terms of patient characteristics stratified by DAA therapy (Table 3). Additional information on DAA regimens used, pill burden, and indications is shown in Online Appendix

Table 1 Baseline Patient Characteristics by Adherence

Characteristic	Total cohort* (n = 1562)	Adherence cohort (n = 1447)	
		Non-adherent patients† (n = 162)	Adherent patients‡ (n = 1285)
	n (%)		
Sociodemographic features			
Age (median (IQR), mean (SD))	60 (54–65)	58 (49–63)	60 (54–65)
< 35	58 (11)	55 (12)	58 (10)
35–55	87 (6)	16 (10)	61 (5)
> 55	375 (24)	48 (30)	300 (23)
Sex	1100 (70)	98 (60)	924 (72)
Female	696 (45)	84 (52)	553 (43)
Male	866 (55)	78 (48)	732 (57)
Race			
Black	505 (32)	70 (43)	401 (31)
White	957 (62)	76 (47)	805 (63)
Other [§]	94 (6)	16 (10)	75 (6)
Education			
Up to high school diploma or GED	832 (54)	78 (49)	691 (54)
Vocational school or higher	713 (46)	82 (51)	580 (46)
Annual income			
Under \$40,000 per year	1133 (74)	131 (83)	911 (73)
\$40,000 or above per year	391 (26)	27 (17)	341 (27)
Socioeconomic status (SES)			
High	843 (55)	90 (57)	694 (55)
Low	688 (45)	69 (43)	564 (45)
Employment			
Working full- or part-time	538 (36)	55 (36)	445 (36)
Unemployed	106 (7)	13 (9)	84 (7)
Disabled/applying	675 (45)	70 (46)	554 (44)
Retired/homemaker/student	190 (13)	13 (9)	163 (13)
Clinical and treatment features			
Genotype			
1, 4, 6	1276 (82)	136 (85)	1047 (82)
2	136 (9)	13 (8)	114 (9)
3	133 (9)	11 (7)	111 (9)
Cirrhosis status			
Non-cirrhotic	818 (53)	91 (56)	675 (53)
Cirrhotic	736 (47)	71 (44)	603 (47)
Creatinine (mg/dL)			
< 2	1469 (97)	150 (94)	1212 (97)
≥ 2	49 (3)	10 (6)	34 (3)
HIV			
No	1471 (97)	145 (97)	1214 (97)
Yes	52 (3)	5 (3)	44 (3)
Treatment experience			
Naive	1135 (82)	109 (81)	946 (82)
Experienced	255 (18)	26 (19)	214 (18)
DAA treatment cohort			
SOF/LED	979 (63)	84 (52)	825 (64)
SOF/VEL	328 (21)	34 (21)	275 (21)
GRZ/ELB	169 (11)	29 (18)	125 (10)
OBV/PTV/r + DSV	67 (4)	14 (8)	47 (4)
SOF/DAC	19 (1)	1 (1)	13 (1)
Ribavirin			
Without	1358 (87)	144 (89)	1116 (87)
With	204 (13)	18 (11)	169 (13)
DAA treatment cohort by ribavirin			
SOF/LED			
Without ribavirin	862 (55)	78 (48)	718 (56)
With ribavirin	117 (7)	6 (4)	107 (8)
SOF/VEL			
Without ribavirin	310 (20)	34 (21)	259 (20)
With ribavirin	18 (1)	0 (0)	16 (1)
GRZ/ELB			
Without ribavirin	154 (10)	27 (17)	116 (9)
With ribavirin	15 (1)	2 (1)	9 (1)
OBV/PTV/r + DSV			
Without ribavirin	18 (1)	4 (2)	13 (1)
With ribavirin	49 (3)	10 (6)	34 (3)
SOF/DAC			
Without ribavirin	14 (1)	1 (1)	10 (1)
With ribavirin	5 (0)	0 (0)	3 (0)
Treatment duration			

(continued on next page)

Table 1. (continued)

Characteristic	Total cohort* (n = 1562)	Adherence cohort (n = 1447)	
		Non-adherent patients† (n = 162)	Adherent patients‡ (n = 1285)
	n (%)		
8 weeks	153 (10)	17 (10)	114 (9)
12 weeks	1286 (82)	135 (83)	1079 (84)
16 or 24 weeks	123 (8)	10 (6)	92 (7)
Symptom burden and medical conditions			
TMSAS			
< 0.2	427 (28)	36 (23)	369 (29)
0.2–1.0	834 (54)	84 (53)	680 (53)
≥ 1.0	291 (19)	39 (25)	229 (18)
Number of medical comorbidities			
0–1	305 (20)	29 (18)	250 (19)
2–3	398 (26)	38 (23)	340 (27)
4+	857 (55)	95 (59)	693 (54)
Mental health and substance use features			
Mental health condition			
No	984 (63)	97 (60)	812 (63)
Yes	572 (37)	65 (40)	467 (37)
Alcohol use¶			
No	1326 (85)	127 (78)	1103 (86)
Yes	229 (15)	35 (22)	175 (14)
Substance use			
No	1201 (77)	120 (74)	995 (78)
Yes	354 (23)	42 (26)	284 (22)

“n” is the number of non-missing values. The percentage (%) is based on the non-missing counts. Missing values for all the characteristics were ≤ 3%, except treatment experience was missing for 11% of patients. Missing values for adherence at T2 or T3 were 7%

SD standard deviation; IQR interquartile range; DAA direct-acting antiviral; SOF/LED sofosbuvir/ledipasvir; SOF/VEL sofosbuvir/velpatasvir; GRZ/ELB grazoprevir/elbasvir; OBV/PTV/r + DSV ombitasvir/paritaprevir/ritonavir + dasabuvir; SOF/DAC sofosbuvir/daclatasvir; TMSAS total score for the Memorial Symptom Assessment Scale

*Total cohort is the patients who had medication adherence at T2 or T3

†Non-adherent patients at T2 or T3

‡Adherent patients at T2 and T3. From the total cohort of patients with medication adherence data at T2 or T3 (n = 1562), there are 1447 patients with information about adherence

§For the total cohort (n = 1562), other race includes 22% American Indian, Alaskan Native, and Pacific Islander; 30% multiracial/biracial; 4% Asian; and 44% not reported or unknown

¶Age: min = 24, max = 86

¶Variables with significant association with medication adherence at $p < \alpha = 0.01$. For binary characteristics, the test statistic was the Pearson chi-square. For non-binary characteristics, the test statistic was the extended Mantel-Haenszel statistic for one stratum

Table 1. Proportions of non-adherence by DAA therapy cohort are reported in Online Appendix Table 2. Patients treated with GRZ/ELB were more likely to be black, have low income, be disabled, or report a higher number of health comorbidities than those treated with SOF-containing regimens or OBV/PTV/r + DSV. Nearly one third of GRZ/ELB-treated patients reported current or past kidney disease and 20% had baseline serum creatinine ≥ 2 mg/dL compared to a minority of patients treated with SOF-containing regimens or OBV/PTV/r + DSV. Patients treated with OBV/PTV/r + DSV were more likely to be white, were less likely to be treatment experienced (8% with OBV/PTV/r + DSV compared to 19–21% with other regimens), and, expectedly, were much more likely to be treated with RBV. Patients treated with OBV/PTV/r + DSV patients were more likely to report mental health conditions and alcohol use. Patient characteristics stratified by adherence versus non-adherence are found in Online Appendix Table 3.

Predictors of Non-adherence with Clinical Follow-up

Among the 1562 patients enrolled in PROP-UP, 262 (17%) were non-adherent with clinical follow-up and had no SVR lab

data after treatment completion despite multiple attempts. A multivariable model predicting non-adherence with clinical follow-up is shown in Table 4. Patients who were younger (age < 35 vs. > 55, OR 2.56 [95% CI 1.50–4.37]; age 35–55 vs. > 55, OR 1.87 [95% CI 1.37–2.54]) and those with higher total baseline symptom burden (TMSAS score ≥ 1.0 vs. < 0.2, OR 2.00 [95% CI 1.25–3.21]) were more likely to be non-adherent with clinical follow-up.

Adherence and SVR

Among the 1287 participants with adherence and SVR data (82% of study sample), a total of 53 patients (4%) failed to achieve SVR. SVR rates were similar for patients with and without mental health conditions (96% for both); 95% and 96% for those with and without alcohol use; and 95% and 96% for those with and without substance use. The overall observed SVR rate was 97% (117/121) for non-adherent patients and 96% (1038/1084) for adherent patients. SVR status was not correlated with non-adherence in a bivariate analysis (phi correlation coefficient = 0.014). Multivariable models for SVR were unreliable and inconclusive due to the small number of treatment failures.

Figure 1 a Proportion of patients who were non-adherent by mental health condition, alcohol use, and substance use at T2 and T3. The 95% confidence intervals were computed using the Wilson score confidence limits. Superscript letter “a”: Among the 1513 patients with medication adherence data at T2, 65 (4%) were non-adherent, and among the 1476 patients with medication adherence data at T3, 119 (8%) were non-adherent. b Proportion of patients who were non-adherent: subgroups defined by sociodemographics, treatment cohort, symptoms burden, and medical comorbidities at T2 and T3. The 95% confidence intervals were computed using the Wilson score confidence limits. Superscript letter “a”: Among the 1513 patients with medication adherence data at T2, 65 (4%) were non-adherent, and among the 1476 patients with medication adherence data at T3, 119 (8%) were non-adherent. Superscript letter “b”: For the total cohort ($n = 1562$), other race includes 22% American Indian, Alaskan Native, Pacific Islander; 30% multiracial/biracial; 4% Asian; and 44% not reported or unknown. DAA direct-acting antiviral; SOF/LED sofosbuvir/ledipasvir; SOF/VEL sofosbuvir/velpatasvir; GRZ/ELB grazoprevir/elbasvir; OBV/PTV/r + DSV ombitasvir/paritaprevir/ritonavir + dasabuvir; SOF/DAC sofosbuvir/dacatasvir; TMSAS total score for the Memorial Symptom Assessment Scale; CI confidence interval.

DISCUSSION

In this large prospective study of DAA non-adherence in a real-world cohort, medication non-adherence early in treatment and/or near the end of treatment was quite low (11%) but increased over time. Though the high adherence rate is

consistent with recent studies, it is remarkable given the high proportion of patients with potential non-adherence risk factors such as low income (74%), mental health conditions (37%), substance use (23%), and alcohol use (15%).^{7, 9, 27}

Figure 2 Reasons for non-adherence to DAA therapy. “n” is the number of responses for non-adherence reasons at T2 and T3.

Non-adherence increased from early to late in treatment, particularly among patients with alcohol use, those younger than 35, and among patients with higher overall symptom burden. Alcohol consumption and misuse had previously exhibited associations with slightly lower SVR rates in the interferon and DAA eras^{28, 29} and lower adherence to DAAs.^{30, 31} Non-adherence was not higher for patients with mental health conditions or substance use. Our results support data from registration trials that included patients on OST and found them to have comparable adherence and SVR to populations without substance use.^{7, 8} However, our findings are in contrast to another phase 2 clinical trial, which found recent

drug use as a risk factor for non-adherence, but not controlled psychiatric disease or depressive symptoms.⁹

We also found that non-white race was associated with non-adherence. This is interesting in light of recent national data from the Veterans Affairs that showed lower SVR rates among black and Hispanic patients.³² Race has also been shown to be a risk factor for non-adherence in the interferon era and during treatment for other chronic diseases, highlighting the need for additional support during DAA therapy.³³

Apart from sociodemographics, two regimen cohorts—GRZ/ELB and OBV/PTV/r + DSV—were associated with higher rates of non-adherence compared to sofosbuvir-containing regimens. While this finding was expected in the OBV/PTV/r + DSV cohort, given the larger pill burden, use of RBV, and twice daily dosing requirements, we were surprised by the higher non-adherence in patients on GRZ/ELB, which is a single-pill once-daily regimen. We observed that higher proportions of patients receiving GRZ/ELB were black, had lower income, were disabled, and had Cr ≥ 2 mg/dL. Although patients with baseline creatinine ≥ 2 mg/dL had twice the rate of non-adherence at T3 (16% vs. 8%), the small sample size of non-adherent patients did not support fitting additional models to evaluate the effect of elevated creatinine. Larger, prospective studies could evaluate this relationship further. We were somewhat surprised by the lack of association between treatment duration and non-adherence; however, in contrast to interferon, DAAs are very well tolerated and treatment duration short, potentially explaining the lack of association.

This study has several important clinical implications. Overall non-adherence to DAAs was low and SVR was high (96%), although the optimal threshold of medication adherence is not known in the DAA era. Given that mental health conditions or substance use did not affect adherence to DAA treatment or SVR in this large, diverse cohort, there is no justification to use these patient characteristics as a basis for clinicians to withhold DAA therapy or for third-party payers to deny access to HCV treatment. Patients with alcohol use were more likely to be non-adherent early in treatment and further increase in non-

Table 2 Multivariable Logistic Model Predicting Medication Non-adherence

Predictor	OR	95% CI	p value
Age			
< 35 vs. > 55	3.40	1.78, 6.50	p = 0.0002
35–55 vs. > 55	1.68	1.14, 2.47	p = 0.0089
Sex			
Female vs. male	1.45	1.03, 2.04	p = 0.0341
Race			
Black vs. white	2.42	1.31, 4.45	p = 0.0045
Other* vs. white	2.26	1.55, 3.28	p = 0.0000
DAA treatment cohort			
SOF/VEL vs. SOF/LED	1.40	0.90, 2.16	p = 0.1357
GRZ/ELB vs. SOF/LED	2.80	1.44, 5.46	p = 0.0025
OBV/PTV/r + DSV vs. SOF/LED	2.04	1.27, 3.27	p = 0.0032
SOF/DAC vs. SOF/LED	0.78	0.13, 4.80	p = 0.7911
Number of medical comorbidities†			
Count +1 vs. count	1.07	1.02, 1.13	p = 0.0065
Mental health condition			
Yes vs. no	1.02	0.71, 1.47	p = 0.9098
Alcohol use			
Yes vs. no	1.96	1.27, 3.01	p = 0.0022
Substance use			
Yes vs. no	1.20	0.81, 1.78	p = 0.3697

OR odds ratio; CI confidence interval; DAA direct-acting antiviral; SOF/LED sofosbuvir/ledipasvir; SOF/VEL sofosbuvir/velpatasvir; GRZ/ELB grazoprevir/elbasvir; OBV/PTV/r + DSV ombitasvir/paritaprevir/ritonavir + dasabuvir; SOF/DAC sofosbuvir/daclatasvir

*For the total cohort (n = 1562), other race includes 22% American Indian, Alaskan Native, and Pacific Islander; 30% multiracial/biracial; 4% Asian; and 44% not reported or unknown

†Number of medical comorbidities is a continuous predictor

Table 3 Baseline Patient Characteristics by DAA Therapy Cohort and Adherence

Characteristic	SOF/LED + SOF/VEL + SOF/DAC	GRZ/ ELB	OBV/PTV/ r + DSV
	Cohort (n = 1326)	Cohort (n = 169)	Cohort (n = 67)
	n (%)		
Sociodemographic features			
Age			
< 35	71 (5)	7 (4)	9 (13)
35–55	317 (24)	40 (24)	18 (27)
> 55	938 (71)	122 (72)	40 (60)
Sex			
Female	587 (44)	78 (46)	31 (46)
Male	739 (56)	91 (54)	36 (54)
Race			
Black or African American	406 (31)	83 (49)	16 (24)
White	830 (63)	78 (46)	49 (73)
Other	85 (6)	7 (4)	2 (3)
Education			
Up to high school diploma or GED	702 (54)	95 (57)	35 (52)
Vocational school or higher	608 (46)	73 (43)	32 (48)
Annual income			
Under \$40,000 per year	945 (73)	138 (83)	50 (75)
\$40,000 or above per year	345 (27)	29 (17)	17 (25)
Socioeconomic status (SES)			
High	726 (56)	81 (48)	36 (54)
Low	570 (44)	87 (52)	31 (46)
Employment			
Working full- or part-time	476 (37)	31 (19)	31 (47)
Unemployed	92 (7)	10 (6)	4 (6)
Disabled/applying	544 (43)	103 (63)	28 (42)
Retired/homemaker/student	167 (13)	20 (12)	3 (5)
Clinical and treatment features			
Genotype			
1, 4, 6	1042 (79)	167 (100)	67 (100)
2	136 (10)	0 (0)	0 (0)
3	133 (10)	0 (0)	0 (0)
Cirrhosis status			
No	695 (53)	90 (54)	33 (49)
Yes	625 (47)	77 (46)	34 (51)
Creatinine (mg/dL)			
< 2	1271 (99)	133 (80)	65 (98)
≥ 2	14 (1)	34 (20)	1 (2)
Current or past kidney disease			
No	1221 (94)	119 (71)	64 (98)
Yes	76 (6)	48 (29)	1 (2)
HIV			
No	1250 (97)	162 (96)	59 (98)
Yes	45 (3)	6 (4)	1 (2)
Treatment experience			
Naïve	967 (81)	112 (79)	56 (92)
Experienced	221 (19)	29 (21)	5 (8)
Ribavirin			
Without	1186 (89)	154 (91)	18 (27)
With	140 (11)	15 (9)	49 (73)
Treatment duration			
8 weeks	152 (11)	0 (0)	1 (1)
12 weeks	1070 (81)	158 (93)	58 (87)
16 or 24 weeks	104 (8)	11 (7)	8 (12)
Symptom burden and medical conditions			
TMSAS			
< 0.2	367 (28)	38 (22)	22 (33)
0.2–1	714 (54)	93 (55)	27 (41)
≥ 1	236 (18)	38 (22)	17 (26)
Number of medical comorbidities			

(continued on next page)

Table 3. (continued)

Characteristic	SOF/LED + SOF/VEL + SOF/DAC	GRZ/ ELB	OBV/PTV/ r + DSV
	Cohort (n = 1326)	Cohort (n = 169)	Cohort (n = 67)
	n (%)		
0–1	272 (21)	17 (10)	16 (24)
2–3	346 (26)	31 (18)	21 (31)
4+	706 (53)	121 (72)	30 (45)
Mental health and substance use features			
Mental health condition			
No	835 (63)	116 (69)	33 (49)
Yes	486 (37)	52 (31)	34 (51)
Alcohol use			
No	1127 (85)	146 (87)	53 (79)
Yes	193 (15)	22 (13)	14 (21)
Substance use			
No	1015 (77)	131 (78)	55 (82)
Yes	304 (23)	38 (22)	12 (18)

DAA direct-acting antiviral; SOF/LED sofosbuvir/ledipasvir; SOF/VEL sofosbuvir/velpatasvir; GRZ/ELB grazoprevir/elbasvir; OBV/PTV/r + DSV ombitasvir/paritaprevir/ritonavir + dasabuvir; SOF/DAC sofosbuvir/daclatasvir; TMSAS total score for the Memorial Symptom Assessment Scale

adherence later in treatment suggesting that point-of-care screening for alcohol use may be useful to identify patients who may require support during DAA therapy to remain adherent. Furthermore, DAA therapy represents a window of opportunity to engage HCV patients in alcohol-related treatment; a recent study showed that receipt of alcohol-related care is under-utilized in patients with HCV.³⁴

Younger patients were also more likely to be non-adherent with medications and clinical follow-up visits, although,

Table 4 Multivariable Logistic Model Predicting Clinical Follow-up Non-adherence

Predictor	Non-adherence to follow-up OR [95% CI] (p value)
Age	
< 35 vs. > 55	2.56 [1.50, 4.37] (p = 0.0006)
35–55 vs. > 55	1.87 [1.37, 2.54] (p = 0.0001)
Sex	
Female vs. male	0.92 [0.69, 1.22] (p = 0.5604)
Race	
Black vs. white	0.70 [0.37, 1.35] (p = 0.2911)
Other vs. white	1.31 [0.97, 1.78] (p = 0.0770)
Socioeconomic status (SES)	
Low vs. high	0.95 [0.72, 1.26] (p = 0.7232)
Cirrhosis status	
Yes vs. no	0.91 [0.68, 1.22] (p = 0.5422)
TMSAS—symptom burden	
0.2–1.0 vs. < 0.2	1.34 [0.94, 1.92] (p = 0.1018)
≥ 1.0 vs. < 0.2	2.00 [1.25, 3.21] (p = 0.0041)
Number of medical comorbidities	
Count +1 vs. count	0.97 [0.92, 1.02] (p = 0.2117)
Mental health condition	
Yes vs. no	1.15 [0.85, 1.55] (p = 0.3749)
Alcohol use	
Yes vs. no	1.29 [0.89, 1.88] (p = 0.1730)
Substance use	
Yes vs. no	0.85 [0.61, 1.18] (p = 0.3276)

OR odds ratio, CI confidence interval, TMSAS total score for the Memorial Symptom Assessment Scale

interestingly, SVR rates among those with complete follow-up were 100%. The association between younger age and loss to follow-up on DAA therapy was recently shown in an inner city cohort.¹³ This finding is important because although young patients are less likely to have advanced fibrosis or cirrhosis, they may be more likely to have recent drug use and to remain as a source of infection if SVR is not achieved, which is salient in light of the ongoing opioid epidemic. For this special population, additional strategies to support follow-up with clinic visits and services embedded within substance use treatment centers may be warranted. Finally, as the most common reasons for non-adherence were forgetfulness or being out of a routine, low-cost, technology-based strategies such as text message reminders may be leveraged to support adherence.

We must acknowledge certain study limitations. Mental health, substance use, and alcohol use were all self-reported. We did not have data on drug use at baseline nor patient adherence behaviors during treatment, although assessment of alcohol use was current. We did not collect data on homelessness, men who have sex with men, or OST. The non-adherence measure was self-reported, may underestimate non-adherence, and does not reflect actual pill-taking behavior. Electronic monitoring was not feasible due to the study size. Pharmacy refill data was not practical due to short-duration regimens.³⁵ We were unable to reliably evaluate the association between medication non-adherence and SVR due to the low rate of treatment failure; however, without accounting for confounders, the bivariate correlation was negligible. As with any observational study, bias due to confounding is a concern.

CONCLUSIONS

Despite a substantial prevalence of mental health conditions, alcohol use, and substance use, DAA non-adherence was low and SVR was high. Psychosocial comorbidities should not serve as a basis for DAA denials either by clinicians or insurance payers. Simple, low-cost solutions such as point-of-care testing for alcohol use and concurrent treatment support, education about the importance of adherence, and medication reminder strategies may promote DAA adherence and appropriate long-term clinical follow-up.

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Corresponding Author: Donna M. Evon, PhD; Division of Gastroenterology and Hepatology, Department of Medicine University of North Carolina, Chapel Hill, NC 27599, USA (e-mail: Donna_evon@med.unc.edu).

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Sites obtained local Institutional Review Board (IRB) approval and all participants provided informed consent.

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