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MAJOR ARTICLE

Predictors of Hepatitis C Treatment Failure After Using Direct-Acting Antivirals in People Living With Human Immunodeficiency Virus

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Background. Little is known about the influence of ongoing barriers to care in the persistence of hepatitis C virus (HCV) viremia after treatment with direct-acting antivirals (DAAs) among people living with human immunodeficiency virus (PLWH).

Methods. We conducted a retrospective cohort analysis of PLWH treated through the standard of care in 3 Western countries, to investigate the predictors of HCV treatment failure (clinical or virologic), defined as having a detectable serum HCV ribonucleic acid within 12 weeks after DAA discontinuation. In addition to HCV and liver-related predictors, we collected data on ongoing illicit drug use, alcohol abuse, mental illness, and unstable housing. Logistic regression analyses were used to identify predictors of HCV treatment failure.

Results. Between January 2014 and December 2017, 784 PLWH were treated with DAA, 7% (n = 55) of whom failed HCV therapy: 50.9% (n = 28) had a clinical failure (discontinued DAA therapy prematurely, died, or were lost to follow-up), 47.3% (n = 26) had an HCV virologic failure, and 1 (1.8%) was reinfected with HCV. Ongoing drug use (odds ratio [OR] = 2.60) and mental illness (OR = 2.85) were independent predictors of any HCV treatment failure. Having both present explained 20% of the risk of any HCV treatment failure due to their interaction (OR = 7.47; $P < .0001$). Predictors of HCV virologic failure were ongoing illicit drug use (OR = 2.75) and advanced liver fibrosis (OR = 2.29).

Conclusions. People living with human immunodeficiency virus with ongoing illicit drug use, mental illness, and advanced liver fibrosis might benefit from enhanced DAA treatment strategies to reduce the risk of HCV treatment failure.

Keywords. DAA; drug use; HCV treatment failure; HIV; mental illness.

Real-world studies have confirmed the high efficacy and excellent tolerability of direct-acting antivirals (DAAs) for the treatment of hepatitis C virus (HCV) infection in people living with human immunodeficiency virus (PLWH). Overall, more than 90% of PLWH treated with DAAs achieve cure [1, 2]. Hence, the World Health Organization proposed goals to eliminate HCV by 2030 [3], and the British HIV Association considered that HCV could be eliminated in PLWH in the United Kingdom by 2021 [4]. To achieve this goal, we need to decrease the proportion of PLWH with ongoing HCV viremia through HCV screening, linkage, treatment uptake, and implementation of harm reduction strategies to prevent HCV reinfection. The causes of HCV treatment failure and resulting ongoing HCV viremia are different depending on whether there is virologic failure or premature treatment discontinuation [5].

Few studies have investigated the predictors of DAA failure among PLWH, defined as lack of sustained viral response (SVR), with variable results [6–8]. One study found that among PLWH treated with DAAs, cirrhosis status was the main clinical factor that decreased the chances of achieving SVR, especially among PLWH with CD4 counts less than 350 cells/mm^3 [7]. Another study acknowledged that PLWH who had a baseline CD4 count lower than 200 cells/mm^3 had lower SVR rates after adjusting for known HCV and liver-related predictors of HCV treatment response [8]. Altogether, these studies suggested that the impaired immune response of PLWH with low CD4 counts could influence their response to DAA treatment. Whether having a low CD4 count reflects underrecognized splenic sequestration due to more advanced liver disease and portal hypertension or unmeasured clinical characteristics of the studied patients that contribute to their advanced human immunodeficiency virus (HIV) infection in the first place remains unclear.

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People living with HIV have a higher prevalence of illicit drug use, alcohol abuse, mental illness, and unstable housing than the HIV-uninfected population [9]. Very few studies have investigated the interaction of complex social and behavioral issues prevalent in PLWH and their influence on DAA treatment outcomes [10]. Therefore, we conducted this study to investigate the negative predictors of SVR among PLWH treated with DAA. In addition to including conventional HCV- and liver-related parameters, we investigated the effect of ongoing barriers to care such as illicit drug use, alcohol abuse, mental illness, and unstable housing in PLWH from different geographic areas.

METHODS

The Hepatitis C Virus-Transatlantic Research Network Cohort

The HCV-HIV Transatlantic Research Network (HCV-TREN) was implemented in March 2016, shortly after scaling-up DAA availability in Europe and the United States for PLWH. The overarching goal of this collaborative effort is to use the network data to inform local health policymakers on areas of clinical service improvement to reach HCV elimination among PLWH. Five academically affiliated HIV clinics in 3 different countries have been included. They comprise Owen Clinic at the University of California, San Diego (UCSD) in the United States, University Hospital of La Coruña in Spain, Puerta de Hierro Research Institute and University Hospital in Madrid, the University Hospital Alvaro Cunqueiro of Vigo in Spain, and the Hospital University of Sassari in Italy. Patients were included in the study if they were 18 years of age or older, had evidence of active HCV infection, and initiated DAA treatment through the local standard of care procedures between January 1, 2014 and December 31, 2017. The study was conducted according to the principles expressed in the Declaration of Helsinki. Patient records/information was anonymized and deidentified before analysis using unique study codes generated at the clinics. Institutional human research protection program (HRPP) approval was obtained at each participating site (UCSD HRPP Protocol no. 171749X).

Data Collected Domains and Procedures

For this retrospective cohort study, data were primarily derived from electronic medical records (EMRs). Data included patients' demographics, HIV transmission risk factors, antiretroviral therapy, CD4 cell count, and HIV viral load. We also collected information on HCV genotype, HCV ribonucleic acid (RNA) levels, prior HCV treatment history, liver fibrosis stage according to the modified Knodell score, cirrhosis status, history and type of prior liver decompensation, and the Model for End-Stage Liver Disease and Child-Turcotte-Pugh scores. Data collection also included (1) DAA regimen with a start and stop dates and (2) comorbidity burden (measured by the Charlson comorbidity index) [11]. For time-varying covariates, the value collected was the one most immediately before, but no longer than 3 months before the date of DAA initiation. All European centers conducted liver fibrosis staging using vibration-controlled transient elastography (FibroScan; Echosens, Paris, France). At UCSD, elastography became available in 2015, and until then fibrosis staging was measured according to liver biopsy results.

For screening of ongoing depression, self-reported illicit drug use, and alcohol abuse within the last 3 months of DAA initiation, patients completed the PHQ-9 inventory [12], the National Institute on Drug Abuse-Alcohol, Smoking, and Substance Involvement Screening Test [13], and the Alcohol Use Disorders Identification Test instruments [14], respectively. We also conducted medical record review for assessment of physician documentation of symptoms and risk behaviors, drug type, and frequency of consumption. The manual chart review included The Substance Abuse and Mental Health Services Administration clinical definition of patient self-report of heavy drinking as 5 or more drinks on the same occasion on each of 5 or more days in the past 30 days [15]. Unstable housing status was collected through diagnosis code abstraction of homelessness or unstable housing. We also collected from the chart documentation of frequent short stays (up to 2 weeks) in motels or different friends or family members' houses. One site (Sassari) required that patients with active drug use be treated with DAAs only if they were on a buprenorphine or methadone replacement or in an institutionalized rehabilitation program. All other centers treated patients with ongoing drug or alcohol use according to their standard of care local protocols.

Having ongoing mental illness was not a contraindication for DAA treatment in any center. Active psychiatric illness was considered if any of the following 3 conditions were documented. First, a documented PHQ-9 score of 9 or higher indicative of ongoing depression symptoms within 3 months of starting DAA treatment. Second, if patients had a mental illness different than depression according to *International Classification of Diseases* (ICD), *Tenth Revision* codes, patients needed to be taking 2 or more active psychotropic medications with medical record documentation of ongoing disease within 3 months of initiating DAA. Third, a documented history of psychiatric hospitalization or suicidal attempt within 24 weeks of DAA treatment initiation. Direct-acting antivirals adherence was measured through local pharmacy-generated medication pickup records. One center also relied on clinical pharmacists conducting pill count when patients came to their HCV clinical appointments.

Endpoints

The primary endpoint was the proportion of patients with HCV treatment failure defined as either having a detectable serum HCV RNA 12 weeks after the estimated date of DAA treatment completion or early DAA discontinuation with resulting ongoing HCV viremia in anyone that took at least 1 dose of DAAs. Secondary outcomes included the proportion of patients with

HCV virologic failure, defined as having a detectable HCV RNA 12 weeks after ending DAA treatment among those who completed the planned DAA treatment period, and HCV clinical failure, defined as the proportion of patients who discontinued DAA therapy prematurely due to any cause including death or loss to follow-up. Patients who were lost to follow-up were considered to have ongoing HCV viremia.

Statistical Analysis

Descriptive statistics were presented using (1) means with 95% confidence interval (CI) and frequencies and (2) percentages. Bivariate analyses with pairwise comparisons were conducted to investigate factors associated with lack of SVR. We used χ^2 test for comparison of categorical variables and 2-sided *t* test (or Wilcoxon rank-sum test) for normally (or nonnormally) distributed numerical variables. To fit parsimonious prediction models for the primary and secondary outcomes, those covariates associated with the outcomes in bivariate analyses ($P \leq .1$) were entered into backward stepwise logistic regression models (probability of removal = 0.05). Model discrimination was assessed using receiver operating characteristic area, and model calibration was evaluated using the Hosmer-Lemeshow χ^2 statistic. Potential predictors of DAA treatment failure included demographics, HIV regimen, CD4, and viral load, HCV-genotype, prior HCV treatment history, HCV viral load, DAA regimen used, fibrosis stage, cirrhosis, prior liver decompensation history, Charlson comorbidity index, active alcohol abuse, any illicit drug use, intravenous drug use (IDU), unstable housing, and active mental illness. Effects are presented as odds ratios (ORs) with their estimated 95% CI. We assessed for 2-way multiplicative interactions using the product of significant covariates in the logistic regression models. Additive interactions were also investigated using the relative excess risk due to interaction (RERI), synergy index (SI), and attributable proportion due to interaction (AP) [16, 17]. Analyses were performed using StataCorp 2016, Stata Statistical Software: Release 15.1 (StataCorp, LLC, College Station, TX).

RESULTS

Patients

During the study period, 784 PLWH coinfected with HCV were treated with DAA in the HCV-TREN cohort. There were baseline differences between the patient's characteristics of participating sites (Table 1). The patients from San Diego, compared with the European sites, had a higher proportion of nonwhite subjects and men who have sex with men. Patients treated in Sassari (Italy) were older with a larger proportion of cirrhosis and a history of prior liver decompensation than the rest of the cohort. Hepatitis C virus genotype 1 infection was the most frequent at all sites (70.8%), but genotype 4 was infrequent in San Diego in contrast to some European sites. The overall prevalence of ongoing alcohol abuse, illicit drug use, unstable housing, and mental illness at the time of DAA initiation in the entire cohort (784 patients) was 30% (235 patients), 26.1% (205 patients of whom 68 were IDU), 9.7% (75 patients), and 27.9% (219 patients), respectively.

Hepatitis C Virus Treatment Outcomes

A total of 92.9% of patients (729 of 784) experienced SVR, including 91.4% of cirrhotics (225 of 245 patients) and 90% of those with prior liver decompensation (40 of 45 patients). Most patients with ongoing barriers to care achieved SVR, including 90.6% with ongoing alcohol abuse (213 of 235 patients), 85.9% with any drug use (176 of 205 patients), 82.4% of IDU (56 of 68 patients), 85.8% with mental illness (188 of 219 patients), and 85.5% with unstable housing (65 of 76 patients). The proportion of SVR did not differ significantly among patients treated at the participating clinics and was independent of the DAA regimen used. The SVR for HCV genotypes 1, 2, 3, and 4 were 92.3% (512 of 555 patients), 94.4% (17 of 18 patients), 92.7% (89 of 96 patients), and 96.5% (111 of 115 patients), respectively.

Seven percent of patients (55 of 784) did not achieve SVR. Among them, 47.3% had an HCV virologic failure (26 of 55 patients), 50.9% had a clinical failure (28 of 55 patients discontinued DAA therapy prematurely, died, or were lost to follow-up), and 1.8% was reinfected with HCV (1 of 55 patients). Most patients (20 of 26) who suffered HCV viral relapse were infected with HCV genotype 1. Eleven patients who suffered virologic failure had cirrhosis, including 7 who had failed prior interferon-containing regimens and 3 with a history of prior liver decompensation. All but 1 relapsed within 5 weeks of DAA treatment discontinuation. There were no virologic failures due to viral breakthrough during DAA therapy. Among the 28 patients who interrupted DAA therapy prematurely, 22 abandoned therapy voluntarily, 3 discontinued due to intolerance to ribavirin, and 3 died (Supplementary Table 1). All patients who abandoned HCV therapy had pharmacy documentation of lack of picking up their DAAs during the second month of therapy. Fourteen patients who abandoned DAA therapy had subsequently documented ongoing HCV viremia, and 8 were lost to follow-up. The mortality causes of the 3 patients who died were advanced liver disease complications (n = 1), aspiration pneumonia (n = 1), and anal cancer complications (n = 1). The single patient who became reinfected had a detectable HCV viral load at week 12 of DAA discontinuation but with a different HCV genotype than the one before DAA initiation. He had a history of IDU and sex with men.

Predictors of Hepatitis C Virus Treatment Failure Using Direct-Acting Antivirals

In bivariate analysis, predictors of any HCV treatment failure included ongoing drug use (including IDU), alcohol abuse, mental illness, unstable housing, and advanced liver fibrosis (Table 2). Stepwise multivariable logistic-regression analyses identified ongoing drug use (OR = 2.60; 95% CI, 1.79–3.79) and

Table 1. Baseline Patient Characteristics and Direct-Acting Antiviral Regimens of Study Participants According to Study Sites

Covariates	San Diego, CA (n = 177)	La Coruña, Spain (n = 286)	Madrid, Spain (n = 112)	Sassari, Italy (n = 59)	Vigo, Spain (n = 150)
DAA Regimen-Simplified, n (%)[a]					
Sofosbuvir plus ribavirin	11 (6.2)	3 (1.1)	1 (0.9)	1 (1.7)	0 (0)
Sofosbuvir plus ledipasvir ± ribavirin	103 (58.2)	77 (26.9)	73 (65.2)	13 (22.0)	99 (66)
Sofosbuvir plus simeprevir ± ribavirin	19 (10.7)	26 (9.1)	2 (1.8)	0 (0)	18 (12)
Sofosbuvir plus daclatasvir ± ribavirin	5 (2.8)	4 (1.4)	10 (8.9)	17 (28.8)	11 (7.3)
PrOD ± ribavirin	3 (1.7)	30 (10.5)	18 (16.1)	8 (13.6)	16 (10.7)
Sofosbuvir plus velpatasvir ± ribavirin	24 (13.6)	90 (31.5)	0 (0)	8 (13.6)	5 (3.3)
Ombitasvir/paritaprevir/ritonavir + ribavirin	0 (0)	10 (3.5)	7 (6.3)	0 (0)	1 (0.7)
Grazoprevir/elbasvir	5 (2.8)	0 (0)	1 (0.9)	7 (11.9)	0 (0)
Glecaprevir/pibrentasvir	7 (3.9)	46 (16.1)	0 (0)	5 (8.5)	0 (0)
Gender, n (%)[b]					
Female	24 (13.6)	89 (31.1)	31 (27.7)	14 (23.7)	34 (22.7)
Male	153 (86.4)	197 (68.9)	81 (72.3)	45 (76.3)	116 (77.3)
Race/Ethnicity, n (%)[a]					
Nonwhite	33 (18.6)	0 (0)	0 (0)	0 (0)	0 (0)
White	144 (81.4)	286 (100)	112 (100)	59 (100)	150 (100)
HIV Risk Factor, n (%)[a]					
Men who have sex with men	43 (24.3)	19 (6.6)	9 (8.0)	0 (0)	1 (0.7)
Heterosexual	29 (16.4)	0 (0)	10 (8.9)	4 (6.8)	40 (26.7)
Hemophilia	4 (2.3)	5 (1.8)	1 (0.9)	0 (0)	1 (0.7)
MSM + intravenous drug use	21 (11.9)	10 (3.5)	1 (0.9)	0 (0)	0 (0)
Heterosexual + intravenous drug use	46 (26.0)	252 (88.1)	91 (88.3)	55 (93.2)	108 (72)
Other	34 (19.2)	0 (0)	0 (0)	0 (0)	0 (0)
Active Alcohol, Baseline, n (%)[a]					
No,	139 (78.5)	171 (59.8)	65 (58.0)	51 (86.4)	123 (82)
Yes	38 (21.5)	115 (40.2)	47 (42.0	8 (13.6)	27 (18)
Active Illegal Drugs, Baseline, n (%)[a]					
No	125 (70.6)	177 (61.9)	89 (79.5)	59 (100)	129 (86)
Yes	52 (29.4)	109 (38.1)	23 (20.5)	0 (0)	21 (14)
Active Intravenous Drug Use, Baseline, n (%)[a]					
No	170 (96.1)	249 (87.0)	109 (97.3)	59 (100)	129 (86)
Yes	7 (3.9)	37 (13)	3 (2.7)	0 (0)	21 (14)
Unstable Housing, n (%)[a]					
No	163 (92.1)	253 (88.5)	108 (96.4)	59 (100)	125 (83.3)
Yes	14 (7.9)	33 (11.5)	4 (3.6)	0 (0)	25 (16.7)
Active Mental Illness, n (%)[a]					
No	137 (77.4)	220 (76.9)	70 (62.5)	51 (86.4)	87 (58.0)
Yes	40 (22.6)	66 (23.1)	42 (37.5)	8 (13.6)	63 (42.0)
HCV Genotype (Grouped), n (%)[a]					
1/1a/1b	140 (79.1)	216 (75.5)	68 (60.7)	31 (52.5)	100 (66.7)
2/2b	7 (4.0)	8 (2.8)	2 (1.8)	1 (1.7)	0 (0)
3/3a/3b	23 (13.0)	30 (10.5)	12 (10.7)	14 (23.7)	17 (11.3)
4	7 (3.9)	32 (11.2)	30 (26.8)	13 (22.1)	33 (22.0)
Fibrosis Score, n (%)[a]					
F0–2	101 (57.1)	171 (59.8)	56 (50)	15 (25.4)	75 (50)
F3–4	76 (42.9)	115 (40.2)	56 (50)	44 (74.6)	75 (50)
HCV Treatment Naive, n (%)[a]					
No	49 (27.7)	131 (45.8)	34 (30.4)	16 (27.1)	37 (24.7)
Yes	128 (72.3)	155 (54.2)	78 (69.6)	43 (72.8)	113 (75.3)
Cirrhosis, n (%)[a]					
No	124 (70.1)	228 (79.7)	74 (66.1)	30 (50.9)	83 (55.3)
Yes	53 (29.9)	58 (20.3)	38 (33.9)	29 (49.1)	67 (44.7)
History Prior Decompensation, n (%)[b]					
No	162 (91.5)	275 (96.1)	103 (92.0)	52 (88.1)	142 (94.7)
Yes	15 (8.5)	11 (3.9)	9 (8.0)	7 (11.7)	8 (5.3)

Table 1. Continued

Covariates	San Diego, CA (n = 177)	La Coruña, Spain (n = 286)	Madrid, Spain (n = 112)	Sassari, Italy (n = 59)	Vigo, Spain (n = 150)
HIV Viral Load in Copies/mL, n (%)[a]					
>50	11 (6.2)	64 (22.4)	6 (5.4)	9 (15.3)	3 (2.0)
≤50	166 (93.8)	222 (77.6)	106 (94.6)	50 (84.8)	147 (98.0)
HCV Viral Load IU/mL, n (%)[a]					
>700 000	125 (70.6)	81 (28.3)	80 (71.4)	38 (64.4)	111 (74)
≤700 000	52 (29.4)	205 (71.7)	32 (28.6)	21 (35.6)	39 (26)
Age (years), mean (95% CI)	50.8 (49.3–52.3)	46.3 (45.3–47.4)	51.7(50.6–52.9)	54. 2 (52.9–55.5)	51.3 (50.3–52.3)
Log_{10} HCV viral load, mean (95% CI)	6.1 (6.1–6.4)	5.4 (5.1–5.5)	6.1 (6.1–6.5)	6.0 (5.9–6.4)	6.2 (6.1–6.4)
Charlson Comorbidity Score, mean (95% CI)	5.5 (4.9–6.1)	8.3 (8.2–8.5)	2.3(1.9–2.7)	2.1 (1.7–2.5)	4.4 (3.9–4.7)
CD4 before DAA initiation, mean (95% CI)	558.2 (512.1–604.3)	433.9 (405.7–462.0)	603.5 (539.9–667.0)	869.3 (737.5–1001.1)	547.3 (489.9–604.8)

Abbreviations: CI, confidence interval; DAA, direct-acting antivirals; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MSM, men who have sex with men; PrOD, paritaprevir/ritonavir-ombitasvir and dasabuvir.

[a]$P < .0001$.

[b]$P < .001$.

mental illness (OR = 2.85; 95% CI, 1.26–6.41) as the only independent predictors for any HCV treatment failure. Ongoing drug use and mental illness were also predictors of DAA clinical failure. The only factors associated with HCV virologic treatment failure were having advanced F3 or F4 liver fibrosis staging (OR = 2.29; 95% CI, 1.15–4.56) and ongoing drug use (Table 3). Table 4 presents estimates of effect for factorial additive interactions between the covariates selected in the final stepwise models. For each outcome model, the effect of both risk factors together was more than twice the effect of either alone. Although the measures reported for additive interaction (RERI, AP, SI) were not significant at conventional levels, power was limited to detect such interactions. For the 3 outcomes modeled, with 2-sided alpha = 0.05 and n = 784 patients, the post hoc power to detect multiplicative and additive interactions (RERI) was 0.58 and 0.22 for any failure, 0.24 and 0.09 for clinical failure, and 0.17 and 0.09 for virologic failure, respectively.

DISCUSSION

In this international cohort of PLWH coinfected with HCV treated with DAAs, we observed high rates of HCV cure (93% overall, including 91.4% of PLWH with cirrhosis) similar to other real-world HCV-coinfected cohorts [18–20] and despite the high prevalence of ongoing barriers to care in our cohort. Among the 7% of patients who failed therapy, patient-related factors prompting premature DAA discontinuation predominated over DAA virologic failure.

The fact that patients with ongoing drug use and mental illness were independent predictors of DAA treatment failure should not be interpreted as a contraindication to treat these patients with DAAs, because most (above 85%) were cured of HCV infection. Our observation that having concurrent drug use and mental illness could account for 20% of HCV treatment failure risk attributable to interaction reinforces similar observations in the HIV literature, pointing out that social conditions such as ongoing drug use and psychosocial syndemics are associated with poor HIV treatment outcomes [21, 22]. Our findings also suggest that although current DAA treatments are as short as 8 weeks of treatment duration, these groups of PLWH would benefit from enhanced clinical follow-up during HCV therapy to maximize DAA adherence, completion, and treatment success through ongoing support and services.

Our results are in line with recent Italian, German, and Spanish HCV multicenter cohorts that found that a subset of PLWH with advanced liver fibrosis have higher rates of DAA virologic failure compared with those without cirrhosis [7, 8, 19]. Unlike the German and Spanish cohorts that identified that low CD4 cell counts (<350 and <200 for the German and Spanish cohorts, respectively) were associated with higher chances of DAA virologic failure, we did not observe a negative effect of low CD4 counts on SVR among PLWH. Although 31% of participants in our cohort had CD4 counts below 350 (unlike 17% in the German cohort), there were fewer patients with CD4 cell counts less than 200 compared with the prior cohorts (11.7% vs 15%) and thus could account in part for the observed differences. Unlike ours, none of the earlier cohorts reported the frequency of patient-related factors such as ongoing drug use that could also affect compliance with DAA regimens. Indeed, we observed that ongoing drug use was an independent factor of DAA failure and additive to the presence of advanced liver fibrosis for the risk of HCV virologic failure.

Race was not associated with DAA treatment response in our study, in line with results from of a pooled analysis of clinical trials [23]. Our finding contrast with results from studies conducted at the Veterans Affair (VA) healthcare system that observed that nonwhites participants (Black and Hispanics) had fewer odds of achieving SVR than white patients when treated with DAA [24, 25]. The VA studies included less than 4% of PLWH and noted that inadequate

Table 2. Bivariate Comparisons of Predictors of Any HCV Treatment Failure Using Direct-Acting Antivirals in People Living With HIV

	Failure	No Failure	Total	
Covariates	n = 55 (7.1%)	n = 729 (92.2%)	n = 784 (100%)	*P* Value
DAA Regimen-Simplified, n (%)				
Sofosbuvir plus ribavirin	1 (1.8)	15 (2.1)	16 (2.0)	.23
Sofosbuvir plus ledipasvir ± ribavirin	25 (44.5)	340 (46.6)	365 (46.6)	
Sofosbuvir plus simeprevir ± ribavirin	9 (16.4)	56 (7.7)	65 (8.3)	
Sofosbuvir plus daclatasvir ± ribavirin	5 (9.1)	42 (5.8)	47 (5.9)	
PrOD ± RBV	2 (3.6)	73 (10.0)	75 (9.6)	
Sofosbuvir plus velpatasvir ± ribavirin	8 (14.6)	119 (16.3)	127 (16.2)	
Ombitasvir/paritaprevir/ritonavir + ribavirin	0 (0)	18 (2.5)	18 (2.3)	
Grazoprevir/elbasvir	0 (0)	13 (1.8)	13 (1.7)	
Glecaprevir/pibrentasvir	5 (9.1)	53 (7.3)	58 (7.4)	
Gender, n (%)				
Female	8 (14.5)	184 (25.8)	192 (24.5)	.08
Male	47 (85.5)	545 (74.8)	592 (75.5)	
Race/Ethnicity, n (%)				
Nonwhite,	3 (5.5)	30 (4.1)	33 (4.2)	.63
White	52 (94.5)	699 (95.9)	751 (95.8)	
HIV Risk Factor, n (%)				
Men who have sex with men (MSM)	3 (5.5)	69 (9.5)	72 (9.2)	.47
Heterosexual	9 (16.4)	74 (10.2)	83 (10.6)	
Hemophilia	1 (1.8)	10 (1.4)	11 (1.4)	
MSM + intravenous drug use (IDU)	4 (7.3)	28 (3.8)	32 (4.1)	
Heterosexual + IDU	36 (65.5)	516 (70.8)	552 (70.4)	
Other	2 (3.6)	32 (4.4)	34 (4.3)	
Active Alcohol, Baseline, n (%)				
No	33 (60.0)	516 (70.8)	549 (70.0)	.09
Yes	22 (40.0)	213 (29.2)	235 (30.0)	
Active Illegal Drugs, Baseline, n (%)				
No	26 (47.3)	553 (75.9)	579 (73.9)	<.001
Yes	29 (52.7)	176 (24.1)	205 (26.1)	
Active Intravenous Drug Use, Baseline, n (%)				
No	44 (78.6)	672 (92.3)	716 (91.3)	<.001
Yes	12 (21.4)	56 (7.7)	68 (8.7)	
Unstable housing, n (%)				
No	44 (80.0)	664 (91.1)	708 (90.3)	.007
Yes	11 (20.0)	65 (8.9)	76 (9.7)	
Active Mental Illness n (%)				
No	24 (43.6)	541 (74.2)	565 (72.1)	<.001
Yes	31 (56.4)	188 (25.8)	219 (27.9)	
HCV genotype (grouped), n (%)				
1/1a/1b	43 (78.2)	512 (70.2)	555 (70.8)	.44
2/2b	1 (1.8)	17 (2.3)	18 (2.3)	
3/3a/3b	7 (12.7)	89 (12.2)	96 (12.2)	
4	4 (7.3)	111 (15.2)	115 (15.2)	
Fibrosis score, n (%)				
F0–2	23 (41.8)	395 (54.2)	418 (53.3)	.08
F3–4	32 (58.2)	334 (45.8)	366 (46.7)	
HCV Treatment Naive, n (%)				
No	20 (36.4)	247 (33.9)	267 (34.1)	.71
Yes	35 (63.6)	482 (66.1)	517 (65.9)	
Cirrhosis, n (%)				
No	35 (63.6)	504 (69.1)	539 (68.8)	.40
Yes	20 (36.4)	225 (30.9)	245 (31.2)	
History of Liver Decompensation, n (%)				
No	50 (90.9)	684 (93.8)	734 (93.6)	.39
Yes	5 (9.1)	45 (6.2)	50 (6.4)	
Cohort, n (%)				

Table 2. Continued

Covariates	Failure n = 55 (7.1%)	No Failure n = 729 (92.2%)	Total n = 784 (100%)	*P* Value
San Diego, CA	17 (30.9)	160 (22.0)	177 (22.6)	.24
La Coruña, Spain	17 (30.9)	269 (36.9)	286 (36.5)	
Madrid, Spain	10 (18.2)	102 (14.0)	112 (14.3)	
Sassari, Italy	1 (1.8)	58 (7.9)	59 (7.5)	
Vigo, Spain	10 (18.2)	140 (19.2)	150 (19.1)	
HIV Viral Load in Copies/mL, n (%)				
>50	8 (14.5)	85 (11.7)	93 (11.9)	.52
≤50	47 (85.5)	644 (88.3)	691 (88.1)	
HCV Viral Load IU/mL, n (%)				
>700 000	32 (58.2)	403 (55.3)	435 (55.5)	.68
≤700 000	23 (41.8)	326 (44.7)	349 (44.5)	
CD4 Cell Count/mm^3				
0–199	5 (9.1)	86 (11.8)	91 (11.6)	.83
200–349	11 (20.0)	147 (20.2)	158 (20.2)	
≥ 350	39 (70.9)	496 (68.0)	535 (68.2)	
Age (years), mean (95% CI)	49.1 (46.9–51.3)	49.7 (49.1–50.2)	49.7 (49.1–50.2)	.49
Log_{10} HCV viral load, mean (95% CI)	5.9 (5.7–6.10	5.8 (5.7–5.9)	5.8 (5.7–5.9)	.48
Charlson Comorbidity Score, mean (95% CI)	5.8 (4.9–6.7)	5.6 (5.4–5.8)	5.6 (5.4–5.8)	.68
CD4 before DAA initiation, mean (95% CI)	465.4 (403.8–526.9)	546.3 (521.2–571.5)	540.6 (516.8–564.5)	.23

Abbreviations: CI, confidence interval; DAA, direct-acting antivirals; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PrOD, paritaprevir/ritonavir-ombitasvir and dasabuvir; RBV, ribavirin.

adherence to DAAs assessed by the medication/possession ratio mitigated the effect of race on SVR [25]. One reason to reconcile the discrepancy of the effect of race on SVR between the VA studies and ours is the different methods used to assess illegal drug use and mental illness that are known factors that influence medication treatment adherence [26, 27]. The VA studies used historical ICD codes, unlike our study that ascertained them using screening inventories at the time of initiating DAA. Another reason is the difference in the duration of certain DAA regimens. Unlike the VA studies, short courses of DAA therapy (8 weeks) using sofosbuvir/ledipasvir were not used in our study because they were not recommended for treating HCV in PLWH. Hence, even if PLWH had imperfect DAA adherence but did not discontinue their therapy during their first 8 weeks of therapy, the longer DAA treatment duration might have allowed them to increase their chances of achieving SVR. This could explain why the observed significant effect of race on SVR using DAA in the VA studies disappeared after extending sofosbuvir/ledipasvir therapy from 8 to 12 weeks [24, 25].

Our study has important limitations. First, we did not collect urine toxicology tests, and risk-behavior collection relied on patient self-report. Underreporting due to social desirability bias is a limitation of self-collected risk inventories [28]. We performed individual medical record review to supplement with clinically documented risk behaviors information, but underestimation of the burden of substance use in our population is possible. Second, we lack systematic measures of DAA adherence to correlate with the study outcomes. One study found that mental illness did not impact DAA adherence, but recent drug use was a risk factor for

Table 3. Adjusted Odds Ratios (95% CI) for Modeled Covariates on Predictors of Hepatitis C Treatment Failure Among People Living With HIV in the HCV-TREN Cohort[a]

Covariates	Any Failure	Clinical Failure	Virologic Failure
Ongoing Mental illness	2.85[b] [1.26–6.41]	2.78[c] [1.71–4.52]	
Ongoing any drug use	2.60[d] [1.79–3.79]	3.13[d] [1.34–7.29]	2.75[d] [1.80–4.19]
F3/F4 liver fibrosis stage			2.29[b] [1.15–4.56]
ROC area	0.71	0.73	0.67
Hosmer-Lemeshow *P* value	.72	.63	.84
Observations	784	757	755

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ROC, receiver operating characteristic; TREN, Transatlantic Research Network.

[a]Exponentiated coefficients; 95% confidence intervals in brackets. Covariates significant at <0.10 in bivariate analysis entered stepwise backward selection model.

[b]$P < .05$.

[c]$P < .01$.

[d]$P < .001$.

Table 4. Models of Additive Interactions Between Significant Covariates for Prediction of HCV Treatment Failure Among Patients Living With HIV in the HCV-TREN Cohort

Any HCV Treatment Failure			HCV Clinical Treatment Failure		HCV Virologic Treatment Failure	
	OR Estimate (95% CI)	*P* Value	OR Estimate (95% CI)	*P* Value	OR Estimate (95% CI)	*P* Value
Any drugs, NOT Mental illness	3.35 (1.45–7.78)	.005	4.70 (1.48–14.87)	.009		
Mental illness, NOT Any drugs	3.57 (1.61–7.95)	.002	4.17 (1.32–13.18)	.015		
Any drugs AND Mental illness	7.47 (3.60–15.50)	<.0001	9.18 (3.25–25.95)	<.0001		
Any drugs, NOT F3/F4 fibrosis					3.79 (0.99–14.39)	.050
F3/F4 fibrosis, NOT Any drugs					2.90 (0.90–9.36)	.075
Any drugs AND F3/F4 fibrosis					6.66 (1.90–23.34)	.003
Relative excess risk due to interaction (RERI)[a]	1.55 (−3.39 to 6.38)	.53	1.31 (−6.63 to 9.26)	.75	0.97 (−5.45 to 7.42)	.77
Attributable proportion[b]	0.20 (−0.37 to 0.78)	.48	0.14 (−0.66 to 0.95)	.73	0.15 (−0.75 to 1.04)	.75
Synergy index[c]	1.31 (0.56–3.10)	.53	1.19 (0.41–3.45)	.75	1.21 (0.35–4.23)	.77

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; OR, odds ratio; TREN, Transatlantic Research Network.

[a]RERI is also sometimes referred to as the "interaction contrast ratio" and gives the direction (positive, negative, or zero) of the additive interaction. Only the direction, rather than the magnitude of RERI, is needed to draw conclusions about the public health relevance of interaction.

[b]Attributable proportion is another measure of additive interaction and essentially measures the proportion of the risk in the doubly exposed group that is due to the interaction itself.

[c]Synergy index measures the extent to which the risk ratio for both exposures together exceeds 1, and whether this is greater than the sum of the extent to which each of the risk ratios considered separately each exceeds 1 (reference [15]).

nonadherence [27]. A limitation of the few studies that measured DAA adherence confidently is that they relied on monitoring tools that may promote participants compliance [29], and patients who do not return adherence tools or abandoned therapy often are excluded from final analyses. Third, our definition of ongoing mental illness (except for PHQ-9 score ≥9) was not standardized. Many studies of mental illness and HIV outcomes have focused on historical psychiatric diagnosis [30], and, given the high prevalence of mental illness in PLWH [31], we consider that it is clinically important to use a measure of disease severity ascertainment. Our criteria could underestimate the burden of mental illness due to providers underreporting in medical records. Fourth, we did not use phylogenetic analysis to differentiate whether patients with HCV virologic failure, in reality, could have been reinfected with HCV. In our cohort, all but 1 patient had an HCV viral relapse that occurred within the first 5 weeks of finishing DAA treatment, consistent with what others have reported that most of the cases of recurrent HCV viremia occurred early after stopping treatment [32]. Finally, the generalizability is also limited due to the small proportion of nonwhite patients studied in this cohort.

Our results highlight that to achieve HCV elimination in PLWH, it is necessary to individualize DAA treatment protocols based on patients' needs using available local infrastructure [33]. A group of our patients would likely benefit from enhanced support and education to finish DAA therapy successfully and facilitate harm-risk behavior reduction to minimize the risk of HCV reinfection [34]. These efforts need to emphasize interdisciplinary collaboration to leverage scarce resources in many healthcare settings.

CONCLUSIONS

In conclusion, we found that PLWH with complex barriers to care can be treated successfully with DAA. People living with HIV with ongoing illicit drug use and mental illness, in particular, and those with advanced liver fibrosis might benefit from enhanced DAA treatment support to prevent the risk of HCV treatment failure.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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