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MAJOR ARTICLE

Effectiveness of Direct-Acting Antiviral Therapy in Patients With Human Immunodeficiency Virus–Hepatitis C Virus Coinfection in Routine Clinical Care: A Multicenter Study

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Background. Direct-acting antiviral (DAA) therapy have been shown to be highly successful in clinical trials and observational studies, but less is known about treatment success in patients with a high burden of comorbid conditions, including mental health and substance use disorders. We evaluated DAA effectiveness across a broad spectrum of patients with human immunodeficiency virus (HIV)–hepatitis C virus (HCV) coinfection in routine clinical care, including those with psychosocial comorbid conditions.

Methods. The primary end point was sustained virologic response (SVR), defined as HCV RNA not detected or <25 IU/mL ≥10 weeks after treatment. We calculated SVR rates and 95% confidence intervals (CIs) in a modified intent-to-treat analysis. We repeated this analysis after multiply imputing missing SVR values.

Results. Among 642 DAA-treated patients, 536 had SVR assessments. The median age was 55 years; 79% were men, 59% black, and 32% white. Cirrhosis (fibrosis-4 index>3.25) was present in 24%, and 17% were interferon treatment experienced; 96% had genotype 1 infection and 432 (81%) had received ledipasvir-sofosbuvir. SVR occurred in 96.5% (95% CI, 94.5%–97.9%). Patients who were black, treatment experienced, or cirrhotic all had SVR rates >95%. Patients with depression and/or anxiety, psychotic disorder, illicit drug use, or alcohol use disorder also had high SVR rates, ranging from 95.4% to 96.8%. The only factor associated with lower SVR rate was early discontinuation (77.8%; 95% CI, 52.4%–93.6%). Similar results were seen in multiply imputed data sets.

Conclusions. Our study represents a large multicenter examination of DAA therapy in HIV/HCV-coinfected patients. The broad treatment success we observed across this diverse group of patients with significant comorbid conditions is highly affirming and argues for widespread implementation of DAA therapy.

Key words. direct-acting antiviral; hepatitis C virus; HIV.

Chronic hepatitis C virus (HCV) infection is common among persons living with human immunodeficiency virus (HIV) infection (PLWH), with prevalence ranging from 15% to as high as 80% among those with a history of injection drug use (IDU) [1–3]. Coinfection with HIV can accelerate the progression of hepatic fibrosis in HCV and result in a more aggressive course of liver disease [4]. Liver disease remains a major cause of non–AIDS-related deaths among PLWH, with up to 80% of deaths attributable to HCV infection [5]. Although HCV treatment should have high priority in PLWH, historically, uptake was limited due to poor treatment outcomes, adverse effects of interferon-based therapy, and comorbid conditions, such as psychiatric conditions and substance use disorders [6].

Interferon-free direct-acting antiviral (DAA) regimens have transformed the HCV treatment landscape since their introduction in 2014, with rates of sustained virologic response (SVR) exceeding 90%. Clinical trial data suggest these safe, well-tolerated regimens have comparable high efficacy in HIV/HCV-coinfected and HCV-monoinfected patients [7]. However, clinical trials of HIV/HCV-coinfected patients were predominantly open-label studies with small numbers of participants and strict eligibility criteria. Patients with drug and alcohol use or medical and psychiatric disorders deemed by investigators to affect study adherence could have been excluded [8–10]. One Canadian study reported that only 6%–10% of their HIV/HCV-coinfected population would have been eligible for these trials [11].

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Observational studies of DAA therapy have reported comparable SVR rates among HIV/HCV-coinfected and HCV-monoinfected patients [12–16], but less is known about real-world treatment outcomes in those with psychiatric disorders or active substance use. DAA effectiveness needs to be examined specifically in these key high-risk patients who face ongoing barriers to HCV treatment [14, 17]. In this multicenter cohort study, we sought to evaluate the effectiveness of all-oral combination DAA therapy among HIV/HCV-coinfected patients in routine clinical care, including those with psychosocial comorbid conditions.

METHODS

Study Population

The Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) is a dynamic prospective clinical cohort of adult PLWH receiving care at 8 participating academic sites across the United States. Comprehensive clinical data collected through electronic medical records and other institutional data systems undergo rigorous quality assessment, are harmonized in a central repository, and are updated on a quarterly basis [18]. The CNICS Data Management Core at the University of Washington works closely with investigators, clinicians and data teams at each site to ensure comprehensive capture of DAA treatment data. Institutional review boards at each site approved the cohort protocol, and the University of Washington institutional review board approved this study.

Patients who received 1 of the following interferon-free DAA regimens (daclatasvir plus sofosbuvir, simeprevir plus sofosbuvir, ledipasvir-sofosbuvir, ombitasvir-paritaprevir-ritonavir with dasabuvir, elbasvir-grazoprevir, sofosbuvir-velpatasvir) and completed therapy before the administrative censor date (4 months before the last available laboratory data for each CNICS site) were eligible for inclusion. For those who received multiple courses of DAA therapy, only the first course was examined. The choice of DAA was based on provider discretion and drug availability, as would occur in routine clinical care. Patients who received treatment as part of a clinical trial or before the respective Food and Drug Administration approval date of these drugs were excluded. Regimens with concurrent ribavirin were noted and included in the analysis.

Outcome Measures

The primary end point was SVR, defined as an HCV RNA level that was not detected or <25 IU/mL ≥10 weeks after the end of treatment. RNA reported below the limit of detection was defined as the median of 0 and the limit of detection. Due to variability in the timing of testing seen in a clinical setting, we included HCV RNA levels collected 2 weeks earlier than the standard 12 weeks after treatment in our primary analysis (as has previously been done [12, 19]); RNA measurements beyond week 4–8 of treatment have high correlation with SVR at 12 weeks (SVR12) [20]. We also examined a strict definition of SVR12 in a secondary analysis. Treatment failure (among those undergoing posttreatment testing) was defined as HCV RNA ≥25 IU/mL ≥4 weeks after completion of therapy. Viral relapse was defined as ≥1 HCV RNA measurement <25 IU/mL during and/or at end of treatment with subsequent detectable HCV RNA after treatment in the absence of SVR.

Patient Characteristics

Demographic characteristics included sex, race/ethnicity, HIV transmission risk category, and age at baseline. The CD4 cell count, HIV RNA, HCV RNA, HCV genotype and fibrosis-4 (FIB-4) components (platelet count and serum alanine and aspartate aminotransferase levels) represented the most recent values before the DAA start, and HIV RNA measurements were restricted to within 1 year before DAA start. Chronic hepatitis B virus coinfection was defined as the presence of either hepatitis B surface antigen or detectable hepatitis B virus DNA. Cirrhosis was defined as an FIB-4 index >3.25 [21]. Patients who received interferon (pegylated interferon alfa-2a or alfa-2b or standard interferon) and/or ribavirin before the DAA initiation date were noted to have treatment experience. Diabetes mellitus was defined as a diagnosis of diabetes mellitus recorded by the treating clinician and the use of diabetes-related medication, use of diabetes-specific medication, or hemoglobin A1C measurement ≥6.5%. Obesity was defined as a body mass index >30 kg/m^2.

Mental health disorder was considered present if the diagnosis was recorded any time by the treating clinician before the DAA start date, and was examined separately as: (1) depression and/or anxiety or (2) psychotic disorders (psychosis, schizophrenia, schizoaffective disorder). Illicit substance use included diagnoses of methamphetamine, cocaine or opiate use disorder and alcohol use disorder included diagnoses of alcohol abuse or dependence [22], all recorded before DAA start. We also evaluated current substance use among patients who completed a patient-reported outcome (PRO) clinical assessment, described elsewhere [23], using the latest date from 1 year before DAA start to the end of DAA treatment. At-risk alcohol use was defined as an Alcohol Use Disorders Identification Test (AUDIT-C) score ≥4 for men and ≥3 for women [24]. Illicit drug use was defined as current use of cocaine, opiates, or methamphetamines noted on the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) questionnaire [25]. Early treatment discontinuation (ETD) was defined as duration of therapy (difference between end and start dates) <70 days (<10 weeks), among patients who received <120 days of therapy.

Statistical Analysis

In the main analysis, SVR rates were calculated as the proportion of patients with SVR among those who underwent SVR

assessment, in a modified intent-to-treat analysis. We compared baseline characteristics of patients with or without SVR assessment, using the Mann-Whitney test for continuous and the χ^2 test for categorical variables. We calculated SVR rates and 95% confidence intervals (CIs) for the overall cohort as well as for subgroups of patients defined by prespecified characteristics. The χ^2 test was also used to assess differences in SVR rates between select subgroups. Analyses were conducted using Stata software, version 14.2.

To evaluate whether our complete case analysis was subject to bias, missing values in SVR and other covariates were multiply imputed with chained equations using fully conditional specification with R package mice (R software; version 3.4.4). Imputation models relied on classification and regression trees [26] and incorporated key covariates as well as treatment duration and follow-up. This process yielded 100 complete data sets. For each complete data set, SVR rates and CIs were calculated, and resulting inferences were pooled using Rubin's rules [27].

RESULTS

In total, 642 patients with HIV/HCV coinfection received 1 of the specified DAA regimens from February 2014 to October 2017. Of these, 536 underwent posttreatment SVR assessment as part of routine clinical care and comprised the main analytic cohort. The patients' median age was 55 years; 79% were men, and 59% were black (Table 1). The distribution of HIV risk factor categories was as follows: 25% men who have sex with men (MSM), 42% IDU, and 14% MSM and IDU. The median CD4 cell count was 540/μL; 496 (98%) of 508 patients who had an HIV viral load assessment within 1 year before starting DAA therapy had an HIV viral load <200 copies/mL. Among the 467 patients (87%) receiving antiretroviral therapy at baseline, >70% had regimens that contained integrase strand transfer inhibitors. Compared with other HIV/HCV-coinfected patients in care at this time, the study cohort was similar in age, sex, race, HIV risk factor, baseline CD4 cell count, and prevalence of mental health and substance use diagnoses.

Among the 507 patients with HCV genotype results available, nearly all (96%) had genotype 1 infection; 69% had genotype 1a, 24% had genotype 1b, and 3% had no subtyping. Cirrhosis was present in 24%, and a baseline HCV RNA level >6 million IU/mL was observed in 21%. Prior treatment experience with interferon-based therapy was documented in 17%.

Consistent with clinical practice during this time frame, 80% of patients (n = 432) received ledipasvir-sofosbuvir, and the rest received simeprevir plus sofosbuvir (n = 41), sofosbuvir-velpatasvir (n = 24), daclatasvir plus sofosbuvir (n = 14), ombitasvir-paritaprevir-ritonavir plus dasabuvir (n = 13), or elbasvir-grazoprevir (n = 12). Only 6% of patients (n = 33) received ribavirin concurrently; a third of these patients received ombitasvir-paritaprevir-ritonavir plus dasabuvir with the ribavirin, as might be expected, given the predominance of genotype 1a infection.

The duration of therapy clustered predominantly around 12 weeks (84 days; interquartile range, 84–85 days) and 24 weeks (168 days; 167–168 days). Among the 476 patients with a treatment duration <120 days, only 18 (3.8%) discontinued treatment early (before 70 days or 10 weeks), with a median duration of 45 days (range 19–61 days).

The 106 patient (16.5%) who did not have SVR results did not differ from the study cohort in age, sex, race, HIV risk factor, or key clinical characteristics (proportion with CD4 cell count <200/μL , HIV RNA <200 copies/mL, FIB-4 index >3.25, and mental health and substance use diagnoses). The duration of DAA treatment in these patients was comparable to that in the study cohort, but they had fewer HCV measurements during treatment (median, 1 vs 2, respectively) and shorter median follow-up after DAA start (227 vs 673 days). Among the 106 patients without SVR measurements, 52 (49%) had HCV RNA not detected or <25 IU/mL at the end of treatment (n = 30) or ≥4 weeks after treatment (n = 22).

Sustained Virologic Response

Overall, SVR occurred in 517 patients, for an SVR rate of 96.5% (95% CI, 94.5%–97.9%) (Table 2). All 19 patients without SVR were confirmed to have treatment failure and evidence of detectable HCV RNA >25 IU/mL ≥4 weeks after the end of DAA therapy. Of these, 13 had viral relapse, 5 had missing HCV RNA measurements during treatment, and 1 had a single low-detectable HCV RNA measurement during treatment before meeting criteria for treatment failure.

SVR rates were examined within key subgroups. Among HCV-specific factors, we found no significant difference by genotype (or subtype), but genotype other than 1 was present in only 4% of those treated. Notably, patients who had potential risk factors for suboptimal treatment response, including high baseline HCV RNA (>6 million IU/mL), cirrhosis (FIB-4 index >3.25), prior treatment experience (pegylated interferon with or without ribavirin), obesity (body mass index >30 kg/m^2), or diabetes mellitus all had high SVR rates, exceeding 95%. Black patients comprised the majority of our cohort and had an SVR rate of 97.2%.

We observed no statistically significant difference in SVR rates between groups stratified by HIV-specific factors, including baseline CD4 cell count <200/μL (92.1%) or ≥200/μL (96.8%; $P = .13$). SVR was achieved in all 13 patients with baseline HIV RNA ≥200 copies/mL.

We also observed high SVR rates in those with a history of mental health or substance use disorders. Among patients with a diagnosis of depression and/or anxiety (n = 374), 96.3% had SVR. Among those with a diagnosis of a psychotic disorder (n = 65), 95.4% had SVR. Patients with a history of either

Table 1. Baseline Characteristics of 536 Patients With Human Immunodeficiency Virus–Hepatitis C Virus Coinfection Treated with Interferon-Free Direct-Acting Antiviral Regimens, 2014–2017

Characteristic	Patients, No. (%)[a]
Age, median (range), y	55 (26–75)
Male sex	426 (79)
Race/ethnicity	
White	170 (32)
Black	315 (59)
Hispanic	34 (6)
Other	15 (3)
HIV risk factor category	
MSM	132 (25)
IDU	228 (42)
MSM and IDU	74 (14)
Heterosexual	85 (16)
Other/unknown	11 (2)/6 (1)
CD4 cell count	
<200/μL	38 (7)
200–499/μL	205 (38)
≥500/μL	293 (55)
Antiretroviral therapy[b]	467 (87)
Tenofovir disoproxil fumarate	270 (58)
Dolutegravir	218 (47)
Abacavir	165 (35)
Raltegravir	95 (20)
Darunavir	91 (19)
Efavirenz	60 (13)
Rilpivirine	56 (12)
Atazanavir	40 (8.6)
Cobicistat-elvitegravir	25 (5.4)
HIV RNA <200 copies/mL[c]	496 (98)
Chronic hepatitis B	54 (10)
Body mass index >30 kg/m^2	131 (25)
Diabetes mellitus[d]	105 (20)
HCV RNA >6 million IU/mL	111 (21)
Fibrosis-4 index >3.25	128 (24)
Prior treatment experience	90 (17)
HCV genotype (n = 507)	
1a	352 (69)
1b	120 (24)
1 not subtyped	15 (3)
2	7 (1)
3	9 (2)
4	4 (1)
DAA regimen	
Ledipasvir-sofosbuvir	432 (81)
Simeprevir + sofosbuvir	41 (8)
Sofosbuvir-velpatasvir	24 (4)
Daclatasvir + sofosbuvir	14 (3)
Ombitasvir-paritaprevir-ritonavir + dasabuvir	13 (2)
Elbasvir-grazoprevir	12 (2)
Concurrent ribavirin	33 (6)
Mental health disorder	
Depression and/or anxiety	374 (70)
Psychotic condition	65 (12)
Substance use disorder	
Illicit drugs (amphetamine, cocaine, opiate)	251 (47)
At-risk alcohol	185 (35)

Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men.

[a]Data represent no. (%) of patients unless otherwise specified.

[b]Antiretroviral therapy categories represent the no. (%) of patients with these agents in their regimen among the 467 patients receiving antiretroviral therapy, recorded before DAA start.

[c]Among the 508 patients who had HIV RNA level assessed within 1 year of DAA start. The CD4 cell count, HIV and HCV viral levels, and fibrosis-4 index represented the most recent values before the DAA start date.

[d]Diabetes mellitus was defined as a diagnosis of diabetes mellitus and use of diabetes-related medication, use of diabetes-specific medication, or hemoglobin A1C ≥6.5%.

illicit drug use or alcohol use disorder before DAA initiation also achieved high SVR rates of 96.4% and 96.8% respectively. Although mental health and substance use disorders can co-occur with potentially greater comorbidity, we observed similar high SVR rates in the subset of patients with depression and/or anxiety and either illicit drug use or alcohol use disorder.

We also evaluated current substance use among the 334 patients (62%) who completed a PRO survey. Among the 40 (12%) who endorsed current illicit drug use, 97.5% (95% CI, 86.8%–99.9%) had SVR, as did all 37 (11%) of those who reported current at-risk drinking by AUDIT-C.

The only factor associated with lower SVR rates was ETD. SVR rate was 77.8% (95% CI, 52.4%–93.6%) among the 18 individuals who had ETD, compared with 96.7% among those who did not ($P < .001$). Among these 18 patients, 4 experienced treatment failure; their duration of therapy ranged from 4 to 6 weeks (26–41 days). In contrast, of the 14 patients with ETD who had SVR despite a shortened course of treatment, only 5 (36%) had durations <6 weeks ($P = .02$). We did not identify any baseline factors (demographic, HIV specific. or liver related) that distinguished patients with ETD from the rest of our cohort.

Secondary Analyses

When we evaluated the SVR outcome more strictly as HCV RNA <25 IU/mL ≥12 weeks after treatment discontinuation, our findings were similar for the 514 participants who had an assessment of SVR12, with a high overall SVR rate of 96.5% (95% CI, 94.5%–97.9%).

In addition, we examined the entire cohort of 642 patients, including the 106 who with missing SVR assessments. When we used multiple imputation to derive missing SVR values using baseline as well as during-treatment characteristics including duration of treatment and follow-up, the pooled SVR rate was 95.9% (95% CI, 94.1%–97.6%), similar to the observed SVR rate of 96.5% in the main cohort (Supplementary Table 1). We found a similarly lower SVR rate of 75% (95% 55, 95.1) among those with ETD. SVR estimates for key subgroups, including those with mental health or substance use, disorders were also comparable.

DISCUSSION

In this multicenter study of HIV/HCV-coinfected patients who received DAA therapy as part of routine clinical care, we observed a high overall SVR rate of 96.5%. This cohort included a wide spectrum of patients, some with poor prognostic features for treatment outcome, including advanced fibrosis, high baseline HCV viral level, and prior treatment experience. Response rates were consistently high across the subgroups evaluated, including those with mental health and substance use disorders, generally exceeding 95%. We observed a low ETD rate, with only 3.8% stopping therapy before 10 weeks, supporting the excellent safety profile and tolerability of these agents. The only factor associated with treatment failure in our study was ETD.

Table 2. Sustained Virologic Response Rates in Patients With Human Immunodeficiency Virus–Hepatitis C Virus Coinfection Treated with Interferon-Free Direct-Acting Antiviral Regimens, Overall and by Key Subgroups

Group	Patients, No. (%)	SVR Rate (95% CI), %
Overall	536 (100)	96.5 (94.5–97.9)
DAA regimen		
Ledipasvir-sofosbuvir	432 (81)	97.0 (94.9–98.4)
Simeprevir + sofosbuvir	41 (8)	95.1 (83.5–99.4)
Sofosbuvir-velpatasvir	24 (4)	87.5 (67.6–97.3)
Daclatasvir + sofsobuvir	14 (3)	92.9 (66.1–99.8)
Ombitasvir-paritaprevir-ritonavir + dasabuvir	13 (2)	100 (75.3–100)[a]
Elbasvir-grazoprevir	12 (2)	100 (73.5–100)[a]
Ledipasvir-sofosbuvir by duration		
12 wk	380 (71)	96.6 (94.2–98.2)
24 wk	52 (10)	100 (93.2–100)[a]
Genotype		
1a	352 (66)	96.3 (93.8–98.0
1b	120 (22)	96.7 (91.7–99.1)
1 not subtyped	15 (3)	93.3 (68.1–99.8)
2	7 (1)	85.7 (42.1–99.6)
3	9 (2)	100 (66.4–100)[a]
4	4 (1)	100 (39.8–100)[a]
Missing	29 (5)	100 (88.1–100)[a]
Age >50 y	385 (72)	96.6 (94.3–98.2)
Female sex	110 (21)	97.3 (92.2–99.4)
Black	315 (59)	97.1 (94.6–98.7)
Body mass index >30 kg/m^2	131 (24)	97.7 (93.5–99.5)
Diabetes mellitus	105 (20)	96.2 (90.5–99.0)
Treatment experienced	90 (17)	98.9 (94.0–99.9)
Fibrosis-4 index >3.25	128 (24)	96.9 (92.2–99.1)
HCV RNA >6 million IU/mL	111 (21)	95.5 (89.8–98.5)
CD4 cell count <200/μL	38 (7)	92.1 (78.6–98.3)
Early treatment discontinuation[b]	18 (3)	77.8 (52.4–93.6)
Mental health disorder[c]		
Depression and/or anxiety	374 (70)	96.3 (93.8–97.9)
Psychotic condition	65 (12)	95.4 (87.1–99.0)
Substance use disorder[c]		
Illicit drug use (amphetamines, cocaine, opiates)	252 (47)	96.4 (93.3–98.4)
At-risk alcohol use	185 (35)	96.8 (93.1–98.8)
Combined mental health and substance use disorder[c]		
Depression and/or anxiety and illicit drug use	211 (39)	96.2 (92.7–98.3)
Depression and/or anxiety and at-risk alcohol use	157 (29)	96.2 (91.9–98.6)

Abbreviations: CI, confidence interval; DAA, direct-acting antiviral; HCV, hepatitis C virus; SVR, sustained virologic response.

[a]One-sided 97.5% CI.

[b]Duration <70 days among patients with treatment duration of <120 days.

[c]Mental health and substance use diagnoses recorded by treating clinician before DAA start.

Our findings are consistent with the high SVR rates reported in registration trials of DAA agents and suggest not only that these treatments are quite robust in real-world settings but that HIV status does not adversely affect treatment outcomes with all-oral regimens as it had with interferon-based therapy [1]. Notably, nearly all of our cohort had evidence of HIV viral suppression during antiretroviral therapy [28] before the start of DAA therapy, and the median CD4 cell count exceeded 500/μL, similar to findings among subjects in the DAA trials [8–10]. Other large-cohort studies in the Veterans Administration system and Europe have demonstrated high rates of effectiveness with DAA therapy in HIV/HCV-coinfected patients similar to that of HCV-monoinfected patients [12, 13, 16]. Together, these data support the shift away from considering patients with HIV-HCV coinfection a special "treatment-refractory" population [7].

Clinician-recorded mental health and substance use disorders were highly prevalent in our cohort, as might be expected of a real-world HIV/HCV-coinfected population [29], and did not seem to be associated with reduced likelihood of treatment success. We observed SVR rates exceeding 95% in patients with depression, anxiety, psychotic disorders, illicit drug use, or

alcohol use disorders. Moreover, those patients who endorsed current at-risk alcohol and drug use on PRO surveys also did very well. These conditions were historically among the leading reasons for treatment ineligibility in the interferon era [30]. We did not assess current IDU, but data from the interferon and DAA eras suggest that recent IDU does not impede treatment success [31–33]. The majority of states in the United States currently restrict DAA access to Medicaid beneficiaries with some form of sobriety restriction, mandating abstinence from drugs and/or alcohol for a specified period of time [34]. Our findings support the feasibility and success of DAA therapy among persons who are actively using drugs or in recovery. Because provider biases and structural barriers continue to complicate the care of persons who use or inject drugs (a group for which DAA treatment must be considered if HCV elimination is to be achieved [35]), it is critical to build an evidence base supporting widespread treatment in this population [17].

All of the CNICS sites that contributed participants to this analysis used a "medical home" model of DAA treatment delivery during our study time frame. That is, HCV treatment was not delegated to specialists outside the HIV clinic, as was typically done in the interferon-based era. This model of primary HCV care has been shown to be highly successful in a variety of care settings [15, 36–38] and may facilitate treatment uptake. However, barriers to successful DAA delivery persist even within well-resourced primary care clinics [39], due to lack of engagement and retention in care.

It is important to note that this represents the first wave of interferon-free DAA-treated individuals who were, even in the real-world setting, not wholly unselected, as their providers perhaps preferentially elected to treat them over other patients. It remains to be seen whether these DAAs are robust enough to perform as well in patients who were delayed in getting treated compared with their peers.

Limitations to our study warrant further discussion. Observational studies are vulnerable to misclassification and incomplete data. Unlike in a clinical trial, we were not able to provide data on adherence, adverse events, or reasons for ETD. We were unable to capture decompensated cirrhosis reliably in our data set or stratify based on this key characteristic. We had very few non–genotype 1 patients, so conclusions outside of genotype 1 may not be generalizable. The number of patients with active substance use by PRO survey was also small, so findings should be interpreted cautiously. Our use of mental health and substance use diagnoses may also suboptimally represent active conditions.

We also opted to evaluate DAA effectiveness as a modified intent-to-treat analysis of those patients who had an SVR assessment, rather than including all those who had no HCV RNA assessment and considering them as treatment failures. Although a full intent-to-treat analysis would reflect a more conservative estimate, this approach could also underestimate true effectiveness. It is possible that the patients who lacked SVR assessments represented those with inadequate adherence, loss to follow-up, or other poor prognostic indicators for treatment success, but the majority of these patients had ≥1 RNA measurement during treatment, and nearly half were undetectable at or after the end of therapy, which suggests engagement in care during treatment. Their baseline characteristics were also similar to those in patients who underwent SVR assessments. Thus, these patients may represent those who had not yet had their follow-up HCV viral testing, rather than actual treatment dropouts. Results of sensitivity analysis suggest that the exclusion of such patients was not likely to have introduced significant bias. Finally, there were too few individuals with treatment failure to evaluate predictors of DAA nonresponse.

Our study represents a large multicenter examination of DAA therapy of HIV/HCV-coinfected patients in routine clinical care. The broad treatment success we observed with DAAs across this diverse group of patients, including those with a variety of comorbid psychosocial conditions, is highly affirming and argues for the widespread implementation of DAA therapy. Further work needs to focus on optimizing HCV screening, linkage, and treatment uptake on a population-based level to overcome the multilevel barriers to HCV elimination. The lessons we have learned in reducing HIV-related morbidity and mortality rates should enhance care delivery for all persons living with HCV infection.

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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