

Improving HCV Cure Rates in HIV-Coinfected Patients—A Real-World Perspective

Seetha Lakshmi, MD; Maria Alcaide, MD; Ana M. Palacio, MD, MPH; Mohammed Shaikhomer, MD; Abigail L. Alexander, MS; Genevieve Gill-Wiehl, BA; Aman Pandey, BS; Kunal Patel, BS; Dushyantha Jayaweera, MD; and Maria Del Pilar Hernandez, MD

Globally, an estimated 30% of the 33 million people living with HIV infection also have hepatitis C virus (HCV) coinfection.¹ The natural history of HCV infection is altered in the HIV-infected host: patients with coinfection are half as likely to spontaneously clear HCV viremia, tend to have higher HCV ribonucleic acid (RNA) levels, and have accelerated progression to hepatic fibrosis and decompensated liver disease.^{2,3} Despite the use of antiretroviral therapy (ART), the proportion of deaths caused by HCV-related end-stage liver disease and hepatocellular carcinoma have increased in the HIV-infected population.⁴

Historically, patients coinfecting with HIV/HCV who are treated with interferon and ribavirin (IFN/RBV) for HCV had lower rates of sustained virological response (SVR) than those without HIV infection.⁵ In contrast to the IFN/RBV treatment, the direct-acting antivirals (DAAs) have demonstrated similar rates of HCV cure in monoinfected and coinfecting patients in clinical trials where strict follow-up is mandated.^{6,7} However, data on rates of HCV cure with the use of DAAs in patients coinfecting with HIV/HCV in real-world settings are lacking.

Treatment of HIV/HCV coinfection poses specific challenges, as it is preferred that patients be on stable ART prior to initiating HCV treatment and that there be careful consideration of drug-drug interactions. In addition, due to the high cost of DAAs, insurance companies may have specific criteria to approve HCV treatment in the HIV-infected population. Access to care, frequent monitoring of HIV treatment, and adherence to ART have been associated with faster time to HIV viral suppression and increased survival in the HIV-infected population.^{8,9} In real-world settings, these and other factors may be less optimal than in randomized clinical trials; therefore, we aimed to describe predictors of HCV cure among patients with HIV/HCV coinfection in 3 large urban outpatient settings. We hypothesized that real-world rates of

ABSTRACT

Objectives: To study rates and predictors of hepatitis C virus (HCV) cure among HIV/HCV-coinfecting patients, and then to evaluate the effect of attendance at clinic visits on HCV cure.

Methods: Retrospective cohort study of adult HIV/HCV-coinfecting patients who initiated and completed treatment for HCV with direct-acting antivirals (DAAs) between January 1, 2014, and June 30, 2015.

Results: Eighty-four participants reported completing treatment. The median age was 58 years (interquartile ratio, 50-66); 88% were male and 50% were black. One-third were cirrhotic and half were HCV-treatment-experienced. The most commonly used regimen was sofosbuvir/ledipasvir (40%) followed by simeprevir/sofosbuvir (30%). Cure was achieved in 83.3%, 11.9% relapsed, and 2.3% experienced virological breakthrough. Two patients (2.3%) did not complete treatment based on pill counts and follow-up visit documentation. In multivariable analysis, cure was associated with attendance at follow-up clinic visits (odds ratio [OR], 9.0; 95% CI, 2.91-163) and with use of an integrase-based HIV regimen versus other non-integrase regimens, such as non-nucleoside analogues or protease inhibitors (OR, 6.22; 95% CI 1.81-141). Age, race, genotype, presence of cirrhosis, prior HCV treatment, HCV regimen, and pre-treatment CD4 counts were not associated with cure.

Conclusions: Real-world HCV cure rates with DAAs in HCV/HIV coinfection are lower than those seen in clinical trials. Cure is associated with attendance at follow-up clinic visits and with use of an integrase-based HIV regimen. Future studies should evaluate best antiretroviral regimens, predictors of attendance at follow-up visits, impact of different monitoring protocols on medication adherence, and interventions to ensure adequate models of HIV/HCV care.

Am J Manag Care. 2016;22(5 Spec Issue No. 6):SP198-SP204

HCV cure in the HIV-infected population are lower than those that have been described in clinical trials, and that attendance at clinical monitoring visits is associated with higher cure rates.

Understanding real-world data is key to inform interventions and treatment protocols and to potentially increase cure rates in the HIV/HCV-coinfected population.

METHODS

Study Design

This was a retrospective cohort study of adult patients coinfecting with HIV/HCV receiving medical care at 3 large outpatient settings in south Florida: 1) the Miami Veterans Affairs (VA) Healthcare System serves approximately 153,000 veterans in 3 counties by operating 372 hospital beds, a community living center, and 7 satellite clinics; 2) the University of Miami Health system (UHealth) is a private academic institution operating 3 hospitals and 30 outpatient facilities serving 4 counties; and 3) the Jackson Health System (JHS), a public academic institution with 6 hospitals, 12 specialty care centers, and 2 long-term care centers, serves as a tertiary referral center for the state of Florida.

We reviewed medical charts of individuals with HIV/HCV coinfection who initiated and completed treatment for HCV with DAAs in any of these 3 institutions between January 1, 2014, and June 30, 2015.

Inclusion Criteria

All adults with HIV/HCV coinfection who initiated and completed HCV therapy with DAAs were included. HCV treatment was provided to patients 18 years or older with no evidence of active drug or alcohol abuse and who were on ART for HIV.

Outcome

Our primary outcome was HCV cure. Cure was defined as an undetectable HCV RNA at 12 weeks after therapy completion (SVR at week 12 [SVR12] post treatment). A relapse was defined as recurrence of HCV RNA in a patient who had an end-of-treatment response (undetectable HCV RNA at the end of treatment). A virologic breakthrough refers to the reappearance of HCV RNA while still on therapy in a patient who had suppressed their viral level earlier in the course of therapy.¹⁰ We defined completion of treatment as self-reported completion of DAA therapy for the duration recommended by the pro-

Take-Away Points

Clinical trials have shown excellent cure rates for hepatitis C virus (HCV) among the HIV/HCV population. We examined data for real-world cure rates of HCV and predictors of cure in this population.

- Real-world HCV cure rates when using direct-acting antivirals in HIV/HCV coinfection are lower than those seen in clinical trials.
- Cure is associated with attendance at follow-up clinic visits and with the use of integrase-based antiretroviral regimens compared with non-integrase-based HIV regimens, such as non-nucleoside analogues and protease inhibitors.
- Future studies should evaluate best antiretroviral regimens, predictors of attendance to follow-up visits, the impact of different monitoring protocols on medication adherence, and interventions to ensure adequate models of HIV/HCV care.

vider. The selection and duration of HCV therapy strictly followed the guidelines of the American Association for the Study of Liver Diseases, and these choices were based on HCV genotype, degree of hepatic fibrosis, risk of drug interactions, etc.

Exposures

Our main exposure was attendance at follow-up clinic visits. Attendance at follow-up clinic visits was defined as attendance at clinic visits at week 4; once during weeks 6, 7, or 8; and week 12 of HCV treatment, independent of attendance at laboratory visits. The 3 study settings have different monitoring protocols for patients coinfecting with HIV/HCV; however, all sites required clinic visits on weeks 4, 6 to 8, and 12. We describe below the monitoring protocols at each site:

The VA outpatient clinics. The treatment is initiated and monitored by the hepatology clinic. The treatment protocol requires clinic and laboratory visits every 2 weeks for the first 2 months, and then monthly thereafter. A key characteristic is that the VA pharmacy dispenses DAAs during follow-up visits only if the medication for the previous period has been completed.

UHealth. The HIV provider or the hepatologist initiates treatment. The treatment protocol recommends follow-up clinic and laboratory visits every 4 weeks. During the initial visit, the patient receives prescriptions with refills to complete HCV treatment. The pharmacy assists in obtaining approval for medications, but medications are provided by community pharmacies based on initial prescription orders and are independent of follow-up visits or laboratory results.

JHS outpatient clinics. The HIV provider initiates treatment for HCV. The treatment protocol recommends follow-up clinic and laboratory visits every 4 weeks; however, during the initial visit, the patient receives prescriptions with refills to complete HCV treatment. The JHS pharmacy assists in obtaining approval for medications

and informs the ordering physician when medications are approved. Medications are provided by community pharmacies based on initial prescription orders and are independent of follow-up visits or lab results.

Other Independent Variables

Other exposure variables included the following: sociodemographic characteristics (age, gender, race, location of treatment); clinical assessments (baseline HIV viral load and median CD4 count, ART regimen during HCV treatment, HCV genotype, HCV viral load, presence of cirrhosis, prior history of HCV treatment and agents used for treatment, presence of hepatitis B coinfection, HCV treatment regimen, concurrent use of ribavirin with DAAs for HCV treatment); attendance at treatment laboratory visits (defined as lab tests done on week 4, once during weeks 6 to 8, on week 12 and at the end of treatment); and posttreatment lab visits.

Study Procedures

We reviewed all medical charts and provider notes, and we collected exposure, outcome, and covariate data. We also collected adverse events documented in the medical chart on each follow-up visit. We reviewed information on all follow-up visits as documented in the medical chart.

Statistical Analysis

We used REDCap version 6.5.2 electronic data capture tools, hosted at University of Miami, to collect and manage study data. We used descriptive statistics to report the baseline characteristics of the population. We conducted univariable analysis with calculation of odds ratio, 95% CI, and χ^2 testing (a *P* value of .05 was considered to indicate statistical significance). In order to identify predictors, we used logistic regression analysis. Our multivariable analysis included the variables that were significant in the univariate analysis, and those that have been described to be associated with cure in the literature (ie, absence of cirrhosis, HCV genotype, aspartate aminotransferase platelet ratio index score, duration of treatment, race, and prior history of treatment). SPSS version 22 statistical software (IBM Corp, Armonk, New York) was used for analysis.

Ethics Statement

Institutional review board approvals from the University of Miami, JHS's Jackson Memorial Hospital, and the VA Hospital administration were obtained prior to performing any study-related procedures. Due to the retrospective nature of this study, a waiver of informed consent was granted.

RESULTS

Characteristics of the Study Population

Eighty-four participants reported completing treatment and were evaluated 12 weeks post treatment. The median age was 58 years (interquartile ratio [IQR], 50-66), 88% were men, and 50% were black (Table 1). Approximately 90% of the patients had an undetectable HIV viral load at baseline and had a median CD4 count of 604 cells/mm³ (IQR, 812-374). Use of ART was as follows: over half of the patients were on an integrase-based HIV regimen and 20% were on a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen. More than two-thirds of our patients were infected with genotype 1a with a median HCV viral load of 14.9 log₁₀IU/mL (IQR, 12.4-17.4). One-third of the population had cirrhosis, and half had a prior history of HCV treatment. Of the prior HCV treatment regimens used, about 40% were interferon-based. Hepatitis B coinfection was found in 16% of the patients.

The most commonly used regimen was sofosbuvir and ledipasvir, which was prescribed to approximately 40% of the patients. The second most common regimen was simeprevir with sofosbuvir (without ribavirin) prescribed to about 30% of the patients, followed by simeprevir with sofosbuvir (with ribavirin) prescribed to about 15% of the patients.

The regimens appeared to be well tolerated with two-thirds of the patients reporting no adverse effects. Patients on ribavirin were noted to have more fatigue and anemia (*n* = 9 and 8) versus those not on ribavirin (*n* = 5 and 0), respectively.

Outcomes

Cure. Among the 84 participants included in the study, 83.3% attained SVR12 (*n* = 70), which, in this study, is defined as having achieved cure; 11.9% relapsed (*n* = 10), 2.3% experienced virological breakthrough (*n* = 2), and 2 patients (2.3%) were deemed not to have completed treatment based on pill counts and follow-up visit documentation (Figure).

Factors associated with cure. Univariate and multivariate analyses of demographics and clinical factors, and their associations with cure, were conducted and are illustrated in Tables 2 and 3. Factors associated with cure in univariate analysis were: attendance at follow-up visits (odds ratio [OR], 7.89; 95% CI, 2.26-27.4), receiving care at the Miami VA site (OR, 3.98; 95% CI, 1.13-13.9), and attending treatment laboratory visits (OR, 6.6; 95% CI, 1.92-22.6). Age, race, genotype, presence of cirrhosis, prior HCV treatment, HCV regimen, hepatitis B virus coinfection, week 4 SVR, CD4 counts, and pre-treatment HCV RNA were not associated with cure.

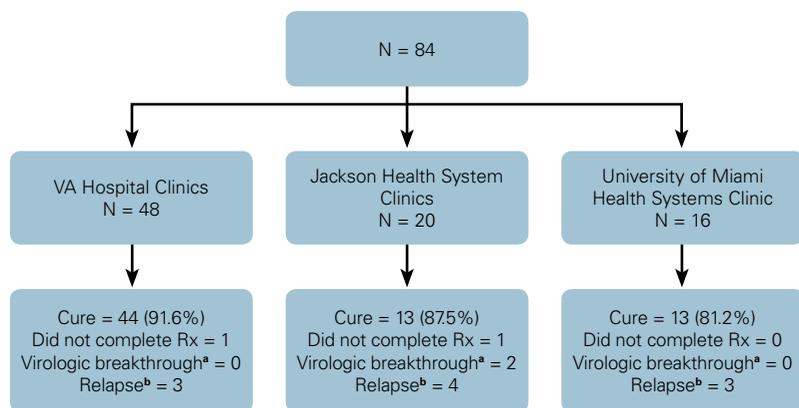
In multivariable analysis, factors associated with cure were attendance at follow-up clinic visits (OR, 9.0; 95%

Table 1. Baseline Demographic Characteristics of Patients (N = 84) and Distribution by Site

Baseline Characteristic	Total N = 84	VA N = 48	JHS N = 20	UHealth N = 16
Age, years (IQR)	58 (50-66)	60 (47-57)	57 (60-52)	54 (61-49)
Male, n (%)	74 (88.1)	47 (97.9)	15 (75.0)	12 (75.0)
Race				
Caucasian, n (%)	28 (33.3)	15 (31.3)	7 (35.0)	6 (37.5)
Black, n (%)	42 (50.0)	28 (58.3)	9 (45.0)	5 (31.3)
Hispanic, n (%)	14 (16.7)	5 (10.4)	4 (20.0)	5 (31.3)
HIV RNA <50 IU/mL, mean (SD)	76 (90.4)	44 (91.7)	18 (90.0)	14 (87.5)
Median CD4 count cells/mm ³ (IQR)	604 (812-374)	570 (775-412)	615 (750-466)	688 (888-580)
HIV antiviral regimen				
Integrase + TDF-FTC, n (%)	25 (29.8)	11 (22.9)	4 (20.0)	10 (62.5)
Integrase + ABC-3TC, n (%)	12 (14.3)	7 (14.6)	3 (15.0)	2 (12.5)
PI/r + TDF-FTC, n (%)	11 (13.1)	8 (16.7)	3 (15.0)	0
Rilpivirine + TDF-FTC, n (%)	5 (6.0)	0	4 (20.0)	1 (6.3)
EFV + TDF-FTC, n (%)	12 (14.4)	7 (14.6)	3 (15.0)	2 (12.5)
Others	19 (22.4)	15 (31.2)	3 (15.0)	1 (6.3)
HCV genotype				
1a, n (%)	59 (70.2)	32 (66.7)	13 (65.0)	14 (87.5)
1b, n (%)	20 (23.8)	13 (27.1)	6 (30.0)	1 (6.3)
2b, n (%)	3 (3.6)	2 (4.2)	1 (5.0)	0
Others (3a and 4), n (%)	2 (2.4)	1 (2.1)	0	1 (6.3)
Median HCV RNA (IQR), log ₁₀ IU/mL	14.9 (12.4-17.4)	6.4 (6.9-5.8)	6.4 (6.6-5.7)	6.5 (7.0-6.3)
Cirrhosis, n (%)	24 (28.6)	15 (31.3)	6 (30.0)	3 (18.8)
Prior HCV treatment experienced, n (%)	49 (58.3)	25 (52.0)	13 (65.0)	11 (68.7)
Prior HCV treatment agents				
PEG IFN/RBV	30 (40.0)	21 (43.8)	6 (33.3)	3 (33.3)
Boceprevir/teleprevir	2 (2.7)	1 (2.1)	1 (5.6)	0
DAAAs	1 (1.3)	1 (2.1)	0	0
Other/not known	8 (10.7)	2 (4.2)	5 (27.8)	1 (11.1)
Hepatitis B coinfection, n (%)	13 (15.9)	8 (16.7)	4 (22.2)	1 (6.3)
APRI score, median (IQR)	0.57 (0.92-0.37)	0.54 (0.75-0.31)	1.2 (2.4-0.6)	0.48 (0.67-0.38)
HCV treatment regimen				
Sofosbuvir + ledipasvir, n (%)	33 (39.3)	19 (39.6)	5 (25.0)	9 (56.3)
Simeprevir + sofosbuvir, n (%)	25 (29.8)	10 (20.8)	10 (50.0)	5 (31.3)
Simeprevir + sofosbuvir + RBV, n (%)	13 (15.5)	13 (27.1)	0	0
Sofosbuvir/IFN/RBV, n (%)	7 (8.3)	2 (4.2)	4 (20.0)	1 (6.3)
Sofosbuvir + RBV, n (%)	4 (4.8)	2 (4.2)	1 (5.0)	1 (6.3)
Ombitasvir + paritaprevir + dasabuvir/r, n (%)	2 (2.3)	2 (4.2)	0	0
Concurrent RBV use for HCV treatment, n (%)	28 (33.7)	21 (43.8)	5 (26.3)	2 (12.5)
Attendance at follow-up clinic visit, n (%)	62 (73.8)	45 (93.7)	6 (30.0)	11 (68.7)

/r indicates ritonavir; ABC-3TC, abacavir-lamivudine; APRI, aspartate aminotransferase to platelet ratio index; CD4, Cluster of Differentiation 4 (a measure of cellular immunity); DAA, direct-acting antiviral; EFV, efavirenz; HCV, hepatitis C virus; IFN, interferon; IQR, interquartile range; IU, international units; JHS: Jackson Health System; PEG IFN/RBV, pegylated-interferon/ribavirin; PI/r, ritonavir-boosted protease inhibitors; RBV, ribavirin; RNA, ribonucleic acid; TDF-FTC, tenofovir-emtricitabine; UHealth, University of Miami Health System; VA, the Miami Veterans Affairs Healthcare System.

■ **Figure. Outcomes per Site**



VA indicates Veterans Affairs.

^aVirologic breakthrough refers to the reappearance of hepatitis C virus (HCV) ribonucleic acid (RNA) while still on therapy in a patient who had suppressed their viral level earlier in the course of therapy.

^bA relapse was defined as recurrence of HCV RNA in a patient who had an end-of-treatment response (also known as EOTR undetectable HCV RNA at the end of treatment).

CI, 2.91-163) and use of an integrase-based HIV regimen versus a non-integrase-based regimen such as NNRTI or protease inhibitors (OR, 6.22; 95% CI, 1.81-141). We excluded attendance at laboratory visits and treatment at the VA from the model due to collinearity with attendance at follow-up clinic visits.

Of the 12 patients who failed treatment, 8 were black, 4 were cirrhotic, 10 were infected with genotype 1a, 2 were infected with genotype 1b, 5 were treatment-experienced, and 7 were treated with simeprevir plus sofosbuvir. Three of the 7 patients treated with simeprevir plus sofosbuvir were cirrhotic. About two-thirds of the patients who failed therapy did not have attendance at follow-up clinic visits. However, race, presence of cirrhosis, HCV genotype, and drugs used for treatment of HCV were not associated with cure. For a detailed description of the patients who failed treatment, and adverse effects experienced, please see the [eAppendix Table](#) (available at www.ajmc.com).

DISCUSSION

HCV cure rates among patients coinfecting with HIV/HCV seeking care in real-world settings are lower than those reported in clinical trials.^{6,7,11,12} Achieving cure (defined by SVR12 in this study) was closely associated with attendance at follow-up clinic visits and to the use of an integrase-based HIV regimen compared with non-integrase-based regimens such as NNRTI or protease inhibitors. Our study did not show an association of black race

or cirrhosis with decreased cure rates, although others have previously found this association.⁶ Nevertheless, our study may lack the sufficient statistical power to detect this association.

The main contribution of our study to real-world clinical practice is the relationship between attendance at follow-up clinic visits and cure rates. Treatment of HCV in the HIV-infected population is challenging due to accelerated liver disease, concomitant comorbidities, and difficulties managing HCV-HIV drug-drug interactions. The importance of adequate adherence to clinical care has previously been described in populations infected only with HIV, in which greater frequency of visits and early linkage to care were associated with faster time to HIV viral suppression.^{9,13,14} The reason for this relationship has not been fully described in HIV, although these authors have hypothesized medication adherence as a possible mediator.

Frequency of clinic visits has been associated with higher medication adherence in populations with other chronic diseases.¹⁵ In our study, we found that attendance at visits was more common among the veterans cared for at the Miami VA. This group was very similar to the other 2—those being treated at UHealth and JHS—with the exception of a higher prevalence of black race and HCV treatment naïve patients (Table 1). However, the Miami VA, being a closed system, used key strategies to incentivize attendance, such as scheduling more frequent visits and only refilling medications at follow-up visits, once the pharmacist has ensured that all medication bottles were empty. This contrasts with the 2 fee-for-service sites that had less-frequent scheduled visits and provided the entire regimen at the beginning of the treatment. Even though this latter protocol may have been designed to improve access to the medications, our findings suggest that providing refills during follow-up visits may be more effective. We could not evaluate the mechanism through which the VA treatment protocol may influence cure; however, we can hypothesize that a likely mechanism is an improvement in medication adherence. Frequent clinic visits may address known barriers to adherence, such as misconceptions on the efficacy of the medication, fear of side effects, low self-efficacy, mistrust, depression, and other psychological factors, to name a few.^{16,17}

Table 2. Univariate Predictors of HCV Cure

Predictor	OR	95% CI	P
Aged <58 years	0.62	0.19-2.04	.433
Race			
Caucasian	1.30	0.37-4.59	.679
Black	0.70	0.22-2.25	.558
Hispanic	1.24	0.24-6.28	.793
Veterans hospital clinic site	3.98	1.13-13.9	.024
Baseline CD4	0.75	0.23-2.43	.643
Integrase-based HIV regimen	3.88	0.99-15.12	.040
HCV genotype 1a	0.34	0.07-1.65	.165
Cirrhosis	0.67	0.19-2.25	.517
APRI score >1 ^a	0.20	0.06-0.70	.007
HCV treatment history	0.67	0.21-2.11	.488
Hepatitis B coinfection	0.63	0.15-2.67	.531
Use of sofosbuvir + ledipasvir	1.03	0.85-1.26	.695
Ribavirin use	0.90	0.27-2.99	.284
Undetectable HCV viral load on week 4 of treatment	0.74	0.23-2.37	.613
Attendance at treatment lab visit ^c	6.60	1.92-22.65	.001
Attendance at follow-up clinic visit ^b	7.89	2.26-27.49	.000
Presence of adverse effects to HCV therapy	0.36	0.11-1.18	.086

APRI indicates aspartate aminotransferase to platelet ratio index; CD4, Cluster of Differentiation 4 (a measure of cellular immunity); HCV, hepatitis C virus; OR, odds ratio.

^aAPRI score >1 has a sensitivity of 76% and specificity of 72% for predicting cirrhosis.

^bAttendance at follow-up clinic visit was defined as attendance at clinic visits at week 4, and once during weeks 6-8 and week 12 of HCV treatment independent of attendance at laboratory visit.

^cAttendance at treatment laboratory visit was defined as lab visits at weeks 4, one visit during weeks 6-8, week 12 and end of treatment.

Bolded rows show univariate analyses that were statistically significant.

Future studies should include measures of adherence to DAAs to better elucidate the mechanisms through which different treatment protocols can achieve HCV cure. Nevertheless, our findings suggest that fee-for-service health systems should work with payers and other stakeholders to develop feasible and successful models of care for HCV treatment in the HIV-infected population. If medical visits facilitate cure through medication adherence, models of care could include ancillary services such as in-person or phone-based behavioral interventions led by counselors, which have been shown to increase medication adherence among patients with HIV.^{18,19} Such interventions could be introduced as a model of care that does not use clinic infrastructure (already at maximum use) and could be a more feasible strategy to provide cost-efficient, high-quality care. Interventions to increase adequate follow-up for HCV treat-

ment in patients coinfecting with HIV have the potential to increase cure rates and reduce treatment costs by ensuring that treatment is provided as prescribed.

In this study, we also found that patients receiving integrase inhibitors for the treatment of HIV had higher rates of cure when treated for HCV. This may be related to the fact that integrase inhibitors have fewer drug-drug interactions with HCV medications (hence lower chances of sub therapeutic drug levels for HCV) than do NNRTIs or protease inhibitors.²⁰ Future studies should evaluate the hypothesis that better tolerability of the integrase-based regimen may improve adherence to the HCV regimen, as well.

Limitations

This study has several limitations related to the retrospective nature of its design and the small sample size. First, we could not compare medication adherence among the 3 groups (which may mediate the effect of follow-up visits) because all clinics used different strategies to address adherence. We also did not collect data on socioeconomic status, health literacy, and depression, all of which have been linked to medication adherence and outcomes, raising the possibility of residual confounding. Additionally, although this study involves 3 large hospital sites, the small sample size precludes generalization of the study findings and increases the chances of a type 2 error, such as the ability to detect associations among cirrhosis, black race, and cure. It should be noted that 3 cirrhotic patients who failed therapy were prescribed only 12 weeks of sofosbuvir/simeprevir treatment (instead of 24 weeks), which would have resulted in inadequate duration of therapy and, therefore, spuriously low cure rates. Finally, we could not adjust the model by provider or specialty, as several providers could deliver follow-up care to the same patient.

Table 3. Multivariate Model of HCV Cure^{a,b}

Predictor	OR	95% CI	P
HCV genotype 1a	2.21	0.02-1.62	.137
APRI score	0.004	0.52-1.83	.948
Integrase-based HIV regimen	6.22	1.81-141	.013
Attendance at follow-up clinic visit	9.00	2.91-163	.003
Cirrhosis	0.119	0.13-4.05	.730

APRI indicates aspartate aminotransferase to platelet ratio index; HCV, hepatitis C virus; OR, odds ratio.

^aModel for the outcome cure was adjusted for HCV genotype, APRI score, integrase HIV regimen, and attendance at follow-up clinic visit.

^bDue to collinearity with attendance at follow-up visit, VA clinic site (the Miami Veterans Affairs Healthcare System) and laboratory visits were excluded from the model.

Bolded rows show multivariate analyses that were statistically significant.

CONCLUSIONS

Real-world HCV cure rates when using DAA in HIV/HCV coinfection are lower than those seen in clinical trials. Cure is associated with attendance at follow-up clinic visits and the use of integrase-based HIV regimens as opposed to NNRTIs or protease inhibitors. Future studies should evaluate predictors of adequate attendance at follow-up visits, the role of medication adherence, and the effect of integrase-based regimen on HCV cure to inform best models of HCV/HIV care.

Acknowledgments

The authors gratefully acknowledge use of the services of the Miami Center for AIDS Research at the University of Miami (P30AI073961).

Author Affiliations: Jackson Memorial Hospital (SL, AMP, MS), Miami, FL; University of Miami Hospital (SL, MA, MS, DJ, MDPH), Miami, FL; University of Miami Leonard M. Miller School of Medicine (ALA, GG-W, AP, KP), Miami, FL; Veterans Affairs Hospital (MDPH), Miami, FL.

Source of Funding: None.

Author Disclosures: Dr Jayaweera is a consultant for Bristol-Myers Squibb (BMS) and Gilead; he has also previously received grants from Gilead, BMS, ViiV, and Janssen. The remaining authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (SL, MA, MDPH, DJ, KP, MS, GG-W); acquisition of data (SL, ALA, MDPH, DJ, AP, KP, MS, GG-W); analysis and interpretation of data (SL, MA, ALA, MDPH, DJ, AMP, AP, KP, GG-W); drafting of the manuscript (SL, MA, MDPH, AMP, AP); critical revision of the manuscript for important intellectual content (MA, ALA, MDPH, DJ, AMP, MS); statistical analysis (SL, MA); provision of patients or study materials (MDPH, MS); administrative, technical, or logistic support (MDPH); and supervision (MA, MDPH).

Address correspondence to: Maria Del Pilar Hernandez, MD, Jackson Medical Towers, Ste 1101, Miami, FL. E-mail: m.hernandez33@med.miami.edu.

REFERENCES

- Price JC, Thio CL. Liver disease in the HIV-infected individual. *Clin Gastroenterol Hepatol*. 2010;8(12):1002-1012. doi: 10.1016/j.cgh.2010.08.024.
- Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis*. 2001;33(4):562-569.
- Soto B, Sánchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol*. 1997;26(1):1-5.
- Rosenthal E, Salmon-Céron D, Lewden C, et al; Mortavic/Mortalité 2005 Study Group. Liver-related deaths in HIV-infected patients between 1995 and 2005 in the French GERMIVIC Joint Study Group Network (Mortavic 2005 study in collaboration with the Mortalité 2005 survey, ANRS EN19). *HIV Med*. 2009;10(5):282-289. doi: 10.1111/j.1468-1293.2008.00686.x.
- Soriano V, Martin-Carbareno L, Maida I, Garcia-Samaniego J, Nuñez M. New paradigms in the management of HIV and hepatitis C virus coinfection. *Curr Opin Infect Dis*. 2005;18(6):550-560.
- Naggie S, Cooper C, Saag M, et al; ION-4 Investigators. Ledipasvir and sofosbuvir for HCV in patients coinfecting with HIV-1. *N Engl J Med*. 2015; 373(8):705-713. doi: 10.1056/NEJMoa1501315.
- Sulkowski MS, Naggie S, Lalezari J, et al; PHOTON-1 Investigators. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. *JAMA*. 2014;312(4):353-361. doi: 10.1001/jama.2014.7734.
- Hall H, Tang T, Westfall AO, Mugavero MJ. HIV care visits and time to viral suppression, 19 U.S. jurisdictions, and implications for treatment, prevention and the national HIV/AIDS strategy. *PLoS One*. 2013;8(12):e84318. doi: 10.1371/journal.pone.0084318.
- Giordano TP, Gifford AL, White AC Jr, et al. Retention in care: a challenge to survival with HIV infection. *Clin Infect Dis*. 2007;44(11):1493-1499.
- Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009;49(4):1335-1374. doi: 10.1002/hep.22759.
- Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med*. 2014;370(17):1594-1603. doi: 10.1056/NEJMoa1315722.
- Afdhal N, Reddy KR, Nelson DR, et al; ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med*. 2014;370(16):1483-1493. doi: 10.1056/NEJMoa1316366.
- Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. *Ann Intern Med*. 1999;131(2):81-87.
- Mugavero MJ, Lin HY, Willig JH, et al. Missed visits and mortality among patients establishing initial outpatient HIV treatment. *Clin Infect Dis*. 2009;48(2):248-256. doi: 10.1086/595705.
- Bailey JE, Hajjar M, Shoib B, Tang J, Ray MM, Wan JY. Risk factors associated with antihypertensive medication nonadherence in a state-wide Medicaid population. *Am J Med Sci*. 2014;348(5):410-415. doi: 10.1097/MAJ.0b013e31825ce50f.
- DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*. 2000;160(14):2101-2107.
- Langebeek N, Gisolf EH, Reiss P, et al. Predictors and correlates of adherence to combination antiretroviral therapy (ART) for chronic HIV infection: a meta-analysis. *BMC Med*. 2014;12:142. doi: 10.1186/PREACCEPT-1453408941291432.
- Palacio AM, Uribe C, Hazel-Fernandez L, et al. Can phone-based motivational interviewing improve medication adherence to anti-platelet medications after a coronary stent among racial minorities? a randomized trial. *J Gen Intern Med*. 2015;30(4):469-475. doi: 10.1007/s11606-014-3139-8.
- Holstad MM, Essien JE, Ekong E, Higgins M, Teplinskiy I, Adewuyi MF. Motivational groups support adherence to antiretroviral therapy and use of risk reduction behaviors in HIV positive Nigerian women: a pilot study. *Afr J Reprod Health*. 2012;16(3):14-27.
- Kiser JJ, Burton JR Jr, Everson GT. Drug-drug interactions during antiviral therapy for chronic hepatitis C. *Nat Rev Gastroenterol Hepatol*. 2013;10(10):596-606. doi: 10.1038/nrgastro.2013.106. ■

www.ajmc.com Full text and PDF

eAppendix Table. Detailed Description of All Patients Who Did Not Achieve HCV Cure, and Adverse Events

No	ID	Location	Sex	Race	Cirrhosis	GT	Pre Rx	Pre Rx Response	HCV VL in Million	HIV Regimen	HCV Regimen	Duration	W4	W6-8	W12	Comment
1	70	VA hospital	M	H	Y	1a	Y	NR	26M	PI+ Truvada	Sof/sim	12	Y	Y	Y	Interaction between PI and simeprevir
2	4	VA hospital	M	B	Y	1a	Y	NR	840	Atripla	Sim/sof/RBV	12	Y	Y	Y	Efavirenz decreases sim levels
3	21	VA hospital	M	B	Y	1a	Y	NR	0.5	Darunavir+raltegravir	Sim/sof	12	Y	N	N	positive for cocaine while on Rx/also had cdiff/ died of liver failure → hepatic encephalopathy
4	71	JHS	M	B	N	1a	Y	NR	50M	PI+ Truvada	Vikera	12	N	Y		Poor HIV control Stopped taking vikera → no reasons mentioned. Took 4 weeks of medication
5	247	JHS	F	W	N	1a	N	NA	27M	Not on Rx	Sim/sof		N	N	N	Long-term nonprogressor low-level HIV viremia. CD4 lowest 296
6	245	JHS	F	B	N	1a	N	NA	4M	Atripla	Sof/INF/RBV	12	Y	N	N	Patient states she was compliant/suffered MVA during Rx
7	213	JHS	M	B	N	1b	N	NA	47M	Atripla	Sof/led	12	N	Y	N	Did not follow up at end of Rx: 1 month post Rx 1503507 HCV RNA
8	210	JHS	M	B	Y	1a	N	NA	0.23	Complera	Sim/sof	12	Y	N	N	Did not follow up/inadequate duration of Rx
9	209	JHS	M	B	N	1b	N	NA	0.076	Truvada+ integrase	Sim/sof	12	Y	N	Y	Did not follow up for SVR 4, SVR 3 was 12,7716
10	255	Uhealth	M	B	N	1a	N	NA	23M	Complera	Sim/sof	12	Y	N	N	Did not follow up
11	306	Uhealth	M	W	N	1a	Y	NR	3.8M	Atripla	Sof/INF/RBV	12	Y	Y	Y	Did not follow up
12	319	Uhealth	M	H	N	1a	N	NA	2.7	Truvada+ integrase	Sof/led	8	N	Y	N	Did not do labs at week 4 or follow up

B, black; cdiff, *Clostridium Difficile* infection; F, female; H, Hispanic; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INF, Interferon; JHS, Jackson Health Systems; Led, ledipasvir; M, male; MVA, motor vehicle accident; N, no; PI, protease inhibitors; RBV, ribavirin; RNA, ribonucleic acid; Sim, simeprevir; Sof, sofosbuvir; SVR, sustained virologic response; VA, Veterans Affairs; VL, viral load; W, week; Y, yes.

Adverse Events Documented While on HCV Therapy

	Total	VA	JHS	UHealth
Rash, n (%)	4 (5.0)	2 (4.1)	2 (10.0)	0
Anemia, n (%)	8 (10.0)	4 (8.3)	3 (15.0)	1 (6.2)
Fatigue, n (%)	14 (17.5)	9 (1.8)	5 (25.0)	0
Worsening bilirubin, n (5)	1 (1.3)	1 (2.0)	0	0
Nausea, n (%)	2 (2.3)	1 (2.0)	0	1 (6.2)
Other, n (%)	3 (3.5)	2 (4.1)	0	1 (6.2)
None, n (%)	53 (66.6)	29 (60.4)	10 (50.0)	13 (81.2)

HCV indicates hepatitis C virus; JHS, Jackson Health Systems; Uhealth, University of Miami Health Clinics; VA, Veterans Affairs Hospital.