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Duration of Hepatitis C Treatment with Direct-acting Antivirals Ledipasvir/Sofosbuvir Not Associated with HIV Co-Infection

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Abstract

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By Craig Patrick Hayes

HARVONI (ledipasvir/sofosbuvir) is a direct acting antiviral used to treat hepatitis C. Previous studies have shown similar success rates when treating HCV with HARVONI in both co-infected and mono-infected populations. We conducted a proportional hazards regression to determine differences in time-to-treat between co-infected and mono-infected patients. The study population consisted of 222 HCV infected patients treated with HARVONI, including 197 HCV mono-infected and 25 HCV/HIV co-infected patients, at the Atlanta Veterans Affairs (VA) Medical Center (Georgia) from January 2015 through March 2016. The two groups had similar age, gender distributions, and HCV viral loads at baseline. Significantly higher numbers of Non-Hispanic Blacks were present in the HCV/HIV co-infected group (18.5% more, p-value = 0.03). A significantly greater proportion of the HCV/HIV co-infected group was found to be adherent to their medication (13.3% higher, p-value = 0.03), but this was not considered a confounder during the analysis. We determined hazard ratios for time to complete treatment and time to complete a normal course of treatment at 1.15 (95% Confidence Interval: 0.75 – 1.76) and 1.07 (95% CI: 0.68 – 1.68), respectively. These results suggest that the time-to-treat HCV for HCV/HIV co-infected patients is no different than for HCV mono-infected patients.

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INTRODUCTION

The Hepatitis C virus (HCV) has infected more than 170 million persons worldwide and recently became the leading cause of death associated with liver failure in the United States (1). Additionally, it is estimated that between four million and five million persons are infected with both HCV and HIV (2.) Evidence suggests that the incidence of HCV-related hepatocellular carcinoma and hepatic decompensation will continue to increase over the next twenty years1. Liver-related deaths are also expected to continue to rise because five-percent to twenty-percent of chronic HCV-infected persons will develop cirrhosis, with one-percent to five-percent dying from cirrhosis or hepatocellular carcinoma (3). HCV/HIV co-infected persons have higher rates of occurrence of cirrhosis, hepatocellular carcinoma, and hepatic decompensation than do HCV mono-infected patients, and these diseases also progress more rapidly (2,4). The duration of survival is less for HCV/HIV co-infected persons on antiretroviral therapy than for HIV mono-infected persons on antiretroviral therapy as well, compounding the need for responsive treatment (5).

Several treatments are available that reduce morbidity and mortality associated with HCV, with patients completing treatment once they achieve sustained virologic response (2). Sustained virologic response (SVR) is defend as the absence of detectable HCV RNA in the serum, or less than 25 IU/mL, eight, 12, or 24 weeks after starting treatment. Patients who achieve SVR develop fewer liver-related complications, incidents of hepatocellular carcinoma, and liver-related deaths, and relapse at a rate of less than one-percent. Prior to 2011, the most effective option for treatment and achieving SVR was pegylated interferon delivered in combination with ribavirin through weekly injections and oral delivery for approximately 48 weeks (1). However, this treatment was only successful in about half of patients mono-infected

with HCV and often at lower rates in patients co-infected with HCV/HIV while producing intolerable adverse events in some due to the non-specific treatment pathway. Due to these issues, the use of pegylated IFN and ribavirin was considered largely ineffective (3,6).

Over the last five years directing-acting antivirals (DAAs) were developed for HCV treatment (4). DAAs directly target HCV replication6, and intolerable adverse events from them are virtually non-existent. In addition to improved tolerability, DAAs involve smaller pill burdens, shorter treatment durations, and higher rates of SVR. The SVR rates of patients treated with first generation DAAs are 67% to 75%, while the rates for those treated with second generation DAAs are consistently found to be over 95% (7, 8). Moreover, treating HCV mono-infected patients and HCV/HIV co-infected patients with DAAs yields similar SVR rates in both groups which simplifies determining the course of treatment (4).

The most commonly prescribed second generation drug, Harvoni, is a combination pill of ledipasvir and sofosbuvir which is produced by Gilead Sciences, Inc (9). Although SVR is achieved in most patients prescribed the drug, the drug is expensive. As of March 2015, the average wholesale cost was $37,800 for 28 tablets (3). Twenty-eight tablets only last for four weeks, whereas the product insert for Harvoni calls for 12 weeks of treatment in most patients with a range for achieving SVR in eight to 24 weeks. With the cost of a full course of the medication ranging from $75,600 to $226,800, critics say that the financial cost is too much of a barrier to those most in need of the drug (10). Patients co-infected with HCV/HIV are of particular concern as they are already shouldering the costs of HIV treatment. As a result, it is important to consider factors such as HCV/HIV co-infection that may contribute to prolonged treatments and additional expenses to the patient.

Using data from the Atlanta VA Medical Center where drug access issues were ameliorated, we investigated differences in the time required for the direct-acting antiviral medication Harvoni (ledipasvir/sofosbuvir) to resolve Hepatitis C infection in HCV mono-infected and HCV/HIV co-infected patients, we hypothesized that SVR would take longer to reach in HCV/HIV co-infected patients than in HCV mono-infected patients.

METHODS

The study population consisted of all HCV infected patients treated with LDF/SOF, including HCV mono-infected and HCV/HIV co-infected patients, at the Atlanta Veterans Affairs (VA) Medical Center (Georgia) from January 2015 through March 2016. For this retrospective, clinic-based cohort study, clinical and demographic data were obtained from the VA's HCV Clinical Case Registry and from HAVACS, the HIV Atlanta VA Cohort Study.

HCV infection status was determined using a second-generation ELISA. HCV RNA levels were measured before treatment, 20 to 45 days after treatment start date, and ≥ 60 days after treatment. A RNA lab value of < 15 was considered undetectable. A detectable RNA value ≥ 60 days after treatment was defined as a relapse. CD4+ cell counts and HIV load data were extracted for two time points: (1) at the start of LDF/SOF treatment and (2) the most recent test. CD4+ cell counts were measured using standard three-color flow cytometry using FACscan (Becton Dickinson), and HIV-RNA loads were measured using PCR (Amplicor RT-PCR). Date of AIDS diagnosis was defined as the date the patient's condition met either the 1987 or 1993 Centers for Disease Control and Prevention (CDC) definition of AIDS. Adherence to medication was defined as ≤ seven days elapsing between medication refills. The patients' race and age at

the date of beginning treatment were included in the analysis. Race was defined as non-Hispanic black, non-Hispanic white, Hispanic, and "other race."

Statistical analysis was performed using SAS software, version 9.4 (SAS Institute). Selected characteristics per HIV infection status of the study participants were compared using chi-square and Fischer's exact tests for categorical variables and t-tests for continuous variables. Event rates and time-to-event analyses were conducted for sustained virologic response of HCV. Time zero was defined as the treatment start date, and the follow-up periods were predefined as 8, 12, and 24 weeks after starting treatment. The Kaplan-Meier technique was used to conduct a survival analysis where patients were stratified by HIV infection status. Univariate and multivariate Cox proportional hazards models were constructed to assess the effect of HIV co-infection on time-to-treat. Coinfection status and variables with $p < 0.05$ were included in the multivariable model.

RESULTS

Among 222 HCV infected patients treated with Harvoni at the Atlanta VA Medical Center from 2015 to 2016, 25 (11.3%) were co-infected with HIV. Most patients were older (mean age at treatment start of 63.1 and 62.2 years for mono-infected and co-infected patients, respectively (p-value = 0.33)) and male (94.9% mono-infected and 100% co-infected patients (p-value = 0.25)). We found a statistically significant difference in racial distributions between populations. While most patients in both groups were Non-Hispanic Black, a greater proportion of the HCV mono-infected group was Non-Hispanic White than in the HCV/HIV co-infected group (p-value = 0.03). There was not a significant difference in average baseline HCV

viral load count between groups. The average duration of treatment was 80.8 days for the HCV mono-infected patients and 76.6 days for the HCV/HIV co-infected patients, a difference that was not significant (p-value = 0.46). The co-infected group had statistically significant higher rates of adherence (96.0%) than the mono-infected group (82.7%) (p-value = 0.03), although, as a non-confounder, this variable was not considered as a cofactor.

Only four of the 25 HCV/HIV co-infected patients had received a previous AIDS diagnosis, and none were naïve to antiretroviral therapy. On average, the co-infected patients experienced an increase in CD4 count of 32.6 cells/mm3 and a reduction in HIV viral load of 21.1 copies/mL from baseline to most recent measure.

We developed a univariate Cox proportional hazards regression model for coinfection as a factor in time to complete treatment as determined by a physician in weeks and produced a hazard ratio of 1.15 (95% Confidence Interval: 0.75 – 1.76) that was not statistically significant. We also considered a model for time to complete a normal course of treatment in weeks and produced a hazard ratio of 1.07 (95% CI: 0.68 – 1.68) that was also not statistically significant. A normal course of treatment was one where the treatment was completed as determined by a physician, where treatment was not discontinued, and where patients did not relapse after treatment. Inclusion of other potential factors in the multivariate model did not provide significant results.

DISCUSSION

The population characteristics seen in this study largely reflect those in the Veterans Aging Cohort Study (VACS) and HIV Atlanta Veterans Affairs Cohort Study (HAVACS),

although mean age is considerably higher for this study (11). This study took place in Atlanta where the HIV rates are much higher for Non-Hispanic Blacks than for Non-Hispanic Whites (12) which likely accounts for the higher ratio of Non-Hispanic Blacks in the HCV/HIV co-infected group than in the HCV mono-infected group. Adherence measures used prescription refills as a proxy rather than pill counts or any molecular diagnostics, but both groups still saw high adherence rates. The higher rate among the HCV/HIV co-infected group may be explained by all co-infected participants having received antiretroviral therapy previously, so they would be more accustomed to taking a daily medication.

The hazard ratios describing the difference in time to complete treatment and the difference in time to complete a normal course of treatment between HCV mono-infected and HCV/HIV co-infected patients were not significant, suggesting that HIV infection does not extended the necessary time to treat HCV. To the author's knowledge, this is the first study to investigate the differences in time to treat HCV in HCV/HIV co-infected and HCV mono-infected populations. Reviewing related literature suggests that HIV status may extend the duration of treatment for tuberculosis (13) and time to serologic response for syphilis (14), but since both disease affect different systems and do so with different pathologies than HCV it stands to reason that HIV status would not necessarily affect the duration of HCV treatment in the same way.

One strength of this study includes recruiting the study participants from the Atlanta VA. Those that use the VA as their primary healthcare provider tend to remain in care, and typical barriers to care such as cost and insurance are reduced. This results in a population that will more accurately reflect the effect of treatment outside of clinical trial conditions, although the results may not be representative of the general population. A major limitation of this study is its small

sample size, particularly for the HCV/HIV co-infected group. As we designed this study to investigate the time-to-treat in a clinical setting and Harvoni was only approved by the FDA in 2014, the small sample size was expected. Future studies may look to expand recruitment to patients seen by other healthcare providers for purposes of generalizability and increasing study power. A larger sample size may also enable stratification of the HCV/HIV co-infected group by HIV-related factors including naivety to antiretroviral therapy and previous AIDS diagnosis.

Previous studies have focused on the similarities in treatment success between mono-infected and co-infected populations while neglecting the time-to-treat for these populations. By demonstrating that there was no significant difference in required treatment durations, this study would suggest that not only is treatment of Hepatitis C with Harvoni as successful and as safe for HIV-positive patients as it is for HIV-negative patients, but that HIV-positive patients would experience no additional burdens associated with remaining on treatment longer than required for HIV-negative patients.

TABLES

Table 1. Selected characteristics of HCV mono-infected and HCV/HIV co-infected patients treated with Harvoni (LDF/SOF) at the Atlanta Veteran's Affairs Medical Center from 2015-2016

*Characteristics*a	**HCV mono-infected (n = 197)**	**HCV/HIV co-infected (n = 25)**	**P-value**b
Age, years	63.1 (4.1)	62.2 (5.2)	0.33
Men	187 (94.9)	25 (100.0)	0.25
Race			0.03
Non-Hispanic White	66 (33.5)	3 (12.0)	
Non-Hispanic Black	129 (65.5)	21 (84.0)	
Hispanic	0 (0.0)	1 (4.0)	
Other	2 (1.0)	0 (0.0)	
Duration of Treatment, days	80.8 (28.3)	76.6 (29.3)	0.46
Adherent to Medicationc	163 (82.7)	24 (96.0)	0.03
HCV Viral Load, at baseline (IU/mL)	2,720,181 (2,493,072)	2,971,000 (2,812,104)	0.64
Completed Treatment	196 (99.5)	24 (96.0)	0.08
Completed Normal Course of Treatmentd	185 (93.9)	21 (84.0)	0.07

Abbreviations: HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; Tx, Treatment; LDF, ledipasvir; SOF, sofosbuvir

aContinuous variables presented as mean (SD) and categorical variables as n (%)

bP-values derived from *t* test for continuous variables and $\chi 2$ test for categorical variables

cAdherence to medication determined by ≤7 days between medication refills

dNormal Course includes those who completed treatment and did not discontinue treatment and did not relapse

Table 2. HIV-related characteristics of HCV/HIV co-infected patients treated with Harvoni from HIV Atlanta VA Cohort Study from 2015-2016

*Characteristics*a	**HCV/HIV co-infected**
Previous AIDS diagnosis	4 (16.0)
ART Naive	0 (0.0)
CD4 count, at baseline (cells/mm3)	585.8 (251.6)
CD4 count, most recent (cells/mm3)	618.4 (259.1)
HIV viral load, at baseline (copies/mL)	117.1 (373.5)
HIV viral load, most recent (copies/mL)	96.0 (186.3)

Abbreviations: HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; AIDS, Acquired Immunodeficiency Syndrome; ART, Antiretroviral Therapy

aContinuous variables presented as mean (SD) and categorical variables as n (%)

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