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Hepatitis C virus treatment response to ledipasvir/sofosbuvir among patients coinfected with HIV and HCV

Real world data in a black population

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Abstract

Treatment of hepatitis C virus (HCV) infection for patients with human immunodeficiency virus (HIV) has improved with direct acting antivirals. However, outcomes among Black persons treated with ledipasvir/sofosbuvir (LDV/SOF) may be inferior to non-Blacks. We assessed responses to LDV/SOF in a cohort of Black HIV/HCV coinfected persons.

Retrospective chart reviews were conducted for Black, genotype 1 (GT1), HIV/HCV coinfected patients treated with LDV/SOF at 3 hospitals in Newark, NJ between January 2014 and July 2016. Data collected included demographics, HCV treatment history, treatment duration, and response.

One hundred seventeen HIV/HCV coinfected Black patients started treatment with LDV/SOF but 5 had no follow-up data and 5 prematurely discontinued treatment (1 due to side effects). We included 107 HIV/HCV coinfected patients who completed LDV/SOF at all 3 sites. The study population was 65% male, median age 58 years, 26% had cirrhosis, and 78% had GT1a. Thirty-one percent were treatment experienced but none with prior NS5a treatment. At baseline, median CD4 count was 680 cells/mm^3, HIV viral load (VL) was <40 copies/mL in 94% and median HCV VL was 2,257,403 IU/mL. Twenty-nine percent of patients changed antiretroviral treatment before LDV/SOF treatment due to drug interactions. Six, 89, and 12 patients completed 8, 12, and 24 weeks of LDV/SOF, respectively. Overall sustained virologic response rate was 93% with 7 relapses.

In this real-world cohort of Black, GT1, HIV/HCV coinfected patients, LDV/SOF had high sustained virologic response 12 weeks post completion of treatment rate of 93%. This data supports the overall high efficacy of LDV/SOF in a historically difficult-to-treat patient population.

Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral treatment, ATV/r = ritonavir-boosted atazanavir, DAAs = direct acting antivirals, DTG = dolutegravir, EFV = efavirenz, FTC = emtricitabine, GT1 = genotype 1, HCV = hepatitis C virus, HCV VL = hepatitis C virus viral load, HIV = human immunodeficiency virus, HIV VL = human immunodeficiency virus viral load, INSTI = integrase strand transfer inhibitor, LDV/SOF = ledipasvir/sofosbuvir, PI = protease inhibitor, PPI = proton pump inhibitor, RAL = raltegravir, RPV = rilpivirine, SVR = sustained virologic response, SVR12 = sustained virologic response 12 weeks post completion of treatment, TDF = tenofovir disoproxil fumarate, VL = viral load.

Keywords: coinfection, hepatitis C virus, HIV/HCV coinfection, ledipasvir/sofosbuvir

1. Introduction

Hepatitis C virus infection (HCV) is a significant cause of morbidity and mortality globally. In the United States, an estimated 1% of the population lives with the disease.[1] About 1/4 of patients with human immunodeficiency virus (HIV) are coinfected with HCV.[2] Patients coinfected with HIV/HCV have more rapid progression to liver failure and hepatocellular carcinoma, compared to HCV mono-infected patients.[3] Persons with HIV/HCV coinfection also have higher rates of mortality and morbidity related to HCV infection than HCV-mono-infected persons.[4] This increased risk persists despite effective treatment of HIV infection.[5–8] The goal of HCV treatment is to achieve and maintain undetectable levels of HCV RNA 12 weeks after completion of therapy, known as sustained virologic response (SVR). Response rates to treatment of HCV infection with pegylated interferon and ribavirin have been poor among those with HIV coinfection.[4] The advent of direct acting antivirals (DAAs) for HCV infection has improved response rates significantly. One such DAA regimen is ledipasvir/sofosbuvir (LDV/SOF); ledipasvir is a HCV nonstructural protein 5A (NS5a) inhibitor with antiviral activity against HCV genotypes 1a and 1b

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and sofosbuvir is a nucleotide polymerase inhibitor approved for treatment of HCV genotypes 1 to 4. The combination LDV/SOF is approved for treatment of HCV genotype 1, 4, 5, and 6. Several randomized controlled trials have demonstrated the efficacy of LDV/SOF in achieving SVR in patients with chronic HCV infection, regardless of prior HCV treatment, length of treatment course, or HIV coinfection. However, data regarding efficacy of LDV/SOF among different racial groups remains unclear. Some studies have demonstrated significantly lower SVR rates amongst Black HIV/HCV coinfected patients; this racial difference in treatment response was not seen in the mono-infected analyses.[9–14] In this study, we conducted a retrospective chart review to assess real-world responses to LDV/SOF in a cohort of Black HIV/HCV coinfected persons in Newark, NJ.

2. Methods

Retrospective chart reviews were conducted at 3 hospitals in Newark, NJ between January 2014 and July 2016. Inclusion criteria for the study were: patients >18 years old who had HIV infection; HCV genotype 1 (GT1) infection; been treated with LDV/SOF; no prior treatment with any NS5a or nonstructural protein 5b inhibitors; and self-identified as Black. Patients with no prior HCV treatment as well as those with prior treatment failure with pegylated interferon only with or without ribavirin were included. At each of the 3 sites, subject records were accessed via the electronic medical record. The study was approved by the institutional review board at each participating site. Data collected included demographics, HCV treatment history, duration of LDV/SOF regimen, treatment response, CD4 count and HIV viral load (VL), antiretroviral treatment (ART), use of proton pump inhibitors (PPI), and adverse events. Descriptive and summary statistics were used to analyze population and SVR rates. Primary efficacy end point was the rate of SVR, defined as absence of quantifiable HCV RNA in serum 12 weeks after the end of therapy. Relapse was defined as obtaining an undetectable HCV VL that became detectable with the same genotype subtype on laboratory data either 4 weeks or 12 weeks post completion of treatment.

3. Results

A total of 117 HIV/HCV coinfected Black patients initiated treatment with LDV/SOF during the study period. Of these patients, 107 completed treatment and follow-up at all 3 sites (Table 1). Five patients did not have follow-up data and 5 patients prematurely discontinued therapy, 1 due to side effects (0.9%). The study population was 65% male, median age 58 years, 26% had cirrhosis, and 78% had GT1a. Thirty-one percent of patients were treatment experienced but none with prior NS5a treatment. At baseline, median CD4 count was 680 cells/mm^3, HIV VL was <40 copies/mL in 94% and median HCV VL was 2,257,403 IU/mL.

Table 1

Demographic characteristics of patients at baseline (N = 107).

Median age (yrs)	58
Male sex; N (%)	69 (65)
HCV 1a genotype; N (%)	83 (78)
Median HCV viral load (IU/mL)	2,257,403
Prior interferon treatment; N (%)	33 (31)
Cirrhosis; N (%)	28 (26)
Median CD4 cell count (cells/μL)	680

HCV = hepatitis C virus.

Table 2

Sustained virologic outcomes.

	SVR12 rates	Relapse
Overall	93%	7/107
By duration		
8 weeks	67%	2/6
12 weeks	96%	4/89
24 weeks	92%	1/12
By ART class		
INSTI	95%	3/65
PI	93%	1/14
Included efavirenz	80%	1/5
Other	91%	2/23
Cirrhotics	96%	1/28

ART = antiretroviral treatment, INSTI = integrase inhibitor strand transfer inhibitor, PI = protease inhibitor, SVR12 = sustained virologic response 12 weeks post completion of treatment.

Patients were continued on HIV treatment during HCV therapy. Twenty-nine percent of patients (31/107) changed ART before LDV/SOF treatment due to anticipated drug–drug interactions with LDV/SOF. Notably, 14/28 (50%) of patients on a protease inhibitor at baseline were switched to integrase strand transfer inhibitor (INSTI) based regimens before starting treatment with LDV/SOF. Of the 12 people on efavirenz at baseline, 7 were switched off efavirenz before LDV/SOF treatment. Majority of the patients were on INSTI based regimens (65/107, or 61%) at week 0 of LDV/SOF treatment. Four of the 31 patients who changed ART regimen before LDV/SOF switched back to their original regimens after completion of HCV treatment. Six, 89, and 12 patients completed 8, 12, and 24 weeks of LDV/SOF, respectively. Duration of the treatment was at the discretion of the treating physician. Of the 6 patients who received 8 weeks of treatment, none were cirrhotic and the median HCV VL at baseline was 1,186,466 copies/mL. Overall SVR rate was 93% (Table 2) with 7 relapses (Table 3).

Treatment was well tolerated, with 19/107 (18%) of patients reporting any new symptoms, most commonly fatigue and headaches. No adverse events reported were thought to be related to LDV/SOF. Seven percent of patients received PPI treatment while on LDV/SOF; all patients receiving PPI during LDV/SOF treatment achieved SVR. Five patients (5%) had HIV VL breakthrough (>200 copies/mL); 3/5 achieved SVR.

4. Discussion

Despite similar rates of SVR demonstrated in clinical trials for HCV mono-infected and HIV/HCV coinfected patients, Black patients had significantly lower response rates than other patients. Black HIV/HCV coinfected patients have been historically considered a difficult-to-treat population secondary to more comorbidities, higher drug–drug interactions, and higher prevalence of ongoing barriers to care (such as neuropsychiatric disease, unstable housing, lower socioeconomic status, active drug/alcohol use).[14] In this retrospective review of 107 Black HIV/HCV coinfected patients who completed treatment with ledipasvir-sofosbuvir, the overall SVR rate was 93%. This rate is comparable to the overall rates of SVR demonstrated in clinical trials and supports real-world high efficacy of LDV/SOF in Black HIV/HCV coinfected patients.

Table 3

Characteristics of patients who relapsed.

Patient	Age	Cirrhosis	Baseline HCV VL (IU/mL)	ART on LDV/SOF	Genotype	Prior tx	Duration (weeks)	HIV VL breakthrough during tx
1	57	No	5,000,000	DTG/ABC/3TC	1a	No	12	No
2	59	Yes	1,740,200	RPV/TDF/FTC	1a	Yes	24	No
3	68	No	9,659,736	RPV/TDF/FTC	1a	Yes	12	No
4	54	No	9,506,970	EFV/TDF/FTC	1a	No	12	Yes
5	56	No	2,205,076	RAL/TDF/FTC	1a	No	8	No
6	61	No	12,815,000	ATV/r/TDF/FTC	1a	No	8	No
7	57	No	7,981,510	DTG/ABC/3TC	1a	Yes	12	Yes

3TC = lamivudine, ABC = abacavir, ART = antiretroviral treatment, ATV/r = ritonavir-boosted atazanavir, DTG = dolutegravir, EFV = efavirenz, FTC = emtricitabine, HCV VL = hepatitis C virus viral load, HIV VL = human immunodeficiency virus viral load, LDV/SOF = ledipasvir-sofosbuvir, RAL = raltegravir, RPV = rilpivirine, TDF = tenofovir disoproxil fumarate, tx = treatment.

Length of therapy noninferiority analysis have previously established 8 week regimens noninferior to 12 week regimens among HCV mono-infected persons. In our study, the SVR rate was 67% in the 8 weeks arm as compared to 96% in the 12-week arm. However, there were only 2 relapses in the 8-week arm and 1 of those patients had a baseline VL of 12,815,000 copies/mL which is higher than the recommended cutoff for short course treatment with LDV/SOF. However, the number of patients receiving 8 week treatments were small and number of patients who had relapse were not sufficient to determine appropriate baseline response variables. Thirty-two percent of patients with cirrhosis underwent 24 weeks of LDV/SOF treatment, the remaining completed 12 weeks of treatment. The 1 patient with cirrhosis who relapsed had completed 24 weeks of therapy.

Since adherence could not be measured in real time, adherence was ascertained through documentation in provider notes and also the failure of concomitant ART with an increase in HIV VL. Only 1 of the 7 patients who relapsed had documented nonadherence to LDV/SOF; adherence data was not available for 6/7. Five patients (5%) had HIV VL breakthrough during treatment with LDV/SOF. Of these, 1 patient self-discontinued ART during treatment with HCV, 2 patients had documented intermittent nonadherence to ART. Two of the 5 patients with HIV VL breakthrough had HCV relapse, 3/5 achieved and sustained HCV suppression throughout the study period. Subgroup analysis of ART regimens in this study indicates a lower SVR rate for patients who were concomitantly taking efavirenz. In our study, there was only 1 participant on an efavirenz-based regimen who experienced a treatment relapse. Given only 5 patients were on efavirenz-based regimens, the 80% SVR rate cannot be considered robust and has high variability (confidence interval 28%, 95%, Fisher exact $P = .317$). Prior studies have suggested that the CYP2B6 polymorphism, more common in Black persons, is associated with higher serum efavirenz levels, though this was not found to be associated with relapse.[15] Fifty-eight percent of patients who had efavirenz in their ART regimen were switched to a different regimen by providers before initiating treatment with LDV/SOF.

Limitations of this study include retrospective data collection and provider dependent decisions. Given the retrospective nature of the study, there may be confounding factors that are unaccounted for. Further, genotype data for those who relapsed was not collected, therefore not definitively excluding the possibility of new infections vs true relapse. While this study achieves the purpose of measuring real-world success of LDV/SOF in a historically difficult-to-treat Black, HIV/HCV coinfected patient population, it also lends insight into provider variability in determining ultimate HCV treatment. Further, we did not capture impact of insurance restrictions as a factor on duration of therapy for this cohort of patients. Therefore, further studies are warranted to develop appropriate ART regimens and length of LDV/SOF therapy required for coinfected patients with and without cirrhosis.

Since the completion of this study, other DAAs and pangenotypic regimens such as glecaprevir/pibrentasvir, sofosbuvir/daclatasvir, and sofosbuvir/velpatasvir have been introduced with reported high SVR rates in chronic HCV treatment.[16–18] However, significant reported drug–drug interactions and restrictions of use in cirrhosis ultimately leads to continued provider variability in regimen choice.[17,19,20] This study demonstrates high SVR rate and efficacy of LDV/SOF in Black, HIV/HCV coinfected patients, though further studies are warranted to determine optimal regimens and durations of therapies while balancing patient characteristics, baseline data, and potential interactions with ART.

5. Conclusion

In conclusion, we found that in this real-world cohort of Black, HIV/HCV coinfected patients, LDV/SOF had a high SVR rate of 93%. This data supports the high overall efficacy of LDV/SOF even in historically difficult to treat populations.

Author contributions

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