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Safety and Efficacy of Ledipasvir-Sofosbuvir in Black Patients With Hepatitis C Virus Infection: A Retrospective Analysis of Phase 3 Data

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Black patients chronically infected with genotype 1 hepatitis C virus (HCV) have historically had lower rates of response to interferon-based treatment than patients of other races. In the phase 3 ION program, the single-tablet regimen of the NS5A inhibitor ledipasvir and NS5B nucleotide polymerase inhibitor sofosbuvir was shown to be safe and highly effective in the general population. The aim of this study was to evaluate the safety and efficacy of ledipasvir/sofosbuvir in black patients using data from the three open-label ION clinical trials, which evaluated the safety and efficacy of 8, 12, and 24 weeks of ledipasvir/sofosbuvir with or without ribavirin for the treatment of treatment-naïve and treatment-experienced patients with genotype 1 HCV, including those with compensated cirrhosis. The primary endpoint was sustained virologic response at 12 weeks after the end of therapy (SVR12). For our analysis, rates of SVR12, treatment-emergent adverse events, and graded laboratory abnormalities were analyzed in black versus non-black patients. Of the 1949 patients evaluated, 308 (16%) were black. On average, black patients were older, had higher body mass index, were more likely to be *IL28B* non-CC, and had a lower serum alanine aminotransferase at baseline than non-black patients. Overall, 95% of black and 97% of non-black patients achieved SVR12. The rate of relapse was 3% in black patients as compared with 2% in non-black patients. The most common adverse events included fatigue, headache, nausea, and insomnia. The majority of adverse events occurred more frequently in the ribavirin-containing arms of the studies. No differences were observed in overall safety by race. *Conclusion*: A once-daily dosage of ledipasvir/sofosbuvir was similarly effective in black and non-black patients with genotype 1 HCV infection. The addition of ribavirin did not appear to increase SVR12 but was associated with higher rates of adverse events. (HEPATOLOGY 2016;63:437-444)

The leading cause of cirrhosis and hepatocellular carcinoma and the most common indication for liver transplantation in the United States is chronic hepatitis C infection.[1] Approximately 3.2 million people in the United States have chronic hepatitis C virus (HCV) infection.[2,3] Although blacks comprise approximately 13% of the United States population, they represent approximately 23% of the population with hepatitis C.[4] An analysis using NHANES III data (1999-2002) revealed that the rate of a positive HCV antibody test was higher in blacks than in whites (3.2% versus 1.5%).[4] Black men have higher rates of infection,

Abbreviations: BMI, body mass index; HCV, hepatitis C virus; RAV, resistance-associated variant; SVR12, sustained virologic response at 12 weeks after the end of therapy.

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and the highest prevalence rate was 9.8% among black men who were 40-49 years of age.[5,6]

The options for treating HCV have shifted toward more tolerable, safe, and effective oral regimens. This represents an opportunity to dramatically reduce the burden of this disease within the population. The previous generation of new direct-acting antivirals (e.g., boceprevir, telaprevir) was shown to have consistently lower HCV treatment response rates among blacks.[7-9] Although the newest generation of direct-acting antivirals presents an opportunity for truly curing HCV at the population level, those individuals disproportionately affected by the disease have traditionally been underrepresented in clinical trials. Hence, the true efficacy and safety of the new medications among those most affected by HCV are not fully known.

Ledipasvir is a new HCV NS5A inhibitor with potent antiviral activity against HCV genotypes 1a and 1b.[10] Sofosbuvir is a nucleotide polymerase inhibitor approved for the treatment of HCV genotypes 1 through 4 in combination with ribavirin[11] with or without peginterferon. There have been three phase 3 clinical trials (ION program) evaluating the safety and efficacy of a fixed-dose oral combination of these two medications for the treatment of HCV genotype 1.

The results of the three ION clinical trials showed that the single-tablet-regimen of ledipasvir and sofosbuvir was safe and effective, with SVR12 rates of >90% in treatment-naïve and previously treated patients.[12-14] The aim of this retrospective analysis was to evaluate the safety and efficacy of this new regimen in black subjects.

Patients and Methods

We evaluated rates of sustained virologic response 12 weeks after the end of treatment (SVR12), adverse events, and graded laboratory abnormalities in black versus non-black subjects in the phase 3 ION program. The ION-1, ION-2, and ION-3 clinical trials evaluated the safety and efficacy of 8, 12, and 24 weeks of the fixed-dose combination of ledipasvir and sofosbuvir with or without ribavirin for treatment of genotype-1 chronic HCV. There was no upper limit to age or body mass index (BMI), and the primary endpoint was SVR12 for all trials.

The ION-1 trial was a phase 3 open-label study involving 865 (16% cirrhotic) previously untreated patients with chronic HCV. In the ION-1 trial, patients were randomly assigned to four arms in a 1:1:1:1 ratio to receive ledipasvir/sofosbuvir in a fixed-dose combination tablet once daily for 12 weeks (with or without ribavirin) or for 24 weeks (with or without ribavirin).[12]

The ION-2 clinical trial was structured similarly to the ION-1 trial; however, it was a phase 3, randomized open-label study involving 440 patients (20% cirrhotic) infected with HCV genotype 1 who had not had a sustained virologic response after treatment with peginterferon and ribavirin, with or without a protease inhibitor.[13] Similar to the ION-1 trial, patients in the ION-2 trial were randomly assigned to receive ledipasvir and sofosbuvir in a once-daily, fixed-dose combination tablet for 12 or 24 weeks with or without ribavirin.

Given the high SVR12 rates seen at 12 weeks for the ION-1 and ION-2 trials, the ION-3 trial was devised to

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Table 1. Patient Demographics

Demographic	Black (n = 308)	Non-Black (n = 1641)
Age, years, mean (range)	57 (26-77)	52 (18-80)
Male sex, n (%)	200 (65)	972 (59)
BMI, kg/m^2, mean (range)	29.5 (18.1-46.8)	26.9 (18.0-56.2)
BMI $\geq$30 kg/m^2, n (%)	125 (41)	376 (23)
Genotype 1a, n (%)	214 (70)	1227 (75)
Cirrhosis, n (%)	22 (7)	202 (12)
IL28B non-CC, n (%)	277 (90)	1190 (73)
HCV RNA $\geq$800,000 IU/mL, n (%)	269 (84)	1336 (81)
Mean ALT level, U/L	61	77
Mean eGFR value, mL/min	104.6	106.8
Treatment-naïve, n (%)	231 (75)	1278 (78)

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus.

evaluate SVR after 8 weeks of treatment.[14] ION-3 was an open-label study with random assignment of 647 previously untreated patients with HCV genotype 1 infection without cirrhosis to receive the combination of ledipasvir and sofosbuvir with or without ribavirin for 8 weeks or ledipasvir/sofosbuvir for 12 weeks.

Using pooled data from the ION trials, we performed an integrated ad hoc analysis to evaluate the efficacy and safety of ledipasvir/sofosbuvir with or without ribavirin in black versus non-black patients. Descriptive summaries were provided by race (black or non-black) for the key demographics and baseline characteristics, including age, sex, BMI, IL28B genotype, and so forth. The SVR12 rate and the two-sided 95% exact confidence interval (Clopper-Pearson method) were calculated by race (black or non-black) and for each subgroup defined by prior HCV treatment experience (treatment-naïve or treatment-experienced), cirrhosis status (cirrhotic versus non-cirrhotic), and baseline HCV RNA (<6 or $\geq$6 million IU/mL). Safety data were analyzed by the number and percent of black versus non-black patients experiencing adverse events.

Results

Demographics. Of the 1952 patients randomized and treated in the ION studies, 308 (16%) self-reported their race as black. Of the remaining 1644 patients in these studies, three declined to report race, leaving 1641 non-black patients for comparison in this analysis. Table 1 shows demographic characteristics by black and non-black patients. The black cohort was slightly older with a greater proportion of men versus women. Overall, approximately one quarter of the patients had a BMI $\geq$30 kg/m^2; this proportion was considerably higher among black patients than it was among non-black patients (41% versus 23%). The majority of both cohorts had genotype 1a HCV. Overall, 12% of patients, but only 7% of blacks, had compensated cirrhosis. As expected, more blacks had non-CC *IL28B* genotypes than non-blacks (90% versus 73%). The mean alanine aminotransferase level for blacks (61 U/L) was lower than that of non-blacks (77 U/L). Among the ION study participants, similar proportions of black and non-black patients were treatment-experienced and had HCV RNA $\geq$800,000 IU/mL.

Efficacy. Overall, 95% of black patients (95% confidence interval [CI], 92%-97%) and 97% of non-black patients (95% CI, 96%-98%) achieved SVR12 (Fig. 1).

Table 2 shows SVR12 rates in black versus non-black patients by treatment history, cirrhosis status, regimen, and combined regimen and baseline viral load. Although these subgroups were not powered for formal comparisons, some general observations may be made. Among treatment-naïve patients without cirrhosis who received 8 weeks of ledipasvir/sofosbuvir with and without ribavirin, the rate of SVR12 was 90% among blacks versus 94% among non-blacks. In most, but not all, subgroups of those receiving 8 weeks of treatment, there are similar differences, with slightly more non-black patients achieving SVR12 than black patients. The largest difference was between black and non-black patients with a high viral load at baseline (HCV RNA $\geq$6,000,000) not receiving ribavirin (83% versus 92%).

Figure 2 shows rates of relapse by race and treatment duration. Overall, 10 black patients (3%) relapsed compared with 26 non-black patients (2%), but among patients receiving 8 weeks of treatment, there was a substantial numerical difference: 9% of black patients relapsed versus 4% of non-black patients. One black patient, a 63-year-old man with HCV genotype 1b who was in the 24-week ledipasvir/sofosbuvir group of ION-1, had virologic breakthrough at week 8 of treatment.

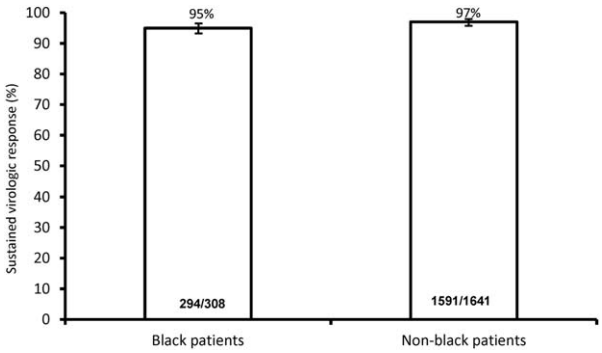

Fig. 1. Percentages of blacks and non-blacks who achieved SVR12.

Table 2. SVR12 by Baseline Factors, Treatment History, and Regimen

	Treatment Duration											
	8 Weeks				12 Weeks				24 Weeks			
	Black		Non-black		Black		Non-black		Black		Non-black	
Response	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
HCV treatment history												
Treatment-naïve	73/81 (90)	81%-96%	330/350 (94)	91%-96%	91/92 (99)	94%-100%	537/553 (97)	95%-98%	55/58 (95)	86%-99%	372/375 (99)	98%-100%
Treatment-experienced	–	–	–	–	39/40 (98)	87%-100%	170/180 (94)	90%-97%	36/37 (97)	86%-100%	182/183 (99)	97%-100%
Cirrhosis status												
No cirrhosis	73/81 (90)	81%-96%	330/350 (94)	91%-96%	119/120 (99)	95%-100%	612/630 (97)	96%-98%	82/85 (96)	90%-99%	450/454 (99)	98%-100%
Cirrhosis	–	–	–	–	11/12 (92)	62%-100%	91/99 (92)	85%-96%	9/10 (90)	55%-100%	103/103 (100)	96%-100%
By regimen												
LDV/SOF alone	41/45 (91)	79%-98%	161/170 (95)	90%-98%	89/90 (99)	94%-100%	431/448 (96)	94%-98%	45/49 (92)	80%-98%	276/277 (100)	98%-100%
LDV/SOF + RBV	32/36 (89)	74%-97%	169/180 (94)	89%-97%	41/42 (98)	87%-100%	276/285 (97)	94%-99%	46/46 (100)	92%-100%	278/281 (99)	97%-100%
By regimen and baseline HCV RNA												
LDV/SOF and HCV RNA <6,000,000	26/27 (96)	81%-100%	93/96 (97)	91%-99%	59/60 (98)	91%-100%	283/294 (96)	93%-98%	31/34 (91)	76%-98%	201/202 (100)	97%-100%
LDV/SOF + RBV and HCV RNA <6,000,000	17/19 (89)	67%-99%	116/119 (97)	93%-99%	28/28 (100)	88%-100%	189/195 (97)	93%-99%	35/35 (100)	90%-100%	195/197 (99)	96%-100%
LDV/SOF and HCV RNA ≥6,000,000	15/18 (83)	59%-96%	68/74 (92)	83%-97%	30/30 (100)	88%-100%	148/154 (96)	92%-99%	14/15 (93)	68%-100%	75/75 (100)	95%-100%
LDV/SOF + RBV and HCV RNA ≥6,000,000	15/17 (88)	64%-99%	53/61 (87)	76%-94%	13/14 (93)	66%-100%	87/90 (97)	91%-99%	11/11 (100)	72%-100%	83/84 (99)	94%-100%

Patients who did not disclose their race or who were missing cirrhosis status were excluded from the analysis.

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response at 12 weeks after the end of therapy.

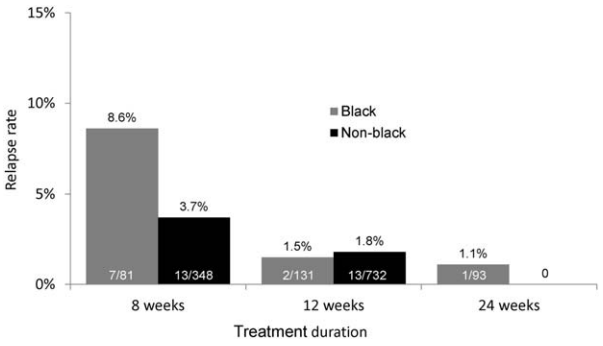

Fig. 2. Rates of relapse by race and treatment duration.

This patient had undetectable plasma concentrations of ledipasvir and the circulating metabolite of sofosbuvir at weeks 8 and 10, suggesting non-adherence to the study treatment. Table 3 shows the characteristics of the 11 black patients who had virologic failure. Four of these 11 patients had NS5A or NS5B resistance-associated variants (RAVs) at baseline, and nine had Y93H or Q30 NS5A RAVs at the time of relapse.

Table 4 shows SVR12 and virologic failure rates in black and non-black patients by presence or absence of baseline NS5A RAVs. Both black and non-black patients with baseline NS5A RAVs at baseline had rates of SVR12 that were numerically lower and rates of virologic failure that were numerically higher than patients without baseline RAVs, but the difference was not large (between 4 and 7 percentage points). Black patients with and without NS5A RAVs had slightly lower rates of SVR12 and higher rates of virologic failure than corresponding groups of non-black patients, but again the numeric differences were slight (between 2 and 5 percentage points).

Differences in response and relapse by race are less evident among patients receiving 12 and 24 weeks of treatment. Overall, rates of SVR12 among treatment-naïve and treatment-experienced patients, as well as those with and without cirrhosis, are similarly high in black and non-black cohorts. The SVR12 rates in treatment-experienced patients receiving a 12-week regimen were 98% for blacks and 94% for non-blacks, and in patients receiving a 24-week regimen, SVR12 rates were 100% for non-blacks and 97% for blacks (Table 2).

Patients with cirrhosis have historically been a difficult-to-treat population. In our analysis, no race-based differences were evident by cirrhosis status in patients receiving 12 weeks of treatment. Both black and non-black patients with cirrhosis had an SVR12 rate of 92%, which was lower than the rate in patients without cirrhosis, but black and non-black patients without cirrhosis had similar rates of SVR12 (99%

Table 3. Characteristics of Black Patients with Virologic Failure

Study	Treatment Group	Age (years)	Sex	HCV Genotype	HCV RNA (log_{10} IU/mL)	IL28B Genotype	Cirrhosis	Treatment History	Type of Virologic Failure	Relevant RAVs			
										NS5A		NS5B	
										Baseline	Post-baseline	Baseline	Post-baseline
ION-1	LDV/SOF 24 weeks	63	M	1b	6.4	CT	No	Naïve	Breakthrough	None	Y93H (>99%)	None	None
		65	M	1b	6.6	TT	Yes		Relapse	Y93H (94%)	Y93H (>99%)	None	None
ION-2	LDV/SOF +RBV 12 weeks	63	M	1a	7.2	CT	Yes	PI + peginterferon + RBV	Relapse	None	Q30K (>99%)	None	None
ION-3	LDV/SOF 8 weeks	65	M	1a	7.0	CC	No	Naïve	Relapse	Q30Y (2.0%) Q30H (1.2%) Y93H (3.6%)	Q30Y (>99%) Y93H (>99%)	F415Y (95.4%)	F415Y (>99%)
		53	F	1a	6.9	CT	No	Naïve	Relapse	None	Q30R (>99%)	None	None
		55	M	1b	7.2	TT	No	Naïve	Relapse	None	Y93H (>99%)	None	None
	LDV/SOF + RBV 8 weeks	71	F	1b	6.8	TT	No	Naïve	Relapse	Y93H (63.8%)	Y93H (>99%)	None	None
		61	M	1a	6.2	CT	No	Naïve	Relapse	None	None	None	None
		56	M	1a	6.9	CT	No	Naïve	Relapse	Y93C (8.7%)	None	None	None
		59	M	1a	6.4	TT	No	Naïve	Relapse	None	S38F (>99%) Y93H (>99%)	None	None
	LDV/SOF 12 weeks	56	M	1b	6.2	TT	No	Naïve	Relapse	None	L31I (>99%) Y93H (>99%)	None	None

Abbreviations: F, female; HCV, hepatitis C virus; LDV, ledipasvir; M, male; PI, protease inhibitor; RAV, resistance-associated variant; RBV, ribavirin; SOF, sofosbuvir.

Table 4. Virologic Outcomes in Black and Non-black Patients by Presence or Absence of Baseline NS5A RAVs

Virologic Outcome*	Black	Non-black
SVR in patients with baseline NS5A RAVs	35/39 (90%)	260/278 (94%)
SVR in patients without baseline NS5A RAVs	257/267 (96%)	1327/1359 (98%)
Virologic failure in patients with baseline NS5A RAVs	4/39 (10%)	15/278 (5%)
Virologic failure in patients without baseline NS5A RAVs	7/267 (3%)	12/1359 (1%)

*For patients for whom sequencing data were available.

versus 97%). In patients receiving 24 weeks of treatment, however, a lower proportion of black patients with cirrhosis had SVR12 (90%) than non-black patients with cirrhosis (100%), However, there were only 10 black patients with cirrhosis in this group.

The efficacy of ledipasvir/sofosbuvir did not appear to be greatly affected by the presence of ribavirin in black or non-black patients. The four analysis groups of patients receiving 12 weeks of treatment—black patients receiving ribavirin, black patients not receiving ribavirin, non-black patients receiving ribavirin, and non-black patients not receiving ribavirin—all had very similar SVR12 rates within the range of 96%-99%. Among patients receiving 24 weeks of treatment, one group—black patients not receiving ribavirin—had an SVR12 rate that was substantially lower (92%) than that of the other groups (99%-100%).

Safety. For a safety analysis, we pooled patients by race (black versus non-black) and drug combination (ledipasvir/sofosbuvir versus ledipasvir/sofosbuvir plus ribavirin). The most common adverse events in all groups were fatigue, headache, nausea, and insomnia (Table 5). Dose modification or interruption was required in 13% of black patients and 14% of non-black patients receiving ledipasvir/sofosbuvir plus ribavirin compared with <1% of black and non-black patients receiving ledipasvir/sofosbuvir alone. In general, a numerically larger percentage of black patients receiving ledipasvir/sofosbuvir plus ribavirin had safety events than black patients receiving ledipasvir/sofosbuvir alone. The same was true for non-black patients; more non-black patients receiving ledipasvir/sofosbuvir plus ribavirin experienced safety events than those receiving ledipasvir/sofosbuvir alone. For both dose combinations, fewer black patients than non-black patients had safety events.

Discussion

In this analysis of data from the ION phase 3 clinical trials evaluating the fixed-dose combination of ledipasvir/sofosbuvir with and without ribavirin in treatment-naïve and previously treated patients with genotype 1 HCV, we found that black patients had rates of SVR12 similar to those in non-black patients, regardless of treatment history, treatment duration, or cirrhosis status. Among the 308 patients who self-identified as black, SVR12 rates were high (≥90%) even among those with compensated cirrhosis and those who had previously failed previous treatment, including treatment with a protease inhibitor and peginterferon/ribavirin. The addition of ribavirin did not appear to increase SVR12 rates but led to higher rates of adverse events. The factor that appeared to be most strongly associated with response was treatment duration; the rate of relapse among black patients in the 8-week

Table 5. Overall Safety by Race

	Ledipasvir/Sofosbuvir		Ledipasvir/Sofosbuvir + Ribavirin	
Patients, n (%)	Black (n = 184)	Non-black (n = 895)	Black (n = 124)	Non-black (n = 746)
Grade ≥3 AE	5 (3)	41 (5)	5 (4)	40 (5)
Serious AE	5 (3)	29 (3)	5 (4)	12 (2)
Treatment-related serious AE	0	4 (<1)	0	1 (<1)
AEs leading to study drug modification/interruption	1 (<1)	5 (<1)	16 (13)	102 (14)
Treatment discontinued due to AE	1 (<1)	5 (<1)	2 (2)	9 (1)
Deaths	0	0	0	0
Common AEs*	123 (67)	685 (77)	97 (78)	653 (88)
Fatigue	33 (18)	208 (23)	32 (26)	300 (40)
Headache	29 (16)	195 (22)	21 (17)	210 (28)
Nausea	12 (7)	100 (11)	11 (9)	142 (19)
Insomnia	12 (7)	71 (8)	7 (6)	147 (20)
Irritability	4 (2)	43 (5)	6 (5)	89 (12)
Rash	9 (5)	39 (4)	9 (7)	85 (11)
Cough	8 (4)	34 (4)	10 (8)	81 (11)

*Events occurring in at least 10% of patients in any treatment group.

Abbreviations: AE, adverse event.

treatment arms of ION-3 was 8.6% compared with 1.5% among blacks receiving 12 weeks of treatment and 1.1% among blacks receiving 24 weeks of treatment. Even so, this result likely understates the difference in response by treatment duration, given that the 8-week group enrolled only treatment-naïve patients without cirrhosis, whereas the groups receiving 12 and 24 weeks of treatment included previously treated patients and those with cirrhosis. If patients receiving the clearly suboptimal duration of 8 weeks are omitted from the analysis, there are not enough patients with virologic failure (n = 3) to make any generalizations concerning factors predictive of treatment success or failure.

Given the known safety profile of ribavirin, higher rates of adverse events in patients receiving ribavirin than in those receiving sofosbuvir-ledipasvir alone were expected. This pattern was evident in comparing black patients who did and did not receive ribavirin and non-black patients who did and did not receive ribavirin. What was unexpected was that black patients receiving ledipasvir/sofosbuvir and those receiving ledipasvir/sofosbuvir plus ribavirin had consistently lower rates of most adverse events than non-black patients (Table 4). The reason for these differences is not known but may be partly explained by the fact that a slightly higher percentage of black patients than non-black patients received 8 weeks of treatment (26% versus 21%) and a lower percentage of black patients had cirrhosis (7% versus 12%). One might have expected, however, that these differences would have been offset by the higher mean age and BMI among black patients.

Our analysis is limited by the retrospective framework and need to combine the black population across all three of the ION studies for these comparisons. Overall, the ION-1, −2, and −3 studies achieved a relatively good level of diversity with black patients representing 16% of the study population. This is significantly better than previous and current studies in HCV treatment. However, even with 300 patients, we lose the necessary means to achieve reliable results when attempting to look at subgroups, such as when examining compensated cirrhosis in blacks (only 38 patients). Therefore, although the ION-1, −2, and −3 studies when combined achieved a relatively diverse population for analysis, the overall population was still too small to perform the nuanced analyses required to definitively show efficacy and safety in diverse populations.

A lack of participation of minorities in clinical trials is a major barrier to identifying treatment regimens for diverse populations. Blacks are disproportionally affected by HCV and represent the majority of patients treated for HCV within certain communities across the United States, yet they are severely underrepresented in HCV clinical trials. Given the known historical differences in SVR based on race, the black population within clinical trials must be increased. A recent report of data from the ION-4 study looking at the fixed-dose combination of ledipasvir and sofosbuvir for treating HCV in coinfected patients highlights the need for these types of analyses.[15] Here, among individuals coinfected with HCV and HIV, the overall SVR12 rate was 96%. Similar SVR rates were achieved for treatment-naïve and treatment-experienced participants (95% and 97%, respectively), and for subjects with and without cirrhosis (94% and 96%, respectively).[15] However, black patients had lower SVR12 rates than non-black patients (90% [95% CI, 83%-95%] versus 99% [95% CI, 97%-100%]; $P < 0.001$). All 10 patients who experienced virologic relapse in this trial were black. In a multivariate analysis, the only factor that remained associated with relapse was self-reported black race. Population pharmacokinetics of ledipasvir was the same when comparing black versus non-black race, efavirenz versus non-efavirenz antiretroviral regimens, and SVR versus relapse. In addition, a CYP2B6 candidate gene study was negative. Whole genome sequencing and genome-wide association studies are underway. This is the first study of direct-acting antivirals to suggest a lower SVR in black patients. This finding needs to be confirmed in other studies, which will only be achieved if future trials are powered with respect to population diversity to address this question.[15]

This is an exciting time in the treatment of viral hepatitis. We are now identifying all-oral, well tolerated, safe, and efficacious treatments for HCV. Future work within this field of hepatology will need to ensure that these regimens are safe and efficacious in all populations affected by HCV. The ION-4 study is an example of the kind of potentially surprising results that can be obtained when a clinical trial includes an appropriate population of underrepresented minorities. Whether the ION-4 findings are an aberration, unique to that trial, or strictly relevant to coinfected populations is unclear; only further studies of diverse populations can settle these questions. Here, we show that an all oral interferon-free regimen has great potential because of its equal efficacy and safety in an underrepresented population. Due to the relatively small population, however, it is important that future studies confirm these findings using study populations that have a larger minority population.

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