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Potential Overestimation of Racial Disparities in Response to the 8-Week Ledipasvir/Sofosbuvir Regimen for Hepatitis C Virus Genotype 1 Infection

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Dear Editors:

Current guidelines from the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) recommend against using the 8-week ledipasvir/sofosbuvir regimen for Black patients with hepatitis C virus genotype 1 (HCV-1) infection. This recommendation is based on evidence from four studies^{1–4} that reported racial disparities in sustained virologic response (SVR) after 8-week courses. These studies compared SVR between races, which is reasonable if the goal is to explore racial disparities, but such comparisons did not address whether the 8-week ledipasvir/sofosbuvir regimen was as effective as the 12-week regimen among Blacks otherwise eligible for 8 weeks (i.e. treatment-naïve, non-cirrhotic, HIV-uninfected, and HCV RNA <6 million IU/mL). To directly inform clinical decision-making, two recent studies compared 8-week and 12-week regimens among Blacks otherwise eligible for the 8-week regimen and reported no difference in SVR compared with Whites.^{5, 6} In addition, even if the aim were to explore potential racial disparities in SVR, the apparent disparities reported in prior studies may be attributable to misinterpretation of the results rather than meaningful differences in treatment effectiveness by race.

Prior studies that assessed the association between race and SVR either did not report a measure of association or reported odds ratios as the measure of association, which may

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have overestimated true differences in risk of SVR by race.¹⁻⁴ Risks are more clinically meaningful measures than odds, and unlike case-control and cross-sectional studies, can be directly estimated in longitudinal cohort studies. A common misconception is that odds ratios can be interpreted as risk ratios. These measures provide similar estimates when the outcome is rare (<10%) but can dramatically diverge as the outcome becomes more common.⁷ This phenomenon resulted in misinterpretation of a highly-publicized report about Blacks being less frequently referred for cardiac catheterization than Whites.⁸ The probability of SVR following the 8-week ledipasvir/sofosbuvir regimen often exceeds 90%, and thus the use of odds ratios for studies of race and SVR could overestimate racial disparities in treatment effectiveness. Therefore, we aimed to assess the magnitude by which racial disparities were overestimated among patients treated with 8-week ledipasvir/sofosbuvir for HCV-1 infection.

We reviewed the literature to identify studies published through March 1, 2018, that reported SVR by race for 8-week ledipasvir/sofosbuvir for HCV-1 infection (methods and references are detailed in the Supplementary Materials). We used data reported on the frequency of SVR by race to estimate crude odds ratios and risk ratios. We computed the relative percentage of overestimation of the risk ratio by the odds ratio using the formula: $|\text{odds ratio} / \text{risk ratio} - 1| * 100$, which quantifies the amount of statistical bias.

Of 128 potentially eligible articles, seven were eligible for analysis (Table 1). All but one study was an observational study. The proportion with SVR ranged between 90% and 96% for Blacks, and 93% and 99% for Whites. The odds ratios comparing SVR between races ranged between 0.25 and 1.16, whereas the risk ratios ranged between 0.96 and 1.00. The odds ratio overestimated the risk ratio in each study (median overestimation=40%, interquartile range=38%–47%). Insufficient information was available in eligible studies to explore potential effect heterogeneity of racial disparities (e.g., by age, sex, or fibrosis).

Our results suggest that prior reports of disparities in SVR following 8-week ledipasvir/sofosbuvir between Blacks and Whites may be overestimated by interpreting odds ratios rather than risk ratios. The absolute difference in risk of SVR between Blacks and Whites was no more than 4% in any of the studies we analyzed. This finding adds to a growing body of evidence suggesting that, contrary to current AASLD/IDSA guidelines, Blacks could be treated with the 8-week ledipasvir/sofosbuvir regimen without compromising treatment effectiveness.^{5, 6}

Odds ratios are ubiquitous in the biomedical literature, partly because logistic regression is the default for assessing exposure-outcome associations. Given the ease of estimating risk, rate, and hazard ratios using common statistical software, investigators do not need to report odds ratios in longitudinal cohort studies. Absolute measures such as risk and rate differences should also be considered for added insight about the association.

In summary, our results suggest that previously reported racial disparities in response to 8-week ledipasvir/sofosbuvir may be the consequence of overestimation rather than meaningful disparities. Given that the results from direct comparison of 8- and 12-week ledipasvir/sofosbuvir regimens among Blacks suggest comparable effectiveness,^{5, 6} neither

evidence from comparison of treatments among races, nor evidence from comparisons between races, supports current guidelines on race and treatment duration. A guideline revision to allow 8-week ledipasvir/sofosbuvir regimens for Black patients may help reduce barriers to HCV treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures:

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Odds ratios and risk ratios comparing sustained virologic response (SVR) between Blacks and Whites treated with 8-week ledipasvir/sofosbuvir for hepatitis C virus genotype 1 infection.

Table 1.

Author	Year	SVR (%)		Odds Ratio (95% CL)	Risk Ratio (95% CL)	Overestimation
		Blacks	Whites			
Kowdley et al.	2014	91.1	94.7	0.57 (0.17, 1.95)	0.96 (0.87, 1.06)	40%
Backus et al.	2016	89.5	93.5	0.59 (0.39, 0.90)	0.96 (0.92, 0.99)	38%
Backus et al.	2016	89.8	93.9	0.56 (0.36, 0.87)	0.96 (0.92, 0.99)	41%
Backus et al.	2017	90.7	94.2	0.59 (0.46, 0.77)	0.96 (0.94, 0.98)	38%
Kowdley et al.	2017	95.9	99.0	0.25 (0.07, 0.85)	0.97 (0.94, 1.00)	75%
Latt et al.	2017	96.1	95.4	1.16 (0.47, 2.86)	1.00 (0.97, 1.04)	16%
Su et al.	2017	93.1	96.3	0.51 (0.29, 0.91)	0.97 (0.94, 1.00)	47%