Reply to Harrington et al

TO THE EDITOR—Harrington et al raise 3 important points in a detailed analysis of pooled data from 12 registrational trials of interferon-free, direct-acting antiviral (DAA) therapies [1]. First, the authors point out that hepatitis C virus (HCV) RNA was detected at the end of treatment in only 0.3% (12/3671) of patients who achieved sustained virological response 12 (SVR12) in the larger trials compared to 29% (28/96) in our studies [2]. As suggested by
Harrington et al, our use of the more sensitive Abbott RealTime HCV assay could have resulted in higher rates of detectable viremia. Conversely, using the Roche COBAS TaqMan HCV test v1.0, only 3.1% (3/96) of patients who achieved SVR12 in our studies had a detectable viral load at the end of therapy. These differences may also be a result of varying treatment durations among the trials: over one-third of our patients were treated for 6 weeks, whereas the majority of subjects from the pooled data were treated for 12–24 weeks. Longer durations of therapy may certainly result in higher rates of viral suppression by the end of treatment.

Second, the authors state that 55% (12/22) of patients with detectable HCV RNA levels at the end of treatment achieved SVR12 in their combined analysis. Although a larger proportion of subjects had detectable viremia after treatment completion in our study, both sets of data demonstrate that HCV RNA levels at the end of treatment are not an absolute predictor of relapse, irrespective of the regimen used and patient characteristics. This conclusion is strikingly different from clinical trials using interferon-based regimens [3–5].

Third, Harrington et al report a lower proportion of on-treatment detectable and quantifiable HCV RNA in the ION-1, -2, and -3 trials compared to what was observed in our studies. We agree that our on-treatment HCV RNA results at week 4 using the Roche COBAS TaqMan HCV test v1.0 assay appear higher than expected, which may be explained by the small sample size of 19 patients treated with ledipasvir and sofosbuvir. Nevertheless, the data presented by the authors support our conclusion that frequent viral load monitoring early on during treatment is not useful in predicting treatment outcome. The vast majority of patients (99.4%, 3771/3792) treated with potent combination DAA regimens have unquantifiable HCV RNA at week 4 of treatment, regardless of future therapeutic response. Frequent monitoring of HCV RNA during therapy is costly, uninformative, and should be used at the provider’s discretion, as in the case of patients with adherence concerns.

The objective of our study was to assess the predictive ability of HCV RNA levels for treatment response during short-duration DAA therapy [2]. However, we were limited in our analysis by a small and selective patient population. We therefore highlighted the importance of further evaluating the clinical utility of HCV viral load monitoring in larger trials, and in particular, in patients with cirrhosis and/or past treatment experience. Therefore, we thank Harrington et al for sharing their combined analysis of HCV RNA data from 12 registrational trials of interferon-free, combination DAA treatments.

Note

Potential conflicts of interest. All authors: No potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Clinical Infectious Diseases® 2015;61(4):667–8
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DOI: 10.1093/cid/civ403