

## New hepatitis C antiviral treatments eliminate the virus

The Cochrane Collaboration has published a topical systematic review<sup>1</sup> and meta-analysis on direct-acting antivirals (DAA) for chronic hepatitis C virus (HCV) infection. Jakobsen and colleagues<sup>1</sup> compared the results of randomised trials of any HCV DAA regimen versus no intervention or placebo. Their review reported data from 138 trials, which included 25 232 participants and encompassed all drugs on the market or under development. The authors confirm treatment has a significant benefit (relative risk 0.44, 95% CI 0.37–0.52,  $p < 0.001$ ), compared with no treatment, in the elimination of the virus from the bloodstream, measured 12–24 weeks after treatment (sustained virological response, SVR); however, they conclude there was “insufficient evidence to judge if DAAs have beneficial or harmful effects on other clinical outcomes for chronic HCV” and that although DAAs might increase SVR, “the clinical implication of the results on this non-validated surrogate outcome is unclear”.<sup>1</sup>

Phase 3 data for the effectiveness of the first all-oral DAAs were published in 2013,<sup>2,3</sup> with many more practice-changing trials subsequently published. Direct randomised evidence that DAA treatment prevents mortality or morbidity is unlikely to emerge, in view of the long time from treatment to liver disease complications or death, except perhaps in certain sub-populations with advanced liver disease and highest risk. Nevertheless, long-term follow-up after treatment is highly likely to provide such evidence in the years to come.

Although Jakobsen and colleagues<sup>1</sup> commendably appraised a vast body of literature, their scepticism of SVR as an important and practical trial endpoint creates a false sense of uncertainty around the benefits of HCV treatment, which needs to be addressed. SVR is

durable long term: previous systematic reviews<sup>4</sup> have shown 98–99% of patients remain cured 4 years after achieving SVR. Additionally, treatment relapses after viral clearance usually occur early (within 24 weeks), and SVR measured at 12 weeks correlates nearly completely (>98%) with SVR at 24 weeks. Accordingly, treatment success can be reliably assessed soon after DAA treatment.<sup>5</sup> SVR also reduces the incidence of liver cancer and improves survival, and although cure of an infection does not always repair liver damage already caused by the virus, it does slow disease progression.<sup>4</sup> SVR is also associated with improved quality of life, including among recipients of DAA treatment.<sup>6</sup>

Failure to treat individuals—or whole populations—while waiting for direct evidence of long-term clinical outcome data will lead to substantial and avoidable excess mortality and morbidity globally. As treatment costs fall dramatically (from headline rates of US\$80 000 to as low as US\$500 in some countries), millions of people and populations worldwide can now benefit from these HCV cures. The available evidence indicates that HCV treatment is life-changing for individuals. For that reason, the media’s portrayal of the key message of Jakobsen and colleagues’ review<sup>1</sup> (ie, that HCV treatment “may have no clinical effect”)<sup>7</sup> should be forcefully rebutted.

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