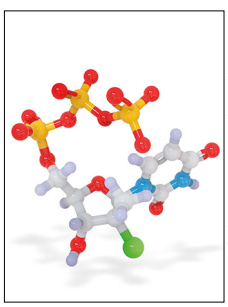
Direct-acting antiviral treatment for hepatitis C



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About 71 million people are chronically infected with the hepatitis C virus (HCV) worldwide.[1] Chronic HCV infection causes substantial morbidity and mortality, with complications including cirrhosis, end-stage liver disease, hepatocellular carcinoma, and death.[2] These complications have tripled over the past 15 years, and models project they will peak between 2030 and 2035.[3] Therapeutic options for chronic HCV infection have evolved over the past 5–7 years, from peginterferon plus ribavirin (associated with suboptimum cure and high treatment-related toxicity) to oral direct-acting antiviral treatment. Direct-acting antivirals can achieve sustained virological responses or cure in a high (>95%) proportion of patients and have few adverse events.[4] Sustained virological response leads to substantial reductions in all-cause and liver-related mortality,[5] liver transplantation,[5] and hepatocellular carcinoma,[6] prompting WHO to set targets for HCV elimination and a reduction of HCV-related complications.[7] In view of the high sustained virological response and excellent tolerability achieved with direct-acting antivirals, it seemed highly plausible to envision reductions in chronic HCV infection-related complications with these drugs.

In *The Lancet*, Fabrice Carrat and colleagues[8] present findings of a large, multicentre, prospective cohort study of more than 10 000 adult patients with chronic HCV infection who were enrolled in the French ANRS Hepather cohort. About three-quarters of the cohort received direct-acting antivirals, thereby providing an untreated control group for comparison. Patients who received direct-acting antivirals were older and had more comorbidities and more severe liver disease compared with untreated patients, consistent with prioritisation of direct-acting antiviral therapy for individuals with more advanced liver disease. The median follow-up period was 33·4 months (IQR 24·0–40·7), an adequate timeframe for development of HCV-related outcomes. Findings of adjusted multivariable analyses showed that exposure to direct-acting antivirals significantly reduced all-cause mortality (hazard ratio [HR] 0·48, 95% CI 0·33–0·70; p=0·0001), liver-related mortality (0·39, 0·21–0·71; p=0·0020), non-liver-related mortality (0·60, 0·36–1·00; p=0·048), and hepatocellular carcinoma (0·66, 0·46–0·93; p=0·018), but not decompensated cirrhosis (1·14, 0·57–2·27; p=0·72). These associations persisted when the analysis was restricted to patients with cirrhosis who achieved sustained virological response. By contrast, failure to achieve sustained virological response was associated with increased risk for hepatocellular carcinoma (HR 2·23, 95% CI 1·37–3·64; p=0·0012).

The study by Carrat and colleagues has some limitations, none of which would be expected to materially affect the overall findings and most likely biased the findings away from clinical benefit with direct-acting antivirals. First, only a few patients underwent liver biopsy to confirm cirrhosis, and either a platelet cutoff less than 150 000 per µL or prothrombin time less than 70% was used to classify cirrhosis in approximately half the patients with cirrhosis (1326 [44%] of 3045). However, in a validation substudy using other non-invasive markers of fibrosis, this method correctly classified cirrhosis in all patients. Second, patients who received more than one course of direct-acting antivirals were considered to have continuous exposure to direct-acting antivirals from the first course through to the last course, even though the first course of direct-acting antivirals might not have been associated with sustained virological response and there could have been a lag time between courses of direct-acting antivirals. However, this scenario would have underestimated rather than overestimated the benefit of these drugs. Third, patients with a history of decompensated cirrhosis and liver transplantation were excluded. These patients are at highest risk for clinical outcomes and, in view of trial data showing improvements in hepatic function in most patients with decompensated cirrhosis who achieved sustained virological response with direct-acting antivirals,[9] it is possible the current study underestimated the potential benefits of direct-acting antivirals by excluding this group.

The association of direct-acting antivirals with increased risk for hepatocellular carcinoma has been investigated in several single-centre reports, which have suggested an increased incidence of hepatocellular carcinoma early after direct-acting antiviral treatment.[10] However, subsequent studies noted no association between direct-acting antivirals and increased risk for hepatocellular carcinoma—rather, they were associated with decreased risk.[11,12] Carrat and colleagues' findings

confirm that the risk for hepatocellular carcinoma is reduced after direct-acting antiviral treatment.

The study by Carrat and colleagues offers substantive evidence that cure of HCV delivered by all-oral direct-acting antiviral regimens is associated with clinical benefits. These findings firmly counter those of a Cochrane review of direct-acting antiviral treatment trials[13] that could neither confirm nor reject if direct-acting antivirals had an effect on long-term HCV-related morbidity and mortality.[14,15] They also provide the best evidence to date to support guidance documents that recommend direct-acting antiviral treatment for all patients with chronic HCV infection. Finally, they provide credence to the achievability of the goals set out by WHO, not only to eliminate HCV but also to substantially reduce its complications.[7]

For **HCV guidance documents** see https://hcvguidelines.org

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