can be expected. Next, investigation of the likelihood of a viral rebound in relation to the size of the HIV reservoir at the time of treatment interruption would be interesting. Thus far, only theoretical estimations exist on how low this reservoir should be before cART can be interrupted with a fair chance to result in a post-treatment controller state. 28 Although two patients, one in each group, reached a post-treatment controller state, another patient transmitted HIV after treatment interruption and a subsequent viral rebound. This finding emphasises one of the pitfalls of treatment interruption, especially when treatment is stopped in the context of a potential cure. Therefore, treatment interruptions to obtain a potential post-treatment controller state should not become common practice before prediction of outcomes has improved.

To end on a positive note, the speed of enrolment (90 patients in less than 16 months in one country) shows that early diagnosis of HIV infection and subsequent treatment is possible. Although not leading to a cure, early treatment can, undoubtedly, make a difference for the long-term outcome of patients and their relatives. 23 Therefore, we hope, despite the sobering findings about the decay of the viral reservoir, that this trial will encourage people to get tested today and, if necessary, start treatment tomorrow.

"Zeger Debyser, Rik Schrijvers
Laboratory for Molecular Virology and Gene Therapy (ZB), and Laboratory of Clinical Immunology (RS), KU Leuven, 3000 Leuven, Flanders, Belgium zeger.debyser@med.kuleuven.be

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Hope for non-responders with hepatitis C virus and cirrhosis

The most important goal of antiviral therapy for infection with hepatitis C virus (HCV) is to prevent progression to severe liver disease. Once cirrhosis has developed, the annual risk of developing hepatocellular carcinoma is 1–5% and of hepatic failure is 3–6%. After an episode of decompensation, the risk of death within 12 months is 15–20%. 1 Unfortunately the response to interferon or interferon plus a first-generation protease inhibitor is frequently abrogated, impaired, or unsafe in patients with advanced liver disease, who are most in need of a cure. Treatment with interferon, therefore, has had a limited effect on mortality in patients with advanced disease.

In The Lancet Infectious Diseases, Marc Bourlière and colleagues 2 report the results of the SIRIUS trial, which enrolled 155 patients with HCV genotype 1 infection and compensated cirrhosis who previously had not achieved a sustained virological response (SVR) after treatment with pegylated interferon and ribavirin then a regimen including telaprevir or boceprevir. 77 were assigned to receive a combination fixed-dose tablet of 90 mg ledipasvir and 400 mg sofosbuvir plus ribavirin for 12 weeks and 78 patients to receive ledipasvir-sofosbuvir without ribavirin for 24 weeks. Cirrhosis was ascertained by transient elastography or (in a third of patients) liver biopsy. Patients with decompensated cirrhosis were excluded. SVR 12 weeks after the end of treatment was achieved in 96% (95% CI 89–99) of those in the ledipasvir-sofosbuvir plus ribavirin group and 97% (91–100) of those in the ledipasvir-sofosbuvir group.
The results augur a quantum leap in the treatment of cirrhosis and suggest that regimens including direct-acting antiviral agents without interferon circumvent the biological insensitivity to interferon.

Sirius is the brightest star system in the Earth’s night sky and has long acted as a stellar compass for navigators, but where do the SIRIUS data steer us? The amalgamated results of treatment with direct-acting antiviral therapy portend remarkable cure rates in patients with HCV genotype 1 infection and cirrhosis. Doctors, patients, purchasers, and providers will breathe a collective sigh of relief at the efficacy of the 12 week ledipasvir-sofosbuvir plus ribavirin regimen, which obviates the high costs of 24 weeks of treatment in those who can tolerate ribavirin. The actions of ribavirin are manifold, and include increased production of the natural-killer cell interferon γ

Notwithstanding the potency of new direct-acting antiviral agents, SVR might be dependent on the innate immune response to complete clearance of HCV. The SIRIUS results also clarify and simplify the recommendations for the use of ledipasvir-sofosbuvir in patients with cirrhosis. The US Food and Drug Administration recommends that treatment-experienced patients with HCV genotype 1 infection and cirrhosis should be treated for 24 weeks. The European Medicines Agency recommends that patients with compensated cirrhosis should be treated for 24 weeks, but 12 weeks can be considered for those deemed at low risk of clinical disease progression and who have subsequent re-treatment options. No doubt the risk of relapse troubled regulators (who do not take cost into account) and the recommendations were swayed by the favourable effect of longer-duration treatment in patients with cirrhosis and previous non-response in the ION-2 study.

Who is at high and who is at low risk of progression and how patients at high risk (ie, with decompensated cirrhosis with portal hypertension) should be treated are not fully determined. In the SIRIUS study most patients had Child-Turcotte-Pugh class A cirrhosis. Mean values for cirrhosis at baseline were Child-Turcotte-Pugh score 5·2 (range 5·0–7·0), model for end-stage liver disease score 7; 27 (17%) had platelet counts lower than $100 \times 10^9$/L and 20 (13%) had albumin concentrations lower than 35 g/L at baseline. Only around a third of the cohort were drawn from the ANRS CO20-CUPIC study, in which patients with severe disease, platelet counts lower than $100 \times 10^9$/L, and albumin concentrations less than 35 g/L were more likely not to respond to a protease-inhibitor regimen than other patients. The question arises why the SIRIUS study excluded patients with decompensated cirrhosis, which meant that the question of optimum therapy for advanced cirrhosis could not be addressed. Higher relapse rates with current direct-acting-antiviral regimens have been seen in patients with decompensated cirrhosis. Retrospective analyses to gauge the likelihood of disease progression, including indicators such as Child-Turcotte-Pugh, model for end-stage liver disease, fibrosis-4 scores, or newer and better validated indices should be done to understand the continuum of cirrhosis and to inform whether these risk assessments can guide the appropriate duration of therapy for patients with decompensated disease. Although there is an urgent need to specify duration by pretreatment and on-treatment host and viral factors that might lead to relapse, and to adjust duration in patients infected with HCV alone or co-infected with HCV and HIV, the evidence so far does not suggest a clear benefit of longer-duration treatment in those with decompensated cirrhosis. Ribavirin is more problematic in such patients.

Patients with few options for re-treatment need to be identified. The combination of sofosbuvir plus an NS5A inhibitor is now a proven rescue therapy for patients who do not respond to protease-inhibitor regimens. In the SIRIUS trial, NS5A resistance-associated variants were detected in 24 (16%) patients at baseline by deep sequencing. The very high SVR12 rates make meaningful interpretation of the effect of NS5A resistance-associated variants at baseline difficult, although some effects, depending on the regimen used, have been shown. The data do not yet suggest that baseline NS5A testing is warranted, but when coupled with the risk of progression these data have piqued the interest of regulators. The numbers of patients who relapse due to the development of resistance to NS5A inhibitors could escalate as more patients with cirrhosis are treated outside clinical trials. These patients will probably need re-treatment with a different antiviral class or with a regimen that includes next-generation NS5A or protease inhibitors that are fully active against NS5A-resistant viruses. Fortunately, potent next-generation combinations
are being developed, which will ensure that we are not always wedded to ribavirin and that the results seen in patients infected with HCV genotype 1 can be extended to all genotypes.

The data in the SIRIUS study offer hope and encouragement to people with HCV infection and cirrhosis. SVR has been correlated with improved clinical outcomes, including death (liver or non-liver related), liver failure, and hepatocellular carcinoma.12 Treatment of patients before hepatic decompensation has occurred would be preferable (and easier). If patients with cirrhosis can be identified and successfully treated, the first effects to assess will be measurable reductions in hospital admissions for HCV-associated cirrhosis and liver transplantations. The data should invite innovative pricing strategies and models to ensure that patients with progressing disease and advanced fibrosis can access treatment. The poet Louis MacNeice wrote in Thalassa “By a high star our course is set, our end is Life. Put out to sea.” Sirius can be seen from almost anywhere on the Earth’s surface. The results of Bourlière and colleagues and similar results that provide illuminating data will be the stars by which a course to reduce the global morbidity from HCV infection can be set.

*Geoffrey Dusheiko, Douglas MacDonald
UCL Institute of Liver and Digestive Health and Royal Free London NHS Foundation, London NW3 2QG, UK
G.dusheiko@ucl.ac.uk
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**Comment**

Applied public health research on the frontline

Prevention of pneumococcal disease in resource-poor countries, including many Asian countries, is desperately needed. The implementation of pneumococcal conjugate vaccines (PCVs) has been slow due to scarce funding, but also because the burden of pneumococcal disease is poorly known. However, with the financial assistance of the GAVI Alliance, the introduction of PCVs has been accelerated.1

In The Lancet Infectious Diseases, Mainga Hamaluba and colleagues’ present results on immunogenicity and safety of the ten-valent PCV (PCV10) among Nepalese infants. This study is an excellent example of tailormade public health research directly applicable to guide decision makers.

There are several important aspects of this study. First, although there have been a considerable number of immunogenicity and safety studies globally on PCVs, there are little data from studies done with PCV10 in Asia. Undoubtedly, local studies are needed to promote large-scale implementation.2 Second, the study compares two vaccination schedules that WHO recommends:3 the 2+1 schedule (at age 6 and 14 weeks with a booster at 9 months) and the conventional 3+0 Expanded Programme on Immunization (EPI) schedule (at age 6,

11 Lawitz E, Gane E, Pearlman B, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet 2014; published online Nov 11. http://dx.doi.org/10.1016/S0140-6736(14)61795-5.