HCV genotype 4 accounts for over 8% of all patients with HCV infection globally. This genotype is predominantly found in patients from Egypt. Its prevalence varies widely by regions, with the highest prevalence reported in the Middle East and sub-Saharan Africa. The geographic distribution of patients with HCV genotype 4 infection is increasing, however, due to migration.

Four all-oral direct-acting antiviral (DAA) combination therapy regimens are recommended as anti-HCV therapy for treatment-naive patients with HCV genotype 4 infection in the guidelines from the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD). The EASL guidelines recommend sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, sofosbuvir/ledipasvir, and grazoprevir/elbasvir. For treatment-experienced patients, on the other hand, the EASL guidelines recommend sofosbuvir/velpatasvir or glecaprevir/pibrentasvir, and the AASLD–IDSA guidelines recommend only the sofosbuvir/velpatasvir/voxilaprevir regimen. All of these regimens have shown high virologic efficacy against genotype 4, with sustained virologic response rates ranging 91%-100%. While these recommendations are based on several clinical trials that have included patients with HCV genotype 4, in most of these trials, patients with HCV genotype 4 were grouped with patients with HCV genotype 1 or several other genotypes. In addition, patients with HCV genotype 4 were in the minority in these trials, probably because of the small number of patients with HCV genotype 4 in the locations where these trials were conducted; indeed, most trials included less than 100 patients with HCV genotype 4. Thus, the optimal regimen for HCV genotype 4, including the best DAA and treatment duration, is still a subject of investigation. The report in this issue of Health Science Reports by Asselah et al. investigated the additional benefit of extending treatment duration of the ombitasvir/paritaprevir/ritonavir regimen to up to 24 weeks for patients with HCV genotype 4 and compensated cirrhosis.

There is substantial genetic heterogeneity in HCV genotype 4, and many subgenotypes have been reported, although, with the exception of subtypes 4a and 4b, the prevalence of these subtypes is low. The efficacy of DAA regimens by subgenotype is unclear and will be the subject of further research. Although some trials that focused on patients with HCV genotype 4 have included more than 100 patients, most patients had HCV subgenotype 4a or 4d. The most recent study by Fourati et al. reported an unexpectedly high rate...
of treatment failure in patients with HCV subgenotype 4r, a genotype which has been reported in African countries but that is rarely found in regions such as Europe and North America, which is associated with a high frequency of baseline resistance-associated substitutions. Based on their report, it could be proposed that subgenotype evaluation should be recommended in patients with HCV genotype 4 when selecting a treatment regimen. However, given the low proportion of 4r in the overall HCV-infected population and the lack of available commercial assays to identify HCV genotype 4 subtypes, universal subtyping of all genotype 4-infected patients to select regimen may be difficult to implement in actual clinical practice at this time.

The ideal DAA regimen for HCV genotype 4 has not been fully established, although there are multiple DAA treatment options for patients with HCV genotype 4, particularly those with the predominant subtypes, and overall efficacy in clinical trials has been reported to be as high as with other genotypes. We expect the accumulation of more findings on the efficacy of various regimens, and on different subtypes, perhaps based on real-world results, to confirm the high rates observed of sustained virologic response in patients with HCV genotype 4.

CONFLICTS OF INTEREST
None declared.

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