limited to genotype 1, required pretreatment genotyping that disqualified a third of recipients, usually required concomitant PEG IFN and ribavirin, had multiple drug-drug interactions and side effects, and was not competitive with the improved combinations that followed; therefore, simeprevir is no longer recommended.

Sofosbuvir: Sofosbuvir, the first nonprotease inhibitor DAA to be approved, has an excellent profile—high potency, high barrier to resistance, pangenotypic activity, very well tolerated with limited adverse effects (most commonly mild fatigue, insomnia, headache, and nausea), once-daily oral administration, and relative freedom from major drug-drug interactions. Sofosbuvir has efficacy in all genotypes (1–6); in treatment-naïve subjects and prior nonresponders to PEG IFN–based and protease-inhibitor-based therapy; with PEG IFN–ribavirin or in IFN-free regimens; in combination with ribavirin or with NS5A inhibitors (see below); and for treatment periods as brief as 8–12 weeks. Currently, sofosbuvir is used in combination with one of two NS5A inhibitors and is a component of three of the five currently recommended DAA regimens (Table 341-6).

Sofosbuvir-ledipasvir: The DAA combination that has had a dominant role in the treatment of hepatitis C is sofosbuvir (400 mg) plus the NS5A inhibitor ledipasvir (90 mg) in a once-a-day, fixed-dose, single pill, approved in October 2014 for genotype 1 and in November 2015 for genotypes 4, 5, and 6. Phase 3 trials were conducted in treatment-naïve noncirrhotic patients, in treatment-naïve cirrhotic and noncirrhotic patients, and in treatment-experienced cirrhotic and noncirrhotic patients treated for 8, 12, or 24 weeks, both with and without ribavirin. In treatment-naïve noncirrhotics, an SVR_{12} was achieved in 97–99% of subjects, and no benefit was observed by extending therapy from 12 to 24 weeks or by adding ribavirin. Moreover, for treatment-naïve, noncirrhotic patients with baseline HCV RNA $<6 \times 10^6$ IU/mL, a treatment duration of 8 weeks was as effective as one of 12 weeks (94–95% SVR_{12}), which may be a consideration for a proportion of patients. In cirrhotic patients, SVR_{12} was achieved in 97–100% of treatment-naïve subjects (no advantage of extending therapy from 12 to 24 weeks or of adding ribavirin); however, for cirrhotic prior