EVR (≥2-$\log_{10}$ HCV RNA reduction) but in whom HCV RNA remains detectable at week 24, an SVR is unlikely, and therapy can be discontinued. Although response rates are lower in patients with certain pretreatment variables, selection for treatment should not be based on symptoms, genotype, HCV RNA level, mode of acquisition of hepatitis C, or advanced hepatic fibrosis. Patients with cirrhosis can respond and should not be excluded as candidates for therapy. For patients being treated with telaprevir and boceprevir, treating physicians should explain the negative impact of non-C *IL28B* genotype and advanced fibrosis on outcome.

Patients who have relapsed after, or failed to respond to (Fig. 362-2), a course of IFN monotherapy are potential candidates for retreatment with PEG IFN plus ribavirin (i.e., a more effective treatment regimen is required), and this approach remains current for patients with genotypes 2, 3, or 4; however, for patients with genotype 1, combination protease inhibitor/PEG IFN/ribavirin therapy is indicated. For patients with genotypes 2, 3, or 4 who were nonresponders to a prior course of IFN monotherapy, retreatment with IFN monotherapy or combination IFN plus ribavirin therapy is unlikely to achieve an SVR; however, a trial of combination PEG IFN plus ribavirin may be worthwhile, although an SVR is the outcome in <15–20% of patients. SVRs to retreatment of nonresponders are more frequent in those who had never received ribavirin in the past, those with genotypes 2 and 3, those with low pretreatment HCV RNA levels, and noncirrhotics, but less frequent in African Americans, those who failed to achieve a substantial reduction in HCV RNA during their previous course of therapy (null responders, Fig. 362-2), and those who required ribavirin dose reductions. Potential approaches to improving responsiveness to PEG IFN–ribavirin in prior nonresponders include longer duration of treatment; higher doses of PEG IFN, ribavirin, or both; and switching to a different IFN preparation; however, as noted above, none of these approaches achieves more than a marginal benefit. Treatment with a protease inhibitor–based regimen should be pursued in patients with genotype 1 who have relapsed after or not responded to prior treatment with IFN monotherapy or PEG IFN plus ribavirin, unless these protease inhibitors are not available or contraindicated (Table 362-7).

Early PEG IFN treatment is indicated for persons with acute hepatitis C; ribavirin, which is used frequently in such instances, has not been shown to improve efficacy over that of PEG IFN alone, and the new protease inhibitors have not been approved for acute hepatitis C **(Chap. 360)**. In patients with biochemically and histologically mild chronic hepatitis C, the rate of progression is slow, and monitoring without therapy is an option; however, such patients respond just as well to combination PEG IFN plus ribavirin therapy or triple-drug, protease-based therapy (for genotype 1) as those with elevated ALT and more histologically severe hepatitis. Therefore, therapy for these patients should be considered and the decision made based on such factors as patient motivation, genotype, stage of fibrosis, age, and comorbid conditions. A pretreatment liver biopsy to assess histologic grade and stage provides substantial information about progression of hepatitis C in the past, has prognostic value for future progression, and can identify such histologic factors as steatosis and stage of fibrosis, which can influence responsiveness to therapy. As therapy has improved for patients with a broad range of histologic severity, and as noninvasive laboratory markers and imaging correlates of fibrosis have gained popularity, some authorities, especially in Europe, place less value on, and do not recommend, pretreatment liver biopsies. On the other hand, serum markers of fibrosis are not considered sufficiently accurate, and histologic findings provide important prognostic information to physician and patient. Therefore, although the contemporary role of a pretreatment liver biopsy commands less of a consensus, a pretreatment liver biopsy still provides useful information and should be considered.

Patients with compensated cirrhosis can respond to therapy, although their likelihood of a sustained response is lower than in noncirrhotics; moreover, survival has been shown to improve after successful antiviral therapy in cirrhotics. Similarly, although several retrospective studies have suggested that antiviral therapy in cirrhotics with chronic hepatitis C, independent of treatment outcome per se, reduces the frequency of HCC, less advanced disease in the treated cirrhotics, not treatment itself (i.e., lead-time bias), may have accounted for the reduced frequency of HCC observed in the treated cohorts in these reports; prospective studies to address this question have failed to demonstrate benefit, unless an SVR is achieved. Patients with decompensated cirrhosis are not candidates for IFN-based antiviral therapy but should be referred for liver transplantation. Some liver transplantation centers have evaluated progressively escalated, low-dose antiviral therapy in an attempt to eradicate hepatitis C viremia prior to transplantation; however, such therapy has been shown to reduce but not to prevent the risk of HCV reinfection after transplantation. After liver transplantation for end-stage liver disease caused by hepatitis C, recurrent hepatitis C is the rule, and the pace of disease progression is more accelerated than in immunocompetent patients **(Chap. 368)**. Current therapy with PEG IFN and ribavirin after liver transplantation is unsatisfactory in most patients, but attempts to minimize immunosuppression are beneficial. Early experience with protease inhibitor–based therapy is encouraging, but inhibition of CYP3A4 by protease inhibitors can lead to markedly increased levels of immunosuppressive calcineurin inhibitors (especially tacrolimus), which requires intensive monitoring and can be very challenging. The cutaneous and renal vasculitis of HCV-associated essential mixed cryoglobulinemia **(Chap. 360)** may respond to antiviral therapy, but sustained responses are rare after discontinuation of therapy; therefore, prolonged, perhaps indefinite, therapy (as reported with IFN-based therapy) is recommended in this group (no indication for prolonged protease inhibitor therapy exists currently). Anecdotal reports suggest that antiviral therapy may be effective in porphyria cutanea tarda or lichen planus associated with hepatitis C.

In patients with HCV/HIV co-infection, hepatitis C is more progressive and severe than in HCV-monoinfected patients. Although patients with HCV/HIV co-infection respond to antiviral therapy for hepatitis C, they do not respond as well as patients with HCV infection alone. Four large national and international trials of antiviral therapy among patients with HCV/HIV co-infection have shown that PEG IFN (both α2a and α2b) plus ribavirin (daily doses ranging from flat-dosed 600–800 mg to weight-based 1000/1200 mg) is superior to standard IFN regimens; however, SVR rates were lower than in HCV-monoinfected patients, ranging from 14 to 38% for patients with genotypes 1 and 4 and from 44 to 73% for patients with genotypes 2 and 3. In the three largest trials, all patients, including those with genotypes 2 and 3, were treated for a full 48 weeks. In addition, tolerability of therapy was lower than in HCV-monoinfected patients; therapy was discontinued because of side effects in 12–39% of patients in these clinical trials. Based on these trials, weekly PEG IFN plus daily ribavirin at a daily dose of at least 600–800 mg, up to full weight-based doses, at doses recommended for HCV-monoinfected patients, if tolerated, is recommended for a full 48 weeks, regardless of genotype. An alternative recommendation for ribavirin doses was issued by a European Consensus Conference and consisted of standard, weight-based 1000–1200 mg for genotypes 1 and 4, but 800 mg for genotypes 2 and 3. A head-to-head trial of combination PEG IFN–ribavirin therapy in HCV/HIV co-infection demonstrated statistically indistinguishable efficacy of the two types of PEG IFN, despite a small advantage for PEG IFN-α2a: For PEG IFN-α2b and -α2a, SVRs occurred in 28% versus 32%, respectively, of patients with genotypes 1 and 4 and in 62% versus 71%, respectively, of patients with genotypes 2 and 3.

Although data are limited and recommendations pending, protease inhibitors may be used for genotype 1; however, because of potential drug-drug interactions between HCV protease inhibitors and HIV antiretroviral drugs (especially in ritonavir-boosted HIV protease inhibitors), HCV protease inhibitors should be used cautiously in HCV-HIV co-infected patients. If protease inhibitors are used, a full 48-week course is recommended without response-guided therapy: for boceprevir, 4 weeks of PEG IFN–ribavirin lead-in, followed by 44 weeks of triple-drug therapy (PEG IFN, ribavirin, boceprevir), and