With more than 170 million people worldwide infected with the hepatitis C virus (HCV), the burden of the disease is indisputably significant. In 2010, there were an estimated 2.7 to 3.9 million cases of chronic HCV in the United States alone, with up to 75% of individuals unaware of their diagnosis. Due to the high prevalence and underdiagnosis of disease, the Centers for Disease Control and Prevention in 2012 and the U.S. Preventive Services Task Force in 2013 modified their guidelines to recommend a one-time screening of adults born between 1945 and 1965.
The goal of identifying undiagnosed adults is to eradicate the virus and avoid the development of cirrhosis and its life-threatening complications. Pegylated interferon (PegIFN) and ribavirin (RBV) have served as the foundations of HCV therapy for years but are accompanied by suboptimal rates of sustained virologic response (SVR) and significant adverse events (AEs). The lack of ideal treatment options was the impetus for further study of HCV and the development of novel therapies.

Hitting the Target (Molecule)

Stages of the HCV life cycle have become targets of newer direct-acting antivirals (DAAs) that target several molecules required for HCV infection, such as the NS3/4a protease, NS5B RNA-dependent RNA polymerase, or the NS5A protein. The NS3/4A serine protease is a noncovalent heterodimer with a catalytic subunit (the NS3 N terminal) and an activating cofactor (NS4A protein), which plays an important role in viral replication through cleavage of 4 sites of the HCV polyprotein. The HCV NSSA phosphoprotein is also essential for viral RNA synthesis and virion assembly and secretion. The exact mechanism of action of NSSA inhibitors is unknown, but one route is through inhibition of hyperphosphorylation, which has an essential role in replication.

The NS5B polymerase is another enzyme involved in viral replication. Inhibitors of this enzyme are classified as either nucleoside/nucleotide or non-nucleoside inhibitors. Non-nucleoside/nucleotide inhibitors bind to sites away from the active site of the polymerase and cause conformational changes in the protein. Nucleoside/nucleotide analogs mimic the natural substrate of the NS5B protein, leading to RNA chain termination.

In 2011, the protease inhibitors (PIs) telaprevir (Incivek, Vertex) and boceprevir (Victrelis, Merck) became the first approved DAAs to be combined with PegIFN/RBV for the treatment of genotype 1 (G1) HCV. The regimens significantly increased SVR rates, serving as a major advance in the treatment of HCV and opening the door for DAA therapy. However, the incremental adverse reactions were significant, and the regimen was not well tolerated by many patients. More recently, the FDA approved sofosbuvir (SOF; Sovaldi, Gilead), an NS5B nucleotide polymerase inhibitor, and simeprevir (Olysio, Janssen), a second-wave PI, used with PegIFN/RBV.

Simeprevir was studied extensively with PegIFN/RBV before its approval. The QUEST-1 and QUEST-2 studies randomized G1, treatment-naive patients to receive simeprevir combined with PegIFN/RBV for 24 or 48 weeks based on response-guided therapy. In QUEST-1, the overall SVR at 12 weeks (SVR12) after therapy with simeprevir was 80% versus 50% in controls; 85% were able to shorten therapy to 24 weeks and 91% of these patients achieved SVR. In QUEST-2, therapy was shortened in 91% of patients, of whom 86% achieved SVR after treatment. The PROMISE trial had a similar study design except study patients had relapsed after prior IFN-based therapy. Results also were similar, reporting SVR rates of 80%. All of these studies showed lower SVR rates in patients with advanced fibrosis and in patients with IL28B non-CC genotype.

Adverse events associated with simeprevir included hyperbilirubinemia related to interactions with transporters but no actual hepatotoxicity; a slight increase in photosensitivity; and in one study, mild pruritus. No additional hemoglobin decline was noted. Based on these studies, the FDA approved simeprevir for use in G1 patients, as a regimen consisting of 12 weeks of triple therapy and 12 to 36 weeks of PegIFN/RBV for treatment-naive or relapsed patients and prior non-responders, respectively, with or without cirrhosis. Response-guided therapy is not a component of the approved regimen but parameters of viral response must be met at 4 weeks (HCV RNA <25 IU/mL) for treatment to continue.

Sofosbuvir also has been studied comprehensively, leading to its approval nearly contemporaneously with simeprevir. The Phase II trials initially demonstrated promising results in G1 patients treated with PegIFN/RBV and SOF with SVR rates of 87% to 92%, which led to the Phase III NEUTRINO study of 12 weeks with the same regimen in patients with HCV genotypes 1, 4, 5, or 6. Most of the study population consisted of G1 patients, who overall achieved 89% SVR. The study also included a significant number of patients with compensated cirrhosis, with an SVR of 80% in patients.

### Table 1. HCV Infection (Antibody Positive Only or RNA Positive) 2011

<table>
<thead>
<tr>
<th>Site</th>
<th>N</th>
<th>Site Population</th>
<th>Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorado</td>
<td>2,901</td>
<td>5,116,796</td>
<td>56.7</td>
</tr>
<tr>
<td>New Mexico</td>
<td>3,188</td>
<td>2,082,224</td>
<td>153.1</td>
</tr>
<tr>
<td>San Francisco</td>
<td>1,944</td>
<td>812,826</td>
<td>239.2</td>
</tr>
<tr>
<td>Minnesota</td>
<td>1,925</td>
<td>5,344,861</td>
<td>36.0</td>
</tr>
<tr>
<td>New York state</td>
<td>7,047</td>
<td>11,220,287</td>
<td>62.8</td>
</tr>
<tr>
<td>Oregon</td>
<td>5,464</td>
<td>3,871,859</td>
<td>141.1</td>
</tr>
<tr>
<td>Connecticut</td>
<td>2,898</td>
<td>3,580,709</td>
<td>80.9</td>
</tr>
<tr>
<td>New York City</td>
<td>8,749</td>
<td>8,244,910</td>
<td>106.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>33,919</td>
<td>40,274,472</td>
<td>84.7</td>
</tr>
</tbody>
</table>

Source: Centers for Disease Control and Prevention
with cirrhosis compared with 92% without cirrhosis. No incremental AEs were ascribed to SOF compared with those historically attributed to PegIFN/RBV alone, and only 2% of patients discontinued treatment due to AEs.

The shortened treatment duration, higher success rate, and superior tolerability compared with the previous standard of care with PIs took IFN-based therapy to a new plateau, the utility of which has only been limited by the even greater paradigm shift to IFN-free regimens.

**New Backbones of Therapy**

The high barrier to resistance imposed on viral replication by nucleotide polymerase inhibitors, related to the highly conserved structure of the polymerase’s active binding site, makes potent nucleotide analogs like SOF highly attractive as a backbone of regimens consisting of DAAs agents. One of the first trials demonstrating success with SOF and RBV was the ELETRON trial, revealing SVR in 84% of 25 treatment-naive patients. Subsequent studies with the same drugs given for 12 to 24 weeks yielded SVR12 rates of 52% to 68% after therapy.

Although promising, this regimen was unsuccessful in the few study patients with cirrhosis, as well in null responders in a separate arm, with only a 10% SVR (1 out of 10), signaling an inability of the regimen to overcome undefined factors linking IFN nonresponsiveness to impaired clearance of virus with SOF as the sole active agent in 12 weeks.

The PHOTON study was the only Phase III study of this regimen in treatment-naive, mainly non-cirrhotic G1 patients, which resulted in 76% SVR in patients with HIV-HCV coinfection. This accounts for the stipulation in the US labeling that SOF and RBV for 24 weeks could be an option for IFN-ineligible patients with G1 infection.

Other regimens of DAAs combined with a nucleoside polymerase inhibitor have shown additional advances in oral treatment relative to the regimen of SOF and RBV alone. For example, the potent pangenotypic activity of the NSSA inhibitor daclatasvir complements the broad genotypic activity and high barrier to resistance of SOF. This was demonstrated in a Phase II trial in which non-cirrhotic treatment-naive patients and patients who had previously failed treatment with a PI received daclatasvir and SOF, with or without RBV. Treatment-naive patients were treated for 12 or 24 weeks, and the previously treated patients were treated for 24 weeks. Collectively, there was a 98% SVR12 after therapy, with all 3 treatment failures being due to loss to follow-up. Two had documented SVR24 after treatment. No patient had virologic breakthrough during treatment, and rates of virologic response were similar across subgroups, including genotype subtypes, IL28B genotype, race, RBV treatment, and PI resistance.

Ledipasvir (LDV) is another NSSA inhibitor that has yielded similar results in combination with SOF and RBV. In additional arms of the ELECTRON trial, treatment-naive patients and previous null responders, which included those who failed prior treatment with PIs, had an SVR of 100%. The Phase II LONESTAR study substantiated these results with SVR rates of 95% to 100% in both treatment-naive patients and those who had previously failed treatment with a PI, including cirrhotics and prior nonresponders. Notably, similarly high rates of SVR were seen in treatment arms with only 8 weeks of therapy, raising the possibility of even shorter regimens. More recent Phase III studies involving 1,952 patients treated with LDV/SOF have focused on optimizing duration, need for RBV, and treatment in subpopulations. ION-1 randomized patients to receive the fixed-dose LVD/SOF for 12 or 24 weeks. All treatment arms had 97% to 99% SVR12 after treatment. Even in patients with cirrhosis, SVR was 94% to 100%. ION-2 used the same regimen in patients who had previously failed IFN-based treatment with or without a PI. Again SVR rates were high; 96% and 94% with and without RBV, respectively, in the 12-week treatment arm and 99% in both 24-week arms. Baseline PI resistance did not affect treatment outcome, but prior treatment failures with cirrhosis had a higher rate of relapse, resulting in SVR of 82% to 86%.

Still with such high overall SVR12 and the results of the LONESTAR trial, the ION-3 trial evaluated 8 weeks of treatment in treatment-naive, non-cirrhotic patients. There was no difference based on the use of RBV (SVR 93%-94%) in the 8-week arm and SVR was 95% in the 12-week arm. Although the frequency of relapse in patients treated for 8 weeks was somewhat higher, these findings introduced the possibility of highly successful treatment with an 8-week regimen. Patients with characteristics historically associated with poorer response, including cirrhosis, G1a subtype, non-CC IL28B allele, and race, all still had SVR rates higher than 90%. Mild AEs were common, including fatigue and insomnia, and were incrementally observed in treatment arms containing RBV. Anemia generally was only seen in RBV recipients. Given that RBV did not improve efficacy, collectively, the data from these trials support the absence of RBV from this regimen. Of note, deep-sequencing analyses revealed that most of the patients who failed to have SVR in these studies had NS5A-resistant variants, some at baseline. Conversely, however, the SVR rates in patients with baseline NS5A-resistant variants were very high.

**Interferon-Free Regimens**

The FDA has not approved simeprevir and SOF for use in combination, but this regimen has been studied as part of Phase II trials. Its success has motivated clinicians to treat selected G1 patients with an IFN-free regimen. Moreover, the new online guidance from the American Association for the Study of Liver Diseases/Infectious Diseases Society of America has recommended the regimen in IFN-ineligible treatment-naive patients, as well as treatment-experienced patients, whether IFN eligible or not, as long as they have not previously received a PI. The COSMOS trial evaluated...
the 2 drugs, with or without RBV for 12 or 24 weeks in G1 patients. There were 2 cohorts, the first of which enrolled previous null responders with META VIR F0-F2 fibrosis. In this group, SVR12 post-therapy ranged between 79% and 93% by intent-to-treat analysis with 4 patients with nonvirologic failure clustered in the group receiving 24 weeks of therapy, including RBV. The second cohort included treatment-naive and prior null responders (without prior PI exposure) with META VIR F3-F4 fibrosis. Overall SVR12 ranged from 93% to 100%; 3 patients who relapsed were in the 12-week arm. Of the 6 patients who relapsed in the entire study, 4 had G1a with the Q80K polymorphism, leaving open the possibility of a small effect of this polymorphism but with insufficient numbers to definitively address the issue until the completion of ongoing Phase III trials.

Although regimens without a nucleotide polymerase inhibitor lack a single class that has the high barrier to resistance of a nucleotide polymerase inhibitor, potent combinations of other classes cumulatively impose the high barrier to resistance needed to attain SVR rates similar to those seen with the nucleotides. One emerging regimen is the combination of the PIs ABT-450/r boosted with low-dose ritonavir and ombitasvir (ABT-257, NSSA inhibitor), coformulated in a single-daily pill, with twice-daily ABT-333 (non-nucleoside NS5B inhibitor) and RBV. This regimen was studied initially in the AVIATOR trial for 12 weeks, yielding SVR rates in non-cirrhotic, treatment-naive patients and prior null responders of 96% and 93%, respectively. With these SVR rates comparing favorably with those obtained with 24 weeks of therapy or with regimens containing 3 of the 4 components previously outlined, the “3D plus RBV” regimen was chosen as the foundation of a robust Phase III program. SAPPHIRE-I studied the 3D plus RBV regimen for 12 weeks in non-cirrhotic, treatment-naive patients. Of the 473 patients, 96% achieved SVR12 after therapy, 95% in G1a, and 98% in G1b, with no difference in outcome due to baseline characteristics including HCV RNA, gender, race, age, fibrosis, and IL28B genotype.

In SAPPHIRE-2, the same regimen was evaluated in treatment-experienced patients, with the same overall SVR12 rate of 96% (96% and 97% in genotypes 1a and 1b, respectively). TURQUOISE-II included both treatment-naive and treatment-experienced patients with compensated cirrhosis. SRV12 after therapy was 92% in patients treated for 12 weeks and 96% in those treated for 24 weeks. With subgroup analysis, it became evident that G1a null responders were the treatment population that drove the difference in SVR based on treatment duration. SRV12 post-therapy was achieved in 93% of the group that was treated for 24 weeks but only 80% in those who were treated for 12 weeks, suggesting a continued effect of prior IFN response, as well as a difference between G1a and G1b patients. SAPPHIRE-1 and SAPPHIRE-2 were both placebo-controlled trials allowing for a true assessment of safety and tolerability of the regimen. Patients receiving active treatment experienced more AEs, although the overall rate of such events was high even among patients who received placebo (88%-91% in treatment arms compared with 73%-83% with placebo). Adverse events were generally mild but included fatigue, headache, nausea, and pruritus. Elevations in alanine transaminase, through which most patients were able to continue treatment, occurred in about 1% of patients. No patient discontinued treatment as a result of laboratory abnormalities. Some patients required a lower dose of RBV, however, the outcome of treatment was not affected. Baseline resistance data were unavailable, however, most patients who failed treatment had 2 or 3 class drug-resistant variants after treatment.

Additional studies include PEARL-4 in G1a treatment-naive patients without cirrhosis who received the 3D regimen for 12 weeks, with or without RBV. In this group, RBV did appear to have an added benefit, with SVR12 after treatment of 97% compared with 90% without RBV. RBV appears to have no effect with G1b infection as demonstrated in the PEARL-2 and PEARL-3 studies in treatment-experienced and treatment-naive patients, respectively (all without cirrhosis). In PEARL-2, 97% of patients achieved SVR with RBV and 100% achieved SVR without RBV. In PEARL-3, SVR was 99% in both groups.

Other non-nucleotide-containing regimens being studied include daclatasvir combined with the PI asunaprevir and BMS-791325, a non-nucleoside inhibitor. This treatment was evaluated in 166 treatment-naive G1 patients for 12 weeks. There was 3% viral breakthrough, all in G1a, and 3.6% viral relapse, also restricted to G1a, resulting in an overall SVR of 92%. This regimen also was well-tolerated, with treatment discontinuation as a result of AEs of only 1.2%. The HALLMARK study looked at asunaprevir and daclatasvir in G1b patients. Patients received 24 weeks of treatment and the study included cirrhotics. SVR ranged from 80% to 90% based on prior treatment history, with the highest SVR rates in treatment-naive patients.

Efficacy Across Genotypes?

The effectiveness of HCV treatment varies with nature of the infection. Genotype 2 and 3 HCV had been more successfully treated with IFN and RBV, with SVR rates of 70% to 85%, compared with the lower rates in G1 infection. Some of the newer DAAs have demonstrated efficacy across genotypes, allowing for IFN-free regimens to be formulated in this population as well. With 100% SVR in G2 and G3 patients treated for 12 weeks with SOF and RBV as part of the original arms of the ELECTRON trial, Phase III studies sought to corroborate the results. The FISSION trial compared 12 weeks of SOF and RBV with the standard of care. The trial demonstrated that G2 and G3 patients could no longer be grouped together appropriately, as 97% of G2 patients achieved SVR compared with only 56% of G3 patients (78% and 63%, respectively, in the standard-of-care arm).

Cirrhosis was a strong predictor of poor outcome in G3 patients, with SVRs of 61% without and 34% with
cirrhosis. Similar outcomes were seen with the POSITRON trial, which studied the SOF and RBV regimen for 12 weeks in G2 and G3 patients who were IFN intolerant to the drugs, or ineligible or unwilling to take them. SVR in G2 was 93% in G2 and 61% in G3. Cirrhosis again predicted poorer outcome, with SVR of 94% in G2 and 21% in G3.

The FUSION trial evaluated the effect of extending treatment to 16 weeks instead of 12 for patients who had failed prior therapy. SVR increased from 86% to 94% with longer treatment in G2 patients, and from 30% to 62% in G3 patients. The additional benefit was seen in cirrhotic patients as well, with SVR increased to 78% from 60% with the additional 4 weeks of treatment in G2 and 61% from 19% in G3. However, the number of G2 patients with cirrhosis was too small to draw meaningful comparisons.

In the VALENCE trial, G2 treatment-naive patients treated for 12 weeks had 97% to 100% SVR, as did 78% of G2 treatment-experienced patients with cirrhosis, and 94% of G2 treatment-experienced patients without cirrhosis. Treatment was extended to 24 weeks in G3 treatment-naive patients, with 95% of patients without cirrhosis achieving SVR compared with 92% in the cirrhotic population. Those who had failed prior therapy had SVR rates of 87% in the non-cirrhotic population and 62% in patients with cirrhosis. These results led to the approval of SOF and RBV for 24 weeks in G3 and 12 weeks in G2 patients.

With still suboptimal results, especially in G3 patients, LONESTAR-2 evaluated the addition of PegIFN to the regimen for treatment-experienced G2 and G3 patients with or without compensated cirrhosis. G2 patients had an overall SVR of 96%. G3 patients, including both cirrhotics and non-cirrhotics, had an SVR of 83%, supporting the concept of an ongoing role of PegIFN at least in treatment-experienced cirrhotic patients. Recent data also show that among patients with G3 cirrhosis, similar outcomes were seen with the POSITRON trial, which studied the SOF and RBV regimen for 12 weeks in G2 and G3 patients who were IFN intolerant to the drugs, or ineligible or unwilling to take them. SVR in G2 was 93% in G2 and 61% in G3. Cirrhosis again predicted poorer outcome, with SVR of 94% in G2 and 21% in G3.

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### Table 2. Interpretation of Results of Tests for HCV Infection and Further Actions

<table>
<thead>
<tr>
<th>Test Outcome</th>
<th>Interpretation</th>
<th>Further Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV antibody nonreactive</td>
<td>No HCV antibody detected</td>
<td>Sample can be reported as nonreactive for HCV antibody. No further action required. If recent HCV exposure in person tested is suspected, test for HCV RNA.</td>
</tr>
<tr>
<td>HCV antibody reactive</td>
<td>Presumptive HCV infection</td>
<td>A repeatedly reactive result is consistent with current HCV infection, or past HCV infection that has resolved, or biologic false positivity for HCV antibody. Test for HCV RNA to identify current infection.</td>
</tr>
<tr>
<td>HCV antibody reactive, HCV RNA detected</td>
<td>Current HCV infection</td>
<td>Provide person tested with appropriate counseling and link person tested to medical care and treatment.</td>
</tr>
<tr>
<td>HCV antibody reactive, HCV RNA not detected</td>
<td>No current HCV infection</td>
<td>No further action required in most cases. If distinction between true positivity and biologic false positivity for HCV antibody is desired, and if sample is repeatedly reactive in the initial test, test with another HCV antibody assay. In certain situations follow up with HCV RNA testing and appropriate counseling.</td>
</tr>
</tbody>
</table>

HCV, hepatitis C virus

a  If HCV RNA testing is not feasible and person tested is not immunocompromised, do follow-up testing for HCV antibody to demonstrate seroconversion. If the person tested is immunocompromised, consider testing for HCV RNA. b  It is recommended before initiating antiviral therapy to test for HCV RNA in a subsequent blood sample to confirm HCV RNA positivity. c  If the person tested is suspected of having HCV exposure within the past 6 months, or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen. Source: Centers for Disease Control and Prevention
who had failed a 12- to 16-week regimen of SOF and RBV, a 12-week retreatment regimen of PegIFN/RBV and SOF can act as a salvage regimen, even in patients with cirrhosis, with higher SVR rates than patients retreated with 24 weeks of SOF and RBV alone.45

Collectively, analysis of the NEUTRINO, FUSION, FISSION, POSITRON, and VALENCE trials has shown that no single AE led to discontinuation in more than 1 patient receiving SOF and RBV, and anemia was the only AE leading to discontinuation of treatment in more than 1 patient receiving IFN, RBV, and SOF.46 However, the use of IFN likely will be unnecessary in the future, as regimens combining SOF with other DAAs, including pan-genotypic NS5A inhibitors, currently in development appear to have high rates of SVR.47

Although limited data exist on treatment in other genotypes, the NEUTRINO trial did include G4, G5, and G6 patients, all of whom had more than 95% SVR, most notably 27 of 28 (96%) G4 patients.19 A small study of G4 Egyptian patients in the United States provided data for the use of SOF and RBV only. In treatment-naive patients, the highest rate of SVR24 was 100%, compared with SVR12 of 79%. In treatment-experienced patients, SVR was 59% with 12 weeks and 87% with 24 weeks of treatment.48 The combination of ABT-450/ritonavir and ombitasvir also was studied in G4 patients in the PEARL-1 trial.49 Treatment-naive patients received the combination, with or without RBV, for 12 weeks. The RBV-free arm had SVR of 91%, and 100% in the RBV-containing arm. In this study, the 2-drug regimen with RBV added was given to 49 treatment-experienced patients, all of whom achieved SVR.

The Most Difficult Patient

The treatment of HCV historically has been the most difficult in patients who need it most urgently, especially those with decompensated cirrhosis. In addition to success rates being dismal, treatment regimens, particularly those containing IFN and RBV, have been intolerable for most of these patients. A safe, well-tolerated oral DAA regimen would be ground-breaking for this population. The initial report of SOF and RBV in patients on the transplant list showed that longer duration of undetectable HCV RNA before transplant (>30 days) predicted prevention, although this study included only patients listed because of hepatocellular carcinoma who were otherwise well compensated.50 An arm of the ELECTRON-2 trial administered LVD/SOF for 12 weeks in patients with decompensated cirrhosis. Of the 20 patients, 13 achieved SVR (65%). Seven of the 13 relapsed.51

Ongoing studies are evaluating additional regimens in the decompensated population. Sofosbuvir also has been studied as a regimen for recurrent HCV in patients who have undergone liver transplantation. As part of a compassionate-use program, 104 patients with severe recurrent hepatitis or fibrosing cholestatic hepatitis were treated with SOF and RBV for 24 to 48 weeks.52 Physicians could add PegIFN at their discretion, which was done in about 25% of patients. Of the patients for whom there are data, 62% achieved SVR. Most patients also had improved liver function tests and clinical outcomes with treatment, including resolution of ascites, even in the absence of SVR. The 3D/RBV regimen also has been studied in the post-transplant population.53 Thirty-four patients received the regimen for 24 weeks. Data so far have shown a 96% (25 of 26) SVR, although patients with more aggressive liver disease were excluded. Importantly, there were no major interactions or apparent effects of immunosuppression, no organ rejections, and no serious AEs associated with the regimen.

Conclusion

With the global burden of HCV, the need for effective, well-tolerated treatment regimens is essential. Elucidation of the HCV life cycle has allowed for newer drugs to be developed, overcoming some of the major disadvantages of prior standard of care with IFN-based therapy. The DAAs are anticipated to completely replace IFN as the foundation of HCV treatment.

Among the major advantages of these oral regimens beyond their increased efficacy has been their relatively clean safety profile. Although AEs are common, they generally are mild, including headache, fatigue, and insomnia, and trivial relative to that of telaprevir and boceprevir.46 The low rate of discontinuation in all the trials further attests to the tolerance of the regimens, even in those containing RBV. In addition, the once-daily dosing and limited drug–drug interactions has minimized the AEs of treatment for most patients. As newer medications and regimens get approved, the next dilemma will be to determine the ideal combination of medications and treatment duration for each patient. Ideally, predictors of response to treatment would aid in the decision making, but none has consistently been identified. Although one study has suggested that early viral kinetics may identify those with a higher risk for relapse,52 such predictive value has not been gleaned from the Phase III databases.

Importantly, these new regimens also have been able to overcome baseline factors previously associated with poorer outcomes including G1a subtype, race, non-CC IL28B allele, and prior treatment history. Although treatment-failure rates now appear to be minimal and routes to treatment failure have all but eliminated nonresponse and viral breakthrough, some patients will relapse. SOF has been associated in vitro with a S282T signature mutation, but it is replicatively unfit54 and rarely found in samples from SOF-treated relapsers, providing a foundation for retreatment with a SOF-containing regimen in these failures. Now that the fundamental paradigm shift toward IFN-free regimens is imminent, further research will be needed to identify effective salvage therapies for patients who have failed both nucleotide-containing and nucleotide-free combination regimens.
References


38. Andreone P, Colombo MG, Enejoisa J V, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced...


