Development of more effective hepatitis C (HCV) antivirals has been rapid. The addition of orally administered medications that target the virus (direct acting antivirals [DAA]) to pegylated interferon and ribavirin have dramatically increased sustained virologic response rates in genotype 1-infected patients. However, the side effect profile remains challenging and the dosing schedule complicated. The DAAs currently in development possess the promise of once- or twice-daily dosing schedules, improved tolerance profiles, higher resistance barriers, and pan-genotypic antiviral activity. Emerging interferon-sparing, combination DAA data demonstrates that an interferon is not essential to achieve sustained virological response. This will expand the proportion of HCV-infected patients who can be considered for therapy and will allow for better-tolerated regimens. Expertise in HCV antiviral resistance, drug metabolism, and drug-drug interactions and optimization of drug adherence are now key requirements in the DAA era.

MORE ANALYSIS OF BOCEPREVIR AND TELAPREVIR DATA

Two new HCV protease inhibitors (boceprevir and telaprevir) have dramatically improved sustained virologic response (SVR) rates in those living with genotype 1 infection [1–4] and are now considered standard of care [5, 6]. The likelihood of SVR is approximately 70% in treatment-naive patients, 80% in prior relapse patients, 50% in partial responder patients, and 35% in null responder patients [5, 6]. For some naive, relapsers, and partial responder patients, antiviral therapy can be markedly shortened by utilizing a response-guided therapy (RGT) approach to treatment based on rapid and sustained HCV RNA suppression.

At AASLD 2011, several presentations were devoted to further analyses of the boceprevir and telaprevir trial data sets. A 4-week lead-in with pegylated interferon and ribavirin is dosed prior to adding boceprevir. Bacon et al assessed the degree of HCV RNA suppression during this lead-in phase and its value in predicting treatment outcome [7]. In those who failed to achieve at least a 1 log reduction in HCV RNA level
during the lead-in and then had <3 log reduction in HCV RNA by week 8 (ie, 4 weeks after the addition of boceprevir), the likelihood of achieving an SVR was 0%. This data supports the use of an 8-week stopping rule for triple therapy with boceprevir. In another key study, the efficacy of boceprevir in prior null responder patients to pegylated interferon and ribavirin was assessed in the Provide rollover study [8]. The SVR rate was 38% by on-treatment analysis (n=42).

Human immunodeficiency virus (HIV)–HCV coinfected individuals are in great need of improved HCV treatment options. At week 24 of a 48-week duration HIV–HCV coinfection trial, 71% (n=38) of telaprevir-pegylated interferon-ribavirin recipients were free of viremia compared with 55% (n=22) in the pegylated interferon and ribavirin control arm [9]. This high on-treatment viral response with telaprevir raises hopes for improved SVR rates.

### Table 1. Direct-Acting Antivirals Discussed at the 2011 Annual Meeting of the American Association for the Study of Liver Disease

<table>
<thead>
<tr>
<th>DAA Class</th>
<th>Genotype Activity</th>
<th>Dosing</th>
<th>Phase of Clinical Development</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boceprevir</td>
<td>1 q8h</td>
<td></td>
<td>Approved</td>
<td>[1, 3, 8]</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>1 q8h</td>
<td></td>
<td>Approved</td>
<td>[2, 4, 21]</td>
</tr>
<tr>
<td>BI 201335</td>
<td>1 qd</td>
<td>3</td>
<td>[10, 26, 30]</td>
<td></td>
</tr>
<tr>
<td>TMC435</td>
<td>1,2,4,5,6 qd</td>
<td>3</td>
<td>[12]</td>
<td></td>
</tr>
<tr>
<td>Danoprevir/r</td>
<td>1,4,6 bid</td>
<td>2</td>
<td>[13]</td>
<td></td>
</tr>
<tr>
<td>Asunaprevir</td>
<td>1,4 bid</td>
<td>2</td>
<td>[25]</td>
<td></td>
</tr>
<tr>
<td>MK 5172</td>
<td>1,2,3 qd</td>
<td>2</td>
<td>[56]</td>
<td></td>
</tr>
<tr>
<td>Narlaprevir/r</td>
<td>1 qd</td>
<td>2</td>
<td>[14]</td>
<td></td>
</tr>
<tr>
<td>Vaniprevir/r</td>
<td>1,2 bid</td>
<td>2</td>
<td>[57, 58]</td>
<td></td>
</tr>
<tr>
<td>ACH-1625</td>
<td>1 qd</td>
<td>2</td>
<td>[59]</td>
<td></td>
</tr>
<tr>
<td>NS5a assembly inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>1,4 qd</td>
<td>3</td>
<td>[15-17, 25]</td>
<td></td>
</tr>
<tr>
<td>PPI-461</td>
<td>All qd</td>
<td>1b</td>
<td>[23]</td>
<td></td>
</tr>
<tr>
<td>GSK2336805</td>
<td>1a, 1b, 2a, 4 qd</td>
<td>1b</td>
<td>[24]</td>
<td></td>
</tr>
<tr>
<td>MK-4882</td>
<td>1–4 qd</td>
<td></td>
<td>Preclinical</td>
<td>[60]</td>
</tr>
<tr>
<td>NS5b inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleotides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSI-7977</td>
<td>1,2,3 qd</td>
<td>3</td>
<td>[18, 29]</td>
<td></td>
</tr>
<tr>
<td>Mericitabine</td>
<td>1–4 bid</td>
<td>2</td>
<td>[36, 61]</td>
<td></td>
</tr>
<tr>
<td>IDX-08189</td>
<td>1, 2, 3 qd</td>
<td>2</td>
<td>[62]</td>
<td></td>
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<tr>
<td>Polymerase inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BI 207127</td>
<td>1 bid/tid</td>
<td>2</td>
<td>[26, 30]</td>
<td></td>
</tr>
<tr>
<td>VX-222</td>
<td>1 bid</td>
<td>2</td>
<td>[21]</td>
<td></td>
</tr>
<tr>
<td>TMC647055</td>
<td>1b TBD</td>
<td>1b</td>
<td>[63]</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: bid, twice daily; DAA, direct-acting agent; q8h, every 8 hours; qd, every 12 hours; TBD, to be determined; tid, three times a day.

### Table 2. Direct-Acting Antiviral Regimen Types Discussed at the 2011 Annual Meeting of the American Association for the Study of Liver Disease

<table>
<thead>
<tr>
<th>Regimen Type</th>
<th>DAA(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadruple therapy (DAAs + PegIFN and ribavirin)</td>
<td>Daclatasvir Asunaprevir [20] Telaprevir VX-222 [21]</td>
<td></td>
</tr>
<tr>
<td>Interferon-sparing plus ribavirin</td>
<td>BI 201335 BI 207127 [26, 27, 30] PSI-7977 [29]</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DAA, direct-acting agent; PegIFN, pegylated interferon.

* Evaluated as monotherapy in genotype 2 and 3 recipients.

b Development of this regimen-type combination abandoned due to suboptimal results.

c /r indicates ritonavir boosting.

d Potential broad genotype activity.

### SINGLE DIRECT-ACTING ANTIVIRAL PLUS PEGYLATED INTERFERON AND RIBAVIRIN

**HCV Protease Inhibitors**

In SILEN-C1, 429 patients were randomly assigned to the once-daily protease inhibitor BI 201335 (120 mg or 240 mg) or placebo; all patients also received 24 weeks of pegylated interferon and ribavirin therapy [10]. Those who did not attain an extended rapid virological response (eRVR), defined in this study as HCV RNA <25 IU/mL at week 4 and undetectable at weeks 8–20, received an additional 24 weeks of pegylated interferon and ribavirin. By this RGT criteria, approximately 87% of study participants were eligible for 24 weeks of therapy. The highest rates of SVR were observed in the 240-mg dosing arm of BI 201335 (83%), which where significantly improved over the control arm of pegylated interferon and ribavirin for 48 weeks (56%). BI 201335 was noted to increase dermatological and gastrointestinal side effects over the control. This study
assessed several key uncertainties related to HCV treatment, including the value of a peglated interferon and ribavirin lead-in and the impact of interleukin 28B (IL-28B) status on treatment outcomes. In the SILEN-C1 study, a 3-day lead-in phase with peglated interferon and ribavirin did not impact SVR or provide any other clear benefit. The IL-28B status influenced SVR in the SILEN-C1 study: SVR was obtained in 100% of patients with a 240-mg BI201335 dose plus peglated interferon and ribavirin vs 82% of patients with peglated interferon and ribavirin in CC study participants and 71% of patients vs 41% of patients who received non-CC treatment. Based on boceprevir and telaprevir data, some have argued that there is little advantage to including a DAA over peglated interferon and ribavirin alone in CC-haplotype recipients because both groups achieved similarly high SVR rates [11]. The SILEN-C1 results suggest otherwise.

TMC435 is a once-daily dosed protease inhibitor in phase 3 development. Doses of 75 mg daily and 150 mg daily were assessed in treatment-naive, genotype 1–infected participants (n = 386) [12]. TMC435 was administered for 12 or 24 weeks in combination with peglated interferon and ribavirin, which was dosed for either 24 or 48 weeks according to RGT criteria. A 24-week duration was assigned if HCV RNA was <25 IU/mL at week 4 and undetectable at weeks 12, 16, and 20. By this criteria, 79%–86% of participants were eligible for shortened therapy. The SVRs were improved in TMC435 recipients, ranging 75%–86% compared with 65% in the 48-week peglated interferon and ribavirin control arm. Although there may have been improved SVR rates with higher-dose TMC435 in genotype 1a recipients (82% vs 66%), no clear advantage with higher dose and/or longer duration TMC435 dosing was identified. Of note, the 150-mg dose is being evaluated in phase 3 studies. The incidences of discontinuation, adverse events, and serious adverse events were comparable between the TMC435 groups and the control arm.

Danoprevir is a protease inhibitor with antiviral activity against multiple genotypes offering a key benefit over currently licensed protease inhibitors. Treatment-naive, noncirrhotic patients with either HCV genotype 1 or genotype 4 infection (n = 225) were randomly assigned to escalating dosing arms of Danoprevir (300 mg every 8 hours, 600 mg every 12 hours [q12h], 900 mg q12h) for 12 weeks in combination with peglated interferon and ribavirin [13]. Patients who achieved an eRVR (weeks 4–20) were eligible for a total of 24 weeks of peglated interferon and ribavirin, whereas the remaining patients completed 48 weeks of dual therapy. The best outcome (SVR = 85%) was achieved in patients receiving 600 mg twice daily. The SVR rates in eRVR participants (65% of all danoprevir recipients) ranged 87%–95%. Four percent of Danoprevir recipients developed resistance. Overall tolerability was similar to that of peglated interferon and ribavirin control. Reversible on-treatment liver enzyme elevation with higher-dose recipients lead to premature discontinuation of the 900-mg twice daily (bid) arm and preclude continued development of this compound using 600- or 900-mg doses. Because Danoprevir is metabolized by the CYP3A4 enzyme, ritonavir can be used to boost lower doses of Danoprevir (ie, 100–200 mg) with the production of a much lower quantity of active metabolite, which is predicted to address liver toxicity concerns with this molecule. These studies are underway. Narlaprevir is another HCV protease inhibitor being evaluated with ritonavir boosting to allow for once-daily dosing [14].

**NS5A HCV Inhibitors**

Nonprotease inhibitor DAAs are also under development. Daclatasvir (BMS 790052) is an NS5a replication complex inhibitor with multigenotype antiviral activity [15]. Triple therapy with Daclatasvir in naive study participants (genotype 1 = 365) achieved viral suppression below the lower limit of quantification at week 12 in 84% of Daclatasvir recipients compared with 53% of peglated interferon and ribavirin control patients by modified intent-to-treat analysis [15]. Daclatasvir was evaluated in combination with ribavirin and either peglated interferon α-2a (n = 43) [16] or α-2b (n = 45) [17] in 2 other studies presented at AASLD 2011. Participants achieving a protocol-defined response (ie, HCV RNA <15 IU/mL at week 4 and undetectable at week 12) received 24 weeks of therapy. Those not meeting this criteria and those randomized to peglated interferon and ribavirin control therapy received 48 weeks of treatment. In both studies, all treatment-naive participants receiving the 60-mg dose were eligible for 24 weeks of therapy. High SVR rates were attained in those achieving a protocol-defined response: 86%–100% in treatment-naive patients receiving 10-mg and 60-mg doses and 67%–86% in prior nonresponders receiving the 60-mg dose [16, 17]. In each of the 3 studies described, the side effect profile with Daclatasvir-based triple therapy was similar to that of peglated interferon and ribavirin control. Final results for these studies are anticipated.

Once-daily PSI-7977, an NS5b nucleotide inhibitor, in combination with peglated interferon and ribavirin for 12 weeks was administered to genotype 1, treatment-naive, noncirrhotic recipients (n = 121). This was followed by an additional 12 or 36 weeks of peglated interferon and ribavirin according to RGT criteria. Nearly all (90 of 95, 95%) PSI-7977 recipients achieved an eRVR, defined as HCV RNA below detection at weeks 4 and 12. The SVR rates ranged from 88% (200-mg dose) to 91% (400-mg dose) by intent-to-treat analysis [18]. The addition of this nucleotide added few side effects beyond that of peglated interferon and ribavirin. The once-daily dosing schedule, good safety and tolerance profile, lack of clinically apparent resistance, and multigenotype activity position this nucleotide as a key DAA going forward. Another
key advantage of PSI-7977 is the lack of drug-drug interactions, which is a significant concern with currently approved HCV protease inhibitors [19].

QUADRUPLE THERAPY

Within the last year, phase 2 studies have demonstrated the high SVR potential of intensive, short-course regimens containing pegylated interferon and ribavirin plus 2 DAAs from different antiviral classes. For example, pegylated interferon, ribavirin, a protease inhibitor (Asunaprevir [BMS 650032] 200-mg bid) plus once-daily Daclatasvir 60 mg dosed for 24 weeks achieved 100% SVR in 10 previous null responder patients [20].

In the ZENITH study, telaprevir 1125-mg bid and VX-222 100 or 400-mg bid, a nonnucleoside polymerase inhibitor, with or without pegylated interferon and ribavirin, was assessed in genotype 1, treatment-naive patients (n = 106) [21]. Of note, the telaprevir and VX-222 dual-therapy study arms were previously discontinued due to high rates of on-treatment viral breakthrough [22]. Initial quadruple therapy was dosed for 12 weeks. An RGT algorithm was utilized to direct whether 12 additional weeks of pegylated interferon and ribavirin was provided. Those with undetectable HCV RNA at weeks 2 and 8 were eligible to stop all treatment at week 12. Interim treatment outcomes for patients receiving quadruple therapy were reported at AASLD 2011. No on-treatment viral breakthrough was detected, and approximately half of participants were eligible to receive only 12 weeks of therapy. The SVR12 was 90% in 400-mg bid VTX 222 recipients and 83% with the 100-mg bid dose. Of note, a fifth arm evaluating these 2 DAAs plus ribavirin without interferon is currently accruing.

Going forward, larger study populations consisting of more challenging populations (advanced fibrosis, genotype 1a, nonfavorable IL-28b haplotypes) require evaluation. Nongenotype 1 patients may also benefit when DAAs with multigenotype viral activity are combined with pegylated interferon and ribavirin [23, 24].

INTERFERON-SPARING THERAPY

Interferon-sparing regimens carry the promise of expanded eligibility for HCV antiviral therapy and will be the primary focus of HCV clinical research over the next decade. One of the first studies to demonstrate that SVR can be achieved without interferon was presented at the European Association for the Study of the Liver 2011 [20]. In this study, 4 of 11 prior null responder patients achieved an SVR following 24 weeks of Asunaprevir and Daclatasvir [20]. At AASLD 2011, further data were presented on this combination in a Japanese population of G1b prior null responder patients [25]. By intent-to-treat analysis, all 10 patients achieved SVR. This population was composed of genotype 1b, which is more virologically responsive and less susceptible to DAA resistance evolution compared with genotype 1a [20, 26].

Building on the earlier results of SILEN-C1 with the BI 201335 protease inhibitor in combination with pegylated interferon and ribavirin, the SOUND-C2 study evaluated 5 different BI 201335 and BI 207127 dosing regimens with or without ribavirin over 16-week to 40-week durations [27]. Preliminary analysis of the 16-week BI 201335 120mg once daily, BI 207127 600-mg three times daily and ribavirin in genotype 1–infected recipients (n = 81) was presented at AASLD 2011. Compared with genotype 1a–infected patients, those with genotype 1b had superior SVR12 rates (69% vs 43%) and lower relapse rates (10% vs 23%). At treatment week 12, rates of virologic suppression were considerably greater (70%–76% vs 57%) and viral failure less frequent (17%–22% vs 37%) in the ribavirin-containing arms. This is consistent with other studies that have demonstrated the added value of ribavirin in interferon plus single DAA treatment [28] and in other interferon-sparing regimens [29].

The potential to successfully treat nongenotype 1 patients with interferon-sparing antiviral therapy was demonstrated by the ELECTRON study [29]. All 10 treatment-naive, genotype 2– and 3–infected recipients of combination PSI-7977 plus ribavirin for 12 weeks achieved an SVR.

IS RIBAVIRIN REQUIRED?

The elimination of ribavirin would address issues related to fatigue, rash, and, most important, anemia. However, the current body of evidence demonstrates that ribavirin will remain essential to optimizing treatment success in the DAA era. Twelve weeks of pegylated interferon α2a plus telaprevir achieved only a 36% SVR rate compared with 60% for these HCV antivirals plus ribavirin [28]. Greater virologic potency, reduced breakthrough, and less resistance were achieved with the inclusion of ribavirin over the initial 28 days of interferon-sparing BI 201335 and BI 207127 dosing [26, 30]. It remains to be determined whether ribavirin is necessary to optimize virologic response in interferon plus NS5a–based regimens. Dual DAA plus interferon regimens with or without ribavirin also require evaluation. In genotype 2– and 3–infected patients only 6 of 10 recipients achieved an SVR with PSI-7977 monotherapy compared with all who received combination PSI-7977 plus ribavirin, suggesting that ribavirin may continue to have a role in nongenotype 1 infection as well [29].

IS RESISTANCE RELEVANT?

In on-treatment patients who fail to rapidly clear viremia, resistance frequently develops with most DAAs [2–4].
Following discontinuation of boceprevir and telaprevir exposure, the proportion of resistant-associated variants diminishes with time [31–33]. However, it remains unclear what the long-term consequences of on-treatment resistance will mean to subsequent antiviral treatment outcomes. Sarazin et al attempted to address this question in 9 genotype 1–infected patients (1a = 6, 1b = 3) exposed to 14 days of telaprevir a median of 5.7 prior to current treatment [34]. Eight had documented resistance mutations immediately following telaprevir exposure. None had resistant virus at levels >1% of the total viral population immediately prior to retreatment with telaprevir, pegylated interferon, and ribavirin. All achieved an initial decline in HCV RNA. One patient was identified with a viral breakthrough at 8 weeks with a resistance profile similar to the one originally identified (V36M + R155I/K). This is the most frequent resistance profile seen in subjects with genotype 1a infection with viral breakthrough during telaprevir-based therapy. Therefore, one cannot be certain whether this was a de novo mutation or a reemergence of the previously identified resistant strain. Two others were noted to have viral levels below the lower limit of quantification (<25 IU/mL) but were still detectable. The others had no detectable virus. Final treatment outcomes are pending. However, this preliminary data suggests that prior high-level HCV antiviral resistance may not have the same negative long-term consequences as in HIV and hepatitis B virus treatment.

Newer HCV protease inhibitors have higher genetic barriers to resistance (eg, TMC435, MK 5172). Furthermore, in vivo resistance does not appear to occur with several nucleosides, including Mericitabine [35, 36] and PSI-7977 [18, 29]. Therefore, it is plausible that in the future HCV antiviral resistance will be of minimal clinical consequence.

**OTHER TARGETS FOR HCV TREATMENT**

The DAAs are the current focus of HCV drug development. However, other viral and host targets are being explored. Alisporivir is an oral cyclophilin inhibitor with demonstrated activity against multiple genotypes [37–40]. Forty-eight week Alisporivir-pegylated interferon-ribavirin regimens have achieved SVR rates as high as 76% percent in genotype 1 recipients (n = 72) compared with 55% with pegylated interferon and ribavirin control recipients (n = 73) [37]. Interferon-free treatment with Alisporivir plus ribavirin achieved early viral suppression in up to half of genotype 2 and 3 study participants (n = 178) within the first 6 weeks of treatment [40]. Other molecules under investigation demonstrating a beneficial effect on SVR include the thiazolide antiparasitic Nitazoxanide [41, 42]; 25-hydroxyvitamin D [43–45]; HMG Co-A reductase inhibitor antilipids [46, 47]; insulin sensitizers including pioglitazone [48, 49]; HCV monoclonal antibodies (MBL-HCV1) [50]; and the selective estrogen receptor modulator raloxifene, which was evaluated in menopausal women receiving pegylated interferon and ribavirin [51]. With the possible exception of Alisporivir, none of these molecules have demonstrated the magnitude of impact on treatment outcome achieved with DAAs. However, each of these may prove to be an important adjunct to standard-of-care therapy.

**FUTURE TREATMENT PARADIGMS**

The AASLD 2011 data add to a body of evidence that suggests that 2 therapeutic tracks are evolving for genotype 1 infection. The first option focuses on maximizing the likelihood of SVR. Triple or quadruple drug regimens containing pegylated interferon will deliver on this objective. It is reasonable to anticipate ≥80% SVR rates with quadruple therapy in treatment-naive and experienced populations. A high burden of side effects and heavy pill count will limit the proportion of those able to benefit from these high-efficacy regimens. For those who cannot tolerate interferon, a double DAA plus ribavirin regimen will provide a 40%–70% chance of SVR. This second treatment track will be accessible to a much greater proportion of the HCV-infected population. If unsuccessful with interferon-sparing therapy, then patients could subsequently consider interferon-DAA salvage regimens.

The ELECTRON data (PSI-7977 and ribavirin) raise the possibility of an all-oral, short-duration, well-tolerated, user-friendly dosing schedule and low pill count regimen with very high SVR rates in genotype 2– and 3–infected patients [29]. Unsuccessful patients could be salvaged with pegylated interferon and ribavirin plus or minus a DAA with genotype 2/3 activity. Cost-effectiveness analyses will be instrumental in determining which regimens are funded and which criteria are utilized for payment decisions [52–55]. Future studies will address this and the many other unresolved questions pertaining to HCV antiviral treatment.

**Notes**

*Acknowledgments.* C. C. is an Ontario HIV Treatment Network Career Scientist and acknowledges the Canadian HIV Trials Network, Canadian Institute for Health Research Influenza Research Network, and University of Ottawa Department of Medicine for research support.

*Potential conflicts of interest.* C. C. has collaborated as a clinical investigator with Merck, Vertex, Roche, BMS, BI, and Janssen. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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