The current standard of care for the treatment of HCV genotype 1 evolved to include a viral protease inhibitor in May 2011, yet rapid developments in HCV antiviral research point toward an imminent new standard of care. The U.S. and European approval of boceprevir and telaprevir, after a decade of dual peginterferon and ribavirin therapy, represented a landmark mechanistic transition in the approach to HCV eradication. The gratifying improvement in SVR rates unfortunately came at the expense of increased treatment complexity and toxicity, risk of antiviral resistance, and an expanded list of patient exclusionary criteria that has precluded treatment for the majority of potential candidates.

Response Predictors and Management Decisions
Post-hoc analyses of the telaprevir and boceprevir registration trials provide insight into both the host and on-treatment factors that are associated with response. The currently available HCV antiviral regimens are particularly beneficial for those treatment naïve individuals with low HCV RNA levels who are adherent to treatment duration, and for those patients who have favorable baseline host factors including IL-28 CC, genotype 1b, and minimal hepatic fibrosis. Favorable on-treatment parameters include interferon-responsiveness and the development of anemia. The presence of less favorable pre-treatment and on-treatment characteristics markedly diminishes the likelihood that such therapy will prove beneficial. Post marketing studies have also shown that telaprevir b.i.d. is as efficacious as q8h, and that ribavirin dose reduction is the preferred course of management of on-treatment anemia.

Treatment Barriers and Benefits
Successful therapy slows liver disease progression yet most infected patients have not received treatment, and in an analysis of a large US private health insurance company database, only 18% of HCV infected patients received therapy. The annual all-cause health care cost to manage patients with end-stage HCV disease was 247% higher than to treat those HCV patients with non-cirrhotic disease. The precise barriers to proper diagnosis may vary by region. In the first international study to explore barriers to care among HCV treatment providers, McGowan et al surveyed nearly 700 physicians from 29 countries. They found that although the specific barriers to HCV treatment differed by region of the world, physician knowledge deficit was a common theme, as was a global physician perception that patients feared treatment side effects. Among blacks, ethnic neutropenia has consistently excluded many potential treatment candidates. Talal et al examined a dataset of 46,000 U.S. HCV patients and found that while only 17.3% had true contraindications to therapy, the authors used a less strict definition of depression and alcohol/substance use. A review of nearly 100,000 HCV infected US Veterans recently showed that only 11.6% received peginterferon and ribavirin and 6.4% completed treatment. Thus, treatment effectiveness for HCV was low in this population, with extraordinarily low rates of antiviral treatment initiation and completion. The majority of patients had contraindications to treatment, usually depression or drug/alcohol use, but also a host of co-morbid medical condition including diabetes, COPD and coronary artery disease.
Despite the recognized toxicities and limitations of currently available interferon-based antiviral regimens, there are recently reported long-term extrahepatic benefits of SVR, including a prevention of the development of insulin resistance and an improvement in cognitive function. A recent long-term follow up report of 168 HCV patients receiving antiviral therapy tested neurocognitive performance before and after treatment, and showed that patients with SVR showed improvement in three of five performance subtasks, whereas non-SVR patients showed no such long-term changes, suggesting that the neurocognitive impairment caused by chronic HCV infection is potentially reversible. Several groups have shown that the benefits of SVR include a reduced occurrence of liver failure, whereas more recently all-cause mortality was shown to be almost 4-fold lower in patients with SVR compared with patients without SVR.

Defining Intolerance and Ineligibility to Treatment
All oral antiviral therapy for interferon intolerant or ineligible patients is an urgent and unmet need, and recent studies have attempted to define this important population with better clarity. Lawitz et al described 160 such subjects and found that the main reasons for ineligibility for IFN based treatment were psychiatric and autoimmune disorders, whereas the most common reasons for IFN intolerance included local/systemic reaction, flu-like illness, and psychiatric disease. A recent Japanese study that used daclatasvir and asunaprevir for genotype 1 infected patients reported 18 ineligible/intolerant due to age > 70 years, cytopenia, depression, hypertension or other. The SVR rate of 63.6% in this group of ineligible/intolerant patients represented the first demonstration of effective treatment for a group of patients who currently have no therapeutic options. A Phase 3 genotype 1b trial of this all oral regimen is in progress, but with strict definitions of interferon intolerance and ineligibility; a recently completed trial of sofosbuvir plus ribavirin for a similar population of intolerant/ineligible genotype 2/3 subjects also included those subjects who were self-defined “interferon unwilling.”

References