Hepatitis C virus (HCV) is the most common blood-borne infection in the United States. HCV infection is a leading cause of chronic liver disease, end-stage liver disease, and liver transplantation. Newly available therapies can clear HCV in most infected persons who receive treatment. However, many persons living with HCV infection are unaware of their infection status, including those born during 1945–1965 (a population at increased risk for chronic hepatitis C in the United States). This review highlights the epidemiology of hepatitis C and the importance of HCV testing and linkage to care in an era of more effective antiviral therapies.

Mathematical modeling of hepatitis C viral kinetics has been an important tool in understanding hepatitis C virus (HCV) infection dynamics and in estimating crucial in vivo parameters characterizing the effectiveness of HCV therapy. Because of the introduction of direct-acting antiviral agents, there is a need to extend previous models so as to understand, characterize, and compare various new HCV treatment regimens. Here we review recent modeling efforts in this direction.

In the direct-acting antiviral (DAA) era of hepatitis C virus (HCV) therapy, health care providers must be knowledgeable about genotype and subtype of HCV infection and interpretation of quantitative HCV viral assays to monitor treatment responses. They may also choose to assess interleukin 28B genotypes or resistance-associated variants after ineffective DAA therapy. DAA therapies require understanding of performance characteristics of quantitative HCV RNA assays and the definitions of terms used to report results. Only quantitative HCV RNA assays with a limit of detection of 10 to 15 IU/mL are appropriate for managing patients on DAA therapy.

Telaprevir is a recently approved direct-acting antiviral against hepatitis C virus (HCV) that works through inhibition of the NS3/4A serine protease
inhibitor. Phase 2b and 3 studies have shown marked increase in sustained virologic response rates in both treatment-naïve and treatment-experienced patients with HCV genotype 1 treated with a telaprevir-containing regimen compared with pegylated interferon (Peg-IFN) and ribavirin alone. The most commonly observed side effects of telaprevir therapy are anemia to a greater degree than that observed with Peg-IFN/ribavirin alone; eczematous rash, which can be severe in a minority of patients; and anorectal discomfort.

**Boceprevir and Treatment of Chronic Hepatitis C**

Paul Y. Kwo

The addition of boceprevir to peginterferon and ribavirin has improved sustained response rates markedly. Boceprevir is effective in treatment naïve, relapsers, partial responders, and null responders. Those with advanced fibrosis require 44 weeks of boceprevir therapy after a 4-week peg/ribavirin lead-in. The main side effect with boceprevir is anemia and ribavirin dose reduction is an effective strategy. This review examines the current treatment paradigm of boceprevir-based treatment of chronic hepatitis C, examining treatment paradigms, predictors of response, futility rules, as well as preliminary results from studies examining boceprevir efficacy in additional populations. Further follow-up in these cohorts will be required.

**Management of the Transplant Recipient with Chronic Hepatitis C**

James R. Burton Jr and Gregory T. Everson

More than one-third of listed potential liver recipients in the US are infected with the hepatitis C virus (HCV). Recurrence of infection with HCV after liver transplantation is associated with accelerated graft loss and diminished patient survival. Current HCV treatments using peginterferon and ribavirin either alone or with first generation protease inhibitors (telaprevir, boceprevir) are limited by suboptimal viral response, drug-drug interaction, and side effects, some of which may be graft- or life-threatening. Rapid advances in new drug therapy for HCV promise to improve outcomes, reduce side effects and drug-drug interaction, shorten treatment duration, and simplify treatment regimens.

**Update on Combinations of DAAs With and Without Pegylated-Interferon and Ribavirin: Triple and Quadruple Therapy More Than Doubles SVR**

Valérie Martel-Laferrière and Douglas T. Dieterich

Monotherapy is an ineffective way to treat hepatitis C and it leads to rapid development of resistance. An increasing number of drugs are currently being developed for the treatment of hepatitis C. This allows combination strategies that can overcome the development of resistance and improve sustained virologic response rates. This article focuses on the 2 main strategies in development: quadruple combination therapies, including pegylated-interferon and triple/quadruple pegylated-interferon free combination therapies. If the first combinations are leading to extremely
high sustained virologic responses, the second ones offer hope that the era of pegylated-interferon will end soon.

Nucleoside/Nucleotide Analogue Polymerase Inhibitors in Development

Paul J. Pockros

Nucleoside/nucleotide analogue polymerase inhibitors (NPIs) are analogues of natural substrates that bind the active site of NS5B and terminate viral RNA chain generation and generally provide a high genetic barrier to resistance and are effective in all genotypes. NPIs such as sofosbuvir (GS-7977) show high antiviral activities that, together with their high genetic barrier to resistance, suggest that they are optimal backbone candidates for all-oral combination therapies. Several trials are ongoing to further define the potential of all-oral regimens with sofosbuvir (GS-7977). Recent interim analyses indicate that many patients treated with only 2 direct-acting antiviral agents experience viral breakthrough, which can be significantly reduced by the addition of ribavirin without pegylated interferon α.

HCV NS5A Inhibitors in Development

Anna Suk-Fong Lok

NS5A protein plays a key role in hepatitis C virus (HCV) replication. Daclatasvir (DCV, BMS-790052) is a first-in-class inhibitor of the HCV NS5A replication complex with potent antiviral activity but a low barrier to resistance. DCV as triple therapy in combination with pegylated interferon and ribavirin resulted in a high rate of early virologic response in treatment-naïve patients with genotype 1 infection; as quadruple therapy in combination with asunaprevir (BMS-650032, NS3 protease inhibitor), pegylated interferon, and ribavirin, it resulted in a high rate of sustained virologic response in genotype 1 prior null responders.

Non-nucleoside Analogue Polymerase Inhibitors in Development

Paul J. Pockros

Non-nucleoside polymerase inhibitors have several limitations including low to moderate potency, a low barrier to resistance, unlikely to cross genotype activity, genotype potency 1b > 1a, and hyperbilirubinemia for 2 of the drugs (tegobuvir and BI-207127). These drugs will have no role in monotherapy and may have only a limited role in triple therapy. They could be part of a quadruple therapy regimen or a triple or quadruple interferon-free regimen. Several issues remain unclear at the time of this review; the role of these compounds including minimal dosing required, safety, and cost remains to be clarified.

Cyclophilin Inhibitors for Hepatitis C Therapy

Fernando E. Membreno, Jennifer C. Espinales, and Eric J. Lawitz

This article highlights a unique time in the history of Hepatitis C therapy. In the last few years new families of direct-acting antivirals have emerged,
that block different viral proteins to interrupt viral replication, such as protease, NS5A inhibitors, and NS5B inhibitors. There are few host-targeted agents in development; currently cyclophilin inhibitors are the only host-targeted agents in advanced development. One of these new agents has now progressed to phase 3 clinical trials; in this review article their potential role as a future therapy to cure Hepatitis C is discussed.