Brave New World?  
Recent developments in Hepatitis C treatment

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Summary
Hepatitis C treatment has come a long way in the last 20 years, but exciting new developments promise to revolutionise treatment. Although we can now cure over 50% of people with chronic hepatitis C, interferon-based treatments are long, expensive and have significant side effects. A new wave of direct-acting antiviral drugs is just around the corner, promising to increase cure rates and reduce duration of treatment. Novel drugs targeting host proteins are also undergoing clinical trials and promise to further improve outcomes. In the future hepatitis C treatment is likely to be tailored to individual patients, as we learn more about the factors that influence response. New initiatives are improving access to treatment for people living with hepatitis C, while public health interventions continue to reduce transmission. With improved treatments and better access we should be able to further reduce the disease burden of hepatitis C in Australia.

Background
Hepatitis C affects 180 million people or 3% of the world’s population (1). It has been estimated that 264,000 people in Australia have been exposed to the virus, of whom 197,000 have chronic hepatitis C (2). With ~10,000 new infections annually, this disease is a major public health priority. Hepatitis C is now the main cause of cirrhosis requiring liver transplant in Australia, and the leading cause of hepatocellular carcinoma (Australian Transplant Registry 2007).

The hepatitis C virus (HCV) is a positive-strand RNA virus, the sole member of the Hepacivirus genus in the Flaviviridae family. The virus was identified in 1989 from a patient with transfusion-acquired non-A non-B hepatitis (3). Of note this was the first infectious agent to be identified by molecular cloning, without prior characterisation by traditional means.

HCV is transmitted by parenteral exposure to blood or body fluids, in Australia most commonly through shared injecting equipment. Prior to blood product screening in 1990 HCV was the main cause of transfusion-acquired hepatitis, as is still the case in many resource-poor countries. Although 90% of acute HCV infections are asymptomatic, approximately 70% of people go on to develop chronic hepatitis C, with a 3% to 9% risk of developing cirrhosis over 20 years (4).

Evolution of interferon treatment
Since the discovery of HCV in 1989 interferon (IFN) has remained the backbone of antiviral therapy. The primary endpoint of most clinical trials is a “sustained virological response” (SVR), defined as the absence of detectable plasma HCV RNA six months after completing therapy and considered a virological cure.

In early studies IFN-α monotherapy achieved SVR in only 10-20% of patients (5, 6). Adding the generic antiviral drug ribavirin to IFN-α improved SVR rates to around 40% overall (35% for genotype 1; 70% for non-genotype 1) (7, 8). Unfortunately IFN has a short half-life, requiring injections to be given three times a week, with variable serum levels. A long-acting form of IFN was developed by adding a polyethylene glycol (PEG) moiety, allowing weekly administration with sustained serum levels. In early trials PEG-IFNα alone was superior to IFNα, with SVR rates of 30-40% (9, 10). Adding ribavirin improved response further, giving an overall SVR of 55% (35-45% for genotype 1; 75-80% for genotype 2/3) (11, 12). Thus the combination of PEG-IFNα and ribavirin, given for 24 or 48 weeks, has become the current standard of care.

Direct-acting antivirals (DAA)
Antiviral drugs specifically targeting HCV have recently been developed, with over 20 currently in Phase II or III clinical trials (13). Most target viral proteins essential for replication, including the HCV protease (NS3/4), polymerase (NS5B) or NS5A protein.

The NS3 protease inhibitors telaprevir (Vertex Pharmaceuticals) and boceprevir (Merck) have now entered Phase III trials, in combination with PEG-IFNα and ribavirin. In Phase 2b studies of treatment-naïve patients with HCV genotype 1, telaprevir improved SVR rates from 41% to 61% (14) and from 46% to 69% (15), with 24 weeks treatment instead of 48. In similar studies boceprevir increased SVR from 38% to 75% (16).

When treating patients who had failed standard therapy, telaprevir increased SVR from 14% to over 50% (17). SVR was more likely in patients who had previously responded to treatment but relapsed (69-76%) than in patients who had not responded (38-39%). Ribavirin was still required to prevent viral relapse (17).

Drugs targeting host proteins
Drugs that target host proteins rather than HCV itself should be active against all HCV genotypes, with less potential for selecting drug-resistant virus (18). Promising drugs target proteins essential for HCV replication, such as the cyclophilin inhibitor Debo 025 (19). HCV induces insulin resistance and hepatic fat accumulation (20-23), so drugs that target lipid pathways or improve insulin signalling may improve treatment response, including pioglitazone (24, 25) and metformin (26). Cholesterol-lowering 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors such as fluvastatin inhibit HCV replication in vitro and suppress HCV viraemia in vivo (27), but clinical trials of these statins in combination with PEG-IFNα and ribavirin have been equivocal (28). Inhibitors of hepatic microRNA-122 effectively suppress HCV in chimpanzees (29), but such compounds are unlikely to be available in clinical trials for several years.

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**Interferon lambda (IFN-λ)**

IFN-λ is a novel type III interferon that has similar antiviral effects to IFN-α, but binds a different receptor complex that is less widely expressed. The three subtypes of IFN-λ are IL-28A, IL28B and IL-29. A PEGylated form of IL-29 is now undergoing clinical trials (30) and appears to have fewer side effects than IFN-α (31).

**Individualised treatments**

As more treatment options become available it will be possible to tailor regimens for individual patients. One challenge has been to predict which patients will respond to standard therapy with PEG-IFNα and ribavirin. Researchers at the Storr Liver Unit, Westmead Millennium Institute recently identified a polymorphism in the IL-28B gene that predicts a 2 fold increase in treatment response (32).

**Improving access to treatment**

HCV treatment programs are now available at many methadone maintenance programs targeting at-risk groups. Finally we must remain vigilant in improving access to treatment, as will hopefully continue.

**Preventing HCV infection**

As always prevention is better than cure, so public health interventions aim to reduce transmission of HCV, particularly among injecting drug users. Needle and syringe programs have been very effective at minimising transmission of HIV within this group, with HIV seroprevalence rates of only 1-2% among Australian drug users (39). In contrast, HCV was already established in the Australian drug using community before these programs were introduced, so transmission has been more difficult to interrupt. HCV seroprevalence among Australian drug users remained stable between 2005 and 2008 at 61-62%, but has now fallen to 50% in 2009, a trend that will hopefully continue.

**References**