Hepatitis C (HCV) is a viral infection that is curable with pegylated interferon and ribavirin (PEG-IFN/RBV) in around 60% of people. However, treatment is prolonged (24-48 weeks), and has considerable side effects.

Two newer therapies, known as direct-acting antiviral (DAA) agents (HCV protease inhibitors), telaprevir and boceprevir, were recently listed on the Australian PBS for treatment of chronic hepatitis C genotype 1.

When combined with PEG-IFN/RBV in triple therapy regimens these DAA agents improve cure rates by 20-25%, and shorten treatment duration from 48 to 24 weeks for around half of patients.

Although cure rates are increased, there are several concerns with these two DAA agents: they are not effective against genotype 2/3; there can be additional toxicity (e.g. rash, anaemia); problematic dosing (three times per day with food); and complex monitoring schedules and stopping rules are required.

Several other DAA agents in development that should become available in 3-4 years appear to be as potent, or possibly more potent, have reduced toxicity, and better dosing schedules (some are once daily).

Several studies of combination DAA treatment (without PEG-IFN/RBV) have been extremely encouraging, demonstrating cure rates of up to 90%.

The first available IFN-free DAA regimen is likely to be sofosbuvir (Nucleotide analogue) and ribavirin with a treatment cure (sustained virological response) of 90% for genotype 2 and 60% for genotype 3.

The future of hepatitis C treatment with DAA therapy is extremely promising - with the potential to cure the vast majority of people commenced on therapy. The challenge now is to increase access to treatment as currently only 1-2% of Australians with chronic hepatitis C commence treatment each year.

As people who inject drugs are the group at greatest risk of hepatitis C, further research and specifically developed treatment programs will be crucial.

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What is the issue?

Hepatitis C (HCV) is somewhat unusual among chronic diseases generally and chronic liver disease specifically – it is eminently curable. Around 60% of people commenced on current standard of care (PEG-IFN/RBV) will be cured of their chronic hepatitis C infection, with most people also having reversal of underlying liver damage. However, current treatment remains problematic due to the considerable side effects, the requirement for contraception during and for six months following treatment (due to the link between RBV and foetal malformation), the relatively prolonged treatment duration (24-48 weeks), and the restrictive settings in which most treatment is provided (tertiary clinics in large hospitals). As such, only 1-2% of people with chronic hepatitis C are commenced on treatment each year in Australia.

The landscape of hepatitis C treatment will alter enormously over the coming decade with the development of direct acting antiviral (DAA) agents that enhance treatment efficacy (that is, more people will be cured of their hepatitis C). The duration of therapy will be shortened with treatment demonstrated to be curative without interferon-based therapy. As new treatments become available, there will be a need to evaluate them among current injecting drug users, the group at greatest risk of hepatitis C infection who have to date been excluded from clinical trials developing these agents. It will also be crucial to improve access to treatment, through specifically developed treatment programs.

What is the evidence?

Over the last 12 months several major milestones have been reached in the clinical development of DAA therapy for chronic HCV infection. The initial HCV protease inhibitors, telaprevir and boceprevir, have been approved in Australia for use in combination with PEG-IFN/RBV for people with HCV genotype 1 who have never previously been treated for hepatitis C (treatment naïve) as well as people previously treated for hepatitis C (treatment experienced).

In treatment naïve populations, telaprevir or boceprevir when added to PEG-IFN/RBV improved the chance of a treatment cure (called a sustained virological response - SVR) from 40-45% to 65-75% and enabled the length of treatment to be shortened from 48 weeks to 24-28 weeks for around half of patients. In treatment experienced populations, telaprevir and boceprevir both provided considerably enhanced but variable SVR when combined with PEG-IFN/RBV (from 30% to 85%).

Although telaprevir and boceprevir are now listed on the Pharmaceutical Benefits Scheme, several concerns remain regarding these two agents, including:

- The problematic dosing schedule of three times per day with a meal (that must be high in fat content for telaprevir), and a large pill burden (boceprevir, 12 pills per day; telaprevir, 6 pills per day);
- A low level of treatment response (efficacy) in patients who have had a minimal reduction in the level of the virus when treated with PEG-IFN/RBV in the past, particularly those with advanced fibrosis (SVR achieved in only 15-20%);
- The potential for drug resistance;
- Increased side effects – in particular rash (with telaprevir) and anaemia (boceprevir and telaprevir); the potential for a large number of drug interactions due to the way that telaprevir and boceprevir are broken down in the liver (they impact on the cytochrome P450 (CYP) 3A4 pathways);
- The strategies for administering telaprevir and boceprevir in particular vary (they have different “start” and “stop” rules) and can be confusing for both patients and doctors; and
- Telaprevir and boceprevir are only approved for use for HCV genotype 1.
There are several important pathways for future DAA clinical development, with many studies recently releasing promising findings. Some of the major areas for development will include:

- **Shortened PEG-IFN/RBV/DAA therapy durations:** A phase III study demonstrated 90% SVR rate for people with HCV genotype 1 (treatment naïve) treated with PEG/RBV and sofosbuvir (nucleotide analogue) with total treatment duration of only 12 weeks;

- **IFN-free DAA regimens:** There are several promising regimens in development. Sofosbuvir and ribavirin should be licensed by the US Food and Drug Administration in late 2013 for HCV genotype 2 (12 weeks) and HCV genotype 3 (16 weeks), based on SVR rates of around 90% for genotype 2 and 60% for genotype 3. Subsequent regimens will combine at least two DAA agents, possibly without the need for ribavirin, and possibly with activity against all HCV genotypes;

- **Over the next five to ten years there will be major improvements in hepatitis C therapy,** with simplified, short duration regimens. Side effects and pill-burden (the number of tablets the person needs to take each day) will also reduce—likely to become a once daily single combination pill.

Preliminary evidence that IFN-free regimens are curative and the development of other promising once-daily agents shines a bright light on the way forward.

**Useful resources**


**Website**

The Treatment Action Group in New York produces excellent community-based reports on hepatitis C treatment developments in their Pipeline Report series. See the chapter titled ‘Hepatitis C drug development goes from pony ride to rocket launch’ by Swan and Kaplan in the most recent report - HIV, Hepatitis C Virus (HCV), and Tuberculosis (TB) Drugs, Diagnostics, Vaccines, and Preventive Technologies in Development (Clayden et al. 2012) Go to the Treatment Action Group website for Pipeline Reports and updates.