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PERSPECTIVE

Miles to go before we sleep

New drugs are generating much excitement, but a cure for all will take generations of therapies, argues **Charles Rice**.

The blood-borne hepatitis C virus (HCV) infects at least 130 million people worldwide. Over decades of chronic infection, patients are at risk of fibrosis, cirrhosis and liver cancer. Currently, HCV infection is treated with a weekly injection of pegylated interferon-α and a twice-daily weight-based dose of ribavirin. This standard of care, which has not changed for almost a decade, is considered suboptimal because of its long duration, side effects and inability to cure about half of all patients. In May this year, boceprevir, a first generation direct-acting HCV inhibitor, was approved for use by the Food and Drug Association. Patients and doctors have been waiting more than twenty years for this breakthrough, but the celebration should be tempered. Achieving a universal cure for HCV will require much more work.

The new drugs generating all the buzz are the inhibitors of the viral NS3/4A protease. Telaprevir (Vertex Pharmaceuticals, based in Cambridge, Massachusetts) and boceprevir (Merck, headquartered in Whitehouse Station, New Jersey) have improved the cure rates for both treatment-naive patients and those who had failed standard therapy. A major caveat of the protease inhibitors, however, is that they must be used in combination with the existing standard of care. This is because the virus can easily overcome a single direct-acting antiviral. HCV replicates in a prolific and highly error-prone manner, leading to the rapid emergence of point mutations that confer drug resistance. The continued need for interferon-α and ribavirin is disappointing because the new agents worsen the problematic side effects of standard therapy, especially rashes for telaprevir and anaemia for both telaprevir and boceprevir. Furthermore, host factors that affect the outcome of interferon-α plus ribavirin treatment continue to be reflected in protease-inhibitor clinical trials, for example African-American ethnicity, advanced liver fibrosis and single nucleotide polymorphisms in the region of the *IL28B* gene — although, to be sure, their adverse impact is reduced.

It is imperative that the HCV drug pipeline be kept flowing. The goal, an interferon-α and ribavirin-free regimen, will require multiple drugs with diverse modes of action. Cocktails of targeted antivirals will make it more difficult for the virus to become resistant — a strategy analogous to highly active antiretroviral therapy against HIV. Early combination trials are under way and showing promise, but it will probably be two to three years before two direct-acting antivirals are approved in combination with the standard of care, and perhaps five years before the first interferon-α and ribavirin-free drug cocktails reach the clinic.

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As second- and third-generation combination regimens for HCV are unveiled, it is important to consider all those who need them. First, the new drugs will have to be tested in diverse patient groups. With at least six genotypes and dozens of subtypes, HCV is one of the most variable viruses known. Most clinical trials have been conducted in the context of genotype 1 — the most common type in Europe and North America. Each drug regimen will need to be tested at several geographical sites to encompass the most prevalent local genotypes. Patient factors must also be considered when evaluating treatment efficacy. Patients with cirrhosis, those receiving liver transplants and groups who are co-infected with HIV or hepatitis B virus are among those with the most critical needs and have traditionally been the hardest to treat. How these patients respond to next-generation drugs has not yet been properly evaluated.

People at the highest risk of the HCV are among the most marginalized groups in society, such as injection drug users, prisoners and those living in endemic regions of the developing world. In parts of Asia and Africa, up to 10% of the population is infected with HCV; in Egypt, the prevalence of anti-HCV antibodies is as high as 15%. As newer, more expensive, treatment options become available, the gap between those who can afford treatment and those who cannot will widen. Advocates for HIV/AIDS care made strides in promoting surveillance, increasing education, reducing stigma, strengthening health infrastructure and implementing harm reduction programmes. Importantly, tiered pricing models for antiretroviral drugs were negotiated, which ensure lower prices in poor countries and help promote universal coverage. The HCV community can learn from the HIV experience, including the need for combination therapy and the importance of integrating education and prevention when deploying new therapies.

A cure is possible — a statement that can't be made about many other chronic diseases. Direct-acting antivirals mark an important first step, but this is no time to lose momentum. Researchers in academia and industry need to keep working on the pipeline to ensure that all those infected with HCV can receive proper treatment, allowing this disease to fade into medical history. ■

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The author declares competing financial interests: go.nature.com/crCD7A