In the past, HCV genotype 3 was thought to be one of the easiest to cure. As a result there was little incentive to develop newer therapies especially since there were fewer people with genotype 3 in developed countries. Now it has turned out that treatment of genotype 3 is the hardest to cure with HCV inhibitor therapy compared to HCV genotypes 1, 2 and 4. HCV genotype 3 also contributes to the development of steatosis (fatty liver disease) and insulin resistance, both of which can directly influence HCV disease progression including cirrhosis and liver cancer.

Prevalence
The worldwide prevalence of hepatitis C is 150-170 million people. But the real prevalence is unknown since most countries have an inadequate surveillance system in place, if any. In this respect, understanding the real prevalence of HCV genotype 3 is difficult, but it is estimated that about 55% (~95 million) of all cases of hepatitis C are genotype 3. The highest concentration of genotype 3 is in Southeast Asia and the Western Pacific countries. HCV genotype 3 is also the most common genotype in India and Pakistan, and accounts for about 30% of the infected population of Greece, Poland, and the Netherlands.

Interestingly, genotype 3a has been found to have existed 200 years ago, and just recently it has been found to follow trends in injection drug use throughout the world. This trend began in the mid-1970’s in Thailand and in the Vietnam war and traveled through the injection drug community in Europe and the United States. Disease progression
HCV genotype 3 has been found to cause steatosis (fatty liver disease), and there is some evidence that
it can cause insulin resistance—a precursor to diabetes. The relationship between genotype 3 and steatosis is not fully understood, but it is believed to be associated with the level of HCV RNA (viral load). The exact cause is unknown; what is known is that when people with HCV genotype 3 are cured with HCV antiviral treatment, the level of steatosis is reduced or completely resolves.

On less firm ground is the correlation of genotype 3 with insulin resistance and diabetes. But it does seem that people who are cured with HCV antiviral medications have improved insulin resistance and reduced incidence of diabetes. More studies are needed to completely prove this theory because it has been proven that there is no relationship between HCV and diabetes—at least in non-genotype 3 people.

Steatosis also increases the risk of disease progression, cirrhosis and liver cancer. The U.S. Veterans Affairs (VA) recently conducted a study of 110,484 patients with hepatitis C of whom 8,337 had genotype 3. The study found that compared to people with genotype 1, patients with genotype 3 were 31% more likely to develop cirrhosis and 80% more likely to develop liver cancer. These results point to the need for more aggressive medical management and the development of more effective (and cheaper drugs) to treat people with genotype 3.

**Treatment**

In the past, the standard of care for treating HCV genotype 3 was the combination of pegylated interferon plus ribavirin for a treatment period of 24 weeks. Now the current standard of care is the combination of sofosbuvir (brand name Sovaldi), plus ribavirin (weight-based) for a treatment duration of 24 weeks. The cure rates are up to 83%. However, the cost of Sovaldi is expensive—$168,000 for a 24 week course of treatment. The alternative recommended regime by the American Association for the Study of Liver Diseases (AASLD) is the combination of Sovaldi, pegylated interferon plus ribavirin for 12 weeks. Gilead—the pharmaceutical company that sells Sovaldi—has a very generous patient assistance program that provides assistance to those who qualify. Gilead also offers support to some poorer countries that may manufacture a cheaper version.

Some countries may also use the older pegylated interferon plus ribavirin since the response rates are somewhat similar, but, unfortunately, the side effects are higher than Sovaldi plus ribavirin. In addition, the presence of significant steatosis and severe liver disease reduces the cure rates especially with PEG/RBV treatment. In this respect, better and cheaper therapies are needed by people who cannot afford them, wherever they reside.

**Drugs in Development**

Due to the high costs, long treatment duration and the lower cure rates compared to HCV genotypes 1, 2, and 4 there are, fortunately, drugs in development to treat genotype 3. The first and second generations of HCV protease inhibitors (telaprevir, boceprevir, simeprevir, asunaprevir, etc.) were not very effective against genotype 3. Sofosbuvir—a polymerase inhibitor—does have antiviral properties against genotype 3, but it requires 24 weeks of treatment and needs to be given with ribavirin, or, if given for 12 weeks, with pegylated interferon and ribavirin. There are on-going clinical trials that should have data released soon including:

- Daclatasvir
- Sofosbuvir plus ribavirin
- Sofosbuvir plus GS5815MK-5172
MK-8742, and sofosbuvir

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