

• • • **New HCV Antivirals and** • • • **Drug Resistance**

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Researchers are investigating new antiviral medications to treat hepatitis C virus infection (HCV). Some of these drugs are referred to as direct antiviral medications since they specifically target the hepatitis C virus. However, unlike current HCV medications, direct antivirals carry the potential for resistance. This fact sheet will discuss the basics of HCV replication and why the hepatitis C virus becomes resistant to the newer drugs.

The Basics

Viruses are like rabbits; what they do best is multiply. The term for this is *viral replication*. However, a virus cannot survive on its own; it can only survive inside of another living cell, known as a *host cell*. Viruses use various pieces of the host cell's genetic material in

order to reproduce, or make more copies of itself. Viruses survive because of their ability to constantly adapt and change when they are under attack from the immune system. Viruses still try to reproduce even while under attack. In a hurry to escape, a virus may make a bad copy of itself, which slightly alters its genetic make-up. The process of change actually produces a variation in the virus, known as a *mutation or quasi-species*.

HCV acts like this. When you are newly infected, your immune system recognizes that an uninvited intruder (HCV) is in your body. Your immune system alerts your body to destroy HCV. However, HCV hurries to escape and makes a sloppy copy of itself, which outwits your immune system. Your immune system is patrolling for the original intruder, not realizing that the virus now looks a bit different. Now HCV can multiply at a faster rate. Eventually your immune system catches on and looks for the bad copy. In a hurry, HCV mutates again. This process may cycle through many, many mutations.

One way to think about this is with Darwin's theory of evolution and *survival of the fittest*. In nature, the strong survive. The weak die and if they die before they reproduce, their weak genetic material dies too. In this way, it is more likely that strong genetic material is passed along. Evolution applies to plants, animals *and* microorganisms.

Current Therapies

The current standard of care for treating hepatitis C is a combination of pegylated interferon (long-acting) plus ribavirin therapy. How pegylated interferon works is not completely understood. What is known is this: 1) interferon boosts the ability of the body's immune system to kill a virus, and 2) it protects non-infected cells from becoming infected. Interferon is used to treat a variety of diseases including hepatitis C.

We also do not understand how ribavirin works against HCV, but, when used with interferon, it seems to interfere with HCV's ability to multiply, or replicate. Ribavirin alone is not effective against hepatitis C. When interferon and ribavirin are combined, there is a *synergistic effect*, which eliminates HCV in about half the people who take this combination. *Synergy* means that the combined total is greater than the sum of the separate parts.

Drug resistance does not develop with interferon and ribavirin since these drugs do not specifically target the enzymes of the virus used in the viral replication process. This means that treatment durations may vary in length and be tailored to patients' needs. Patients may also undergo multiple treatments using the same drug(s). It is also the reason why people may interrupt or stop therapy without the development of drug resistance.

all of the copies will have that same mistake. This is referred to as *translation*. Drugs are being developed to interfere with this process, but so far, none have been found to be effective in stopping the translation process.

The next step involves an enzyme called the *protease*. HCV genetic material uses the protease enzyme to 'cut up' the genetic material into smaller pieces before additional viral processing. If this process is interrupted, then the virus cannot make copies of itself. Protease inhibitors are exciting prospects in drug development to treat HCV since there are many potential protease enzymes involved in the replication process of the hepatitis C virus. The drugs in human clinical trial development that look the most promising are telaprevir, and boceprevir .

The HCV Replication Process and Direct Antivirals

The hepatitis C virus is a single-stranded RNA virus of the *flavivirus* family with a very rapid turnover or replication rate. HCV enters the body and targets the liver – the main replication site of HCV. The virus attaches itself to the outer coating of the liver cell or *hepatocyte*, and enters the cell. After entering the cell, HCV releases its genetic material and hijacks the cell's internal processes.

Now that HCV has taken over, it binds to various *ribosome* sites within the cell. A ribosome is like a factory with printing presses. If a master copy of a document has a mistake in it,

Other materials that viruses depend on for replication are polymerase enzymes. HCV cannot multiply without these enzymes. Polymerase inhibitors are drugs used to stop this process. HCV polymerase inhibitors in human clinical trials include ABT-450 HCV, R7128, and VCH-759

Viral replication relies on the *helicase* enzyme to complete the process. There are no HCV helicase inhibitors currently in development. Most experts believe that it will be difficult, if not impossible, to develop helicase inhibitors.

Resistance and Direct Antivirals

The new direct antivirals work by inhibiting the entry of the virus or by inhibiting the specific enzymes during one of the replication processes. The medications that look the most promising are the HCV protease and polymerase inhibitors. During the normal lifecycle of HCV, the body's immune system exerts pressure on the replicating virus. This pressure produces mutations that escape the host's immune response.

In a similar way, drugs to treat hepatitis C will exert pressure on the virus to change and mutate in order to survive. For this reason, it is believed that most of the direct antiviral medications will eventually produce drug resistant mutations, especially if these drugs are taken for a long time. This in turn may make the new medications ineffective in treating the new viral mutations.

Drug resistance is expected. However, scientists are looking for ways to prevent or interfere

with drug resistance. For instance, drug resistant mutations may be identified earlier in the process, such as during the test tube development phase.

Preventing and Reducing Drug Resistance

The reduction or prevention of drug resistance depends on a number of factors. Some of these are:

- ***Eradicating HCV:*** Unlike HIV and HBV, hepatitis C does not become part of the host cell. We have been able to rid HCV from the body with the use of current medications – pegylated interferon and ribavirin. In addition, HCV is an RNA virus. Since it does not integrate into the host cell's DNA, as mentioned above, it will be easier to eliminate HCV without the risk of the virus changing or mutating.
- ***Combination of direct and indirect antivirals:*** Direct antivirals can be given for a shorter period of time – this reduces the chances for the virus to 'resist' the drug. When used in combination with indirect antivirals – peginterferon and/or ribavirin, the chances of the virus developing resistance to the drug is lower. An example of this is extending the duration of treatment with peginterferon and/or ribavirin after stopping the direct HCV antiviral. This may prevent drug resistance while allowing for continual and hopefully complete viral suppression. For instance, a new clinical trial of telaprevir is underway to test the theory of taking telaprevir for 12 weeks with pegylated interferon plus ribavirin, followed by additional treatment period just using pegylated interferon plus ribavirin. The study is also testing to see if the treatment duration can be shortened to 24 weeks instead of the current 48 weeks of treatment. Hopefully, this trial will test these theories and, more importantly, find out if taking this new antiviral will result in permanently getting rid of the virus.
- ***Potent direct antivirals:*** The development of potent direct antivirals that quickly distribute throughout the body and reach high blood concentrations in a short time period will put enough pressure on the virus before it has a chance to mutate. If the drugs are not potent enough, the escaped viral mutations may become the dominant virus, rendering the antiviral medication ineffective.

■ **Combination direct antivirals:** The use of direct antivirals that inhibit several different protease and/or polymerase enzymes at the same time will reduce the ability of the virus to mutate.

■ **Adherence:** Current HCV medications require adherence to prescribed doses and durations to be more effective in treating HCV. The new direct antivirals will require strict adherence. Doses that are skipped or forgotten could lead to viral mutations and drug resistance.

HCV research has benefited from what we know about HIV and HBV drug resistance and hopefully will be able to contribute to this body of knowledge. As we begin this era of new HCV medications, now is the right time to develop strategies to make HCV therapy more effective. Now is also the time to reduce the chances of the surfacing of drug resistance that could potentially negate some of the benefits of new therapies. The best strategy for moving forward depends on using knowledge from the past in order to discover the future.

For more information about drugs in development to treat hepatitis C, visit our HCV Drug pipeline.

www.hcvadvocate.org/hepatitis/hepC/HCVDrugs.html

For information about current clinical trial enrollment visit:

www.clinicaltrials.gov

**Visit the HCV Advocate Web Site:
www.hcvadvocate.org**

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