HCV: Wait for Something New or Treat Now?

Some people coinfected with both HIV and hepatitis C virus (HCV) are holding out for new treatments that will improve their chances of permanently clearing HCV. David Evans talks with HCV/HIV coinfection activist Tracy Swan to find out whether the current crop of experimental agents will be worth the wait.

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Some people coinfected with both HIV and hepatitis C virus (HCV) have told AIDSmeds.com during the past year that they are waiting on the arrival of new HCV protease and polymerase drugs before staring HCV treatment. Their rationale is that the new treatments might be much less toxic and more effective than today's pegylated interferon-ribavirin combination therapy.

Waiting for better treatments is not an unreasonable desire. The side effects of interferon and ribavirin are sometimes quite serious and debilitating, and frequently unpleasant. To make matters worse, the side effects aren't matched with high rates of treatment success. HCV treatment is effective for only 15 to 30 percent of coinfected people in the United States because most of them are infected with the most insidious strain of HCV: genotype 1.

The risks of waiting to start hep C treatment are not inconsequential, however. Liver damage from HCV develops and progresses more rapidly in people coinfected with HIV and HCV. People with serious liver scarring from hepatitis C—called cirrhosis—are at risk for liver failure and liver cancer.

To get the scoop on the progress of experimental treatments for HCV and their possible influence on treatment for people who are coinfected, AIDSmeds checks in with Tracy Swan, hepatitis/HIV project director of the Treatment Action Group in New York City.

People are hoping that the new treatments might allow people to forgo using pegylated interferon and/or ribavirin. What are the prospects for that?

The ultimate goal is to get rid of peg-interferon and ribavirin, but it's clear from trials that ribavirin is here to stay for a while, at least for use in combination with newer agents, since it boosts response rates and lowers the risk of relapse after HCV treatment.

As far as interferon, nobody knows whether a combination of antiviral drugs will be enough to get

rid of HCV for good, or just keep it suppressed during treatment. Interferon and ribavirin work to stimulate the immune system and fight viruses, so it is not clear whether fighting the virus without kick-starting the immune system will do the job.

In terms of what that means for when those newer drugs might become available for people who are coinfected, are we talking about a couple of years after the trials first start?

Well, the development plan [for people infected with only HCV] is further along, and if everything goes well they should be on the market by 2011.

In that case, even though the coinfection studies may not be completed, or have fully reported their results, it might still be possible for people who are coinfected to have access to the new drugs?

Yes, doctors can prescribe them, and one reason why activists have been fighting so hard for coinfection trials is that we need to see if the drugs are safe and effective in people who are coinfected. We also need to know if there are any drug interactions that would make them difficult to use with HIV drugs. The first coinfection trials are slated to open later this year with hepatitis C protease inhibitors, Schering-Plough's boceprevir and Vertex's telaprevir.

Each of the drugs has a different profile. Both of them seem to be boosting response rates in Phase II studies, but they're not going to make the current standard of care less toxic—and they add side effects, because you're adding another drug.

When we're looking at a response rate in people who are coinfected of about 15 to 30 percent, what might be considered a sufficient improvement to warrant the additional side effects?

There's so much room for improvement. I think the things that would be most appealing would be a shorter course of treatment and higher response rates.

Might there be success with shorter duration of treatment in people who are coinfected?

I suspect no, only because people who are coinfected have higher hepatitis C viral loads than people who are infected with HCV alone and current therapy is less effective in coinfected people. You could look at people infected with just HCV, who haven't responded to a first round of HCV treatment and are getting retreated, and that might be the closest comparison group. This is where I think that Jules Levin [from the National AIDS Treatment Advocacy Project] has a good idea.

And what's that good idea?

Because of the higher viral loads and because current therapy doesn't work as well in people who are coinfected, it's probably going to be best to wait until there are drugs from different classes that can be combined with each other and with pegylated interferon and ribavirin to lower the risk of HCV drug resistance.

This is because the new drugs are similar to many HIV drugs, in that it is easy to develop drug resistance?

Exactly. In fact it may be easier with the hepatitis C drugs.

If a person becomes resistant to one of the new drugs, is he or she likely to have cross-resistance with other similar drugs in the pipeline?

Yes, unfortunately. In HIV, with protease inhibitors, they're not all cross-resistant; you still have other options within that family of drugs. So far it's looking like that's not the case with hepatitis C drugs.

Some people are trying to weigh the risks of starting HCV treatment versus waiting. Given what we know about the more rapid progression of liver damage in people who are coinfected, what should people consider to help them make that decision?

It's kind of complicated. About 30 percent of coinfected people appear to be rapid progressors with their hepatitis C. People who are heavy drinkers and people with fewer than 200 CD4 cells are at greater risk for serious liver disease from hepatitis C, but there's a whole lot we don't know about who might be a rapid progressor. People can do a few things, like reduce the amount of alcohol they drink, or not to drink at all. If they're not on antiretroviral therapy, getting the CD4 count up may help prevent the liver damage, but those aren't really substitutes for getting a biopsy and finding out what's going on inside the liver.

Basically, the more liver damage a person has, the less likely that HCV treatment is going to work. So you don't want someone to wait too long, because we don't really have a salvage therapy. If someone is stable, they're not a rapid progressor and they've been successful at making some of the very difficult lifestyle changes, they might decide that they're comfortable with just monitoring their liver progression and waiting for a little while.

Do we know when we might see these new experimental drugs tested in combination with each other?

Actually, Roche is doing a study right now combining a hepatitis C protease inhibitor (R7227) with a hepatitis C polymerase inhibitor (R626), and the results from that short Phase I study will be presented at the [American Association for the Study of Liver Diseases] in November.

So we might have a first glimpse quite soon?

Yeah, I'd say it's a glimmer or a proof of concept, and I think it's very exciting and could be the way forward—but one limitation is that the current hepatitis C therapy works both by stimulating the immune system and fighting the virus directly, and we just don't know what's going to happen without interferon, that immune component. So we'll have to see, or we're going to be stuck in the same treatment paradigm.

Do any studies look at how or when it might be possible to treat HCV without interferon?

No, this is the first pioneering study, because they had to see if the drugs could be used together in the first place, and how much will they drop the virus, and will it stay suppressed after you take the drugs away?

Anything else you think people should consider about deciding when to treat HCV?

It's a really tough decision, and a lot depends on how comfortable someone feels with risk in either direction: the risk of trying a treatment that has a lot of side effects and might not work, versus the risk of waiting and getting more liver damage. So it's a really tough thing. I think that talking to other people who've been through treatment, and maybe getting a second medical opinion might really help people get to the point where they're comfortable with whatever they decide.

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