They are a cure, yes. The good news is that a lot of what I was going to talk about has been covered very nicely this morning. So, I think what I am going to try to do is give you some examples of some of the challenges that we have had. And I am probably fairly loud. Am I too loud? Okay, good, because I tend to be loud.
Of the challenges addressed today, one of the big things, that patients with underlying hepatitis C don’t have specific definitions for application for drug-induced liver injury. Hy’s Law was not made for these patients. Although it has been used as a screening for evaluation and patients at risk, obviously, for potential drug-induced liver injury, it was not intended for that.

We have a challenge with evaluation of the liver biochemistries. We know now, with these very potent direct-acting antiviral therapies, the DAAs, that, in general, all patients get improvement of their liver biochemistries once they start these therapies. So, they start at an elevated baseline. They come down nicely to a normal value, and then, how should we evaluate them? And this has been addressed today. Should we be evaluating them from a baseline, from the nadir on treatment, or should we be using that standard times upper limit of normal, which is usually used in most protocols at this time?

Also, we know that presentations, clinical presentations, can vary quite a bit, and it can vary of lots of different factors, the comorbidities, concomitant medications, the stage of disease, and, also, potentially, genetic factors.

So the FDA DILI guidance doesn’t have a lot of information about what you do with
patients with chronic hepatitis C. In fact, it is planned to be updated, as we talked about today. We have also touched on what is the type of injury and how these things may affect what you see and what the clinical management would be.
And then, also, what discontinuations and followup criteria are appropriate for different hepatitis C patient populations? What cutoffs should be used? What should be used in protocols? What should be used in clinical management? And the balance between safety and not discontinuing too early because of adaptation or other issues that are ongoing, and where that is, we don’t want to have loss of efficacy and development of resistance as well, which is another complication with a viral disease.

Currently, the therapies are basically multiple investigational drugs often being used together. This poses another challenge that is important to think about. Because you are having several unapproved products within a regimen, it makes attribution for a particular product more difficult. So, you have to look at totality of data. You have to consider the class. We take lessons learned, for example, from the HIV realm, where protease inhibitors, for example, have been known to have a risk of hepatotoxicity.
And then, as I already talked about, the different host-factors and, also, an immune response to clearing of the virus, you know, when we are starting to see these new DAA regimens used in combination without interferon products, and is there some difference in certain patients, in certain populations where an immune response may be responsible for some of the injuries?
This is an example of a published case that came out in Hepatology in 2015 in January. This is daclatasvir and asunaprevir. So, daclatasvir is an NS5A inhibitor used in combination with asunaprevir, an NS3/4A protease inhibitor. These drugs are approved in Japan currently for treatment of chronic hepatitis C. They are not approved in the United States at this point.
DCV/ASV Immunoallergic Hepatitis Case Report

- 57 year old male with GT1b CHC on a planned 24 week treatment with daclatasvir (DCV) and asunaprevir (ASV)
- At Day 15, developed fever and eosinophilia, ALT was normal and HCV RNA decreased to 50 IU/mL from 12.6 million IU/mL
- At Day 29: ALT was 609 U/L, Alk P 320 U/L and bilirubin 3.3 mg/dL and further increase in eosinophilia to 2,876 mm3; DCV and ASV were stopped
- Day 36 liver biopsy: interface hepatitis with bridging fibrosis and focal lobular necrosis with eosinophils, lymphocytes and plasma cells in the hepatic lobules and portal areas.
- Day 37 prednisone taper started with rapid resolution of liver biochemistry abnormalities

Hepatology, 2015 Jan;61(1):400-1.

This case report, the details are there that you can look at, but it is a little bit easier to look at this in the graphic representation here.
So, this is a 57-year-old male who had genotype 1B and was started on the combination of daclatasvir and asunaprevir for a planned course of 24 weeks. As you can see, in the dark line, the black line is the ALT trend, and the red line is the eosinophil. You can see that he started with a normal eosinophil count and a slightly-elevated ALT at around 100. It came down nicely when he started therapy with daclatasvir and asunaprevir. By week two, he had clearance of or improvement in his HCV RNA level. And he developed fever and a rise in his eosinophil count.

At about week four, he was re-seen and had an ALT up to about 600 and a fever still, with a significant rise in eosinophils. At that time, drugs were stopped and the patient had a liver biopsy. That revealed focal lobular necrosis with inflammatory infiltrates of eosinophils, lymphocytes, and plasma cells, and hepatic lobules in portal areas. And he also had interface hepatitis and some bridging fibrosis.

The therapy was stopped and he was started on a prednisone course, represented in purple. It was tapered over time, and he nicely responded to prednisone with resolution of ALT abnormalities. Unfortunately, this patient did not have a virologic success and did develop some resistance-associated polymorphisms.
So, the authors of this article state the overall clinical syndrome was typical of a drug fever or a drug hypersensitivity syndrome rather than DRESS (drug rash with eosinophilia and systemic signs).

In the Japanese trials for daclatasvir and asunaprevir, 16 percent of the subjects had ALT elevations and 9 percent had ALT above 5x ULN. This syndrome as well as ALT elevations/fever appeared more frequently in Japanese than in US/EU trials.

Authors suggest genetic basis for liver findings.

So, the authors of this article state the overall clinical syndrome was typical of a drug fever or a drug hypersensitivity syndrome rather than DRESS. There was not a rash component with this product or this case.

In the Japanese trials for daclatasvir and asunaprevir, 16 percent of the subjects had ALT elevations and 9 percent of those had ALTs five times above upper limit of normal. Now this syndrome as well as the ALT and fever appeared to be more frequent in the Japanese patients when compared to the U.S. and EU counterparts. The author suggests that a genetic basis may be prevalent for these liver findings.
Another example is the impact of the stage of disease. So, it is unknown how patients with more advanced liver disease may respond to many of these regimens. We don't have large safety databases with advanced cirrhotic subjects most frequently at approval. And these patients are also the ones most in need of urgent treatment, and this leads often to use for compassionate reasons, which is understandable.
In fact, for the case of sofosbuvir, which is an NS5B polymerase inhibitor, and simeprevir, which is a protease inhibitor, this combination was actually recommended in the treatment guidelines prior to approval and is now approved as a combination in November of 2014. Basically, it was often used in patients with advanced disease. Simeprevir itself is labeled as not recommended for patients with severe hepatic impairment.
Okay. So, has been published online. This is two cases of hepatic decompensation using the combination of sofosbuvir/simeprevir as a compassionate use for these patients.

Now both of these patients developed marked hyperbilirubinemia out of proportion to their aminotransferases elevations, despite clearance of their HCV-RNA. And the authors' point is that it could be due to the impaired metabolism or underexpression of specific hepatic transporters, and they state that the protease inhibitor simeprevir should be used with great caution, if at all, in patients with more advanced disease.
Another example of some challenges that we have had is with another recently-approved product, Viekira Pak. This is a co-packaged and fixed-dose combination of ombitasvir, which is the NS5A inhibitor, paritaprevir, which is the protease inhibitor, along with ritonavir, which is used as a booster. And then, it is co-packaged with dasabuvir, which is the NS5B-palm polymerase inhibitor.
So, some of the factors that have complicated evaluations of potential DILI with this product are within a healthy volunteer trial. For drug/drug interaction with estrogen-containing oral contraceptives there was a noticeable increase in ALTs. At risk of elevation in ALTs in females using systemic estrogens was also seen in the Phase 3 trials with a percent, about 9 percent incidence over 1 percent for the overall population.

Paritaprevir is a known inhibitor as well of the bilirubin transporter OATP1B1. That led to asymptomatic elevations of predominantly indirect bilirubin levels. This is also complicated by the fact that patients are usually using Viekira Pak in combination with ribavirin, and ribavirin causes a hemolytic anemia that also increases indirect bilirubin levels. So, it gets very difficult to sometimes tease out all these variables in particular patients across clinical trials and ascertain the etiology of potential drug-induced liver injury.
In summary, these confounding issues that we have gone over today, you know, the drugs that we are talking about, the DAAs, they do concentrate and are also metabolized in the liver, have various transporter effects. And so, drug/drug interactions are an issue. Patients have various stages of disease and may have very different presentations (asymptomatic to obvious decompensation). Genetic factors may play a role for some drugs. Class affects may be important.
So, there is a lot of commonality between what FDA reviewers are grappling with and what has been presented today. We are in the same boat.

How often are we supposed to monitor these patients, not only really from what is reasonable in the clinical trial, but also what is reasonable or what clinicians will do once we make some sort of recommendation potentially in labeling or what should happen down the road?

What levels of change warrant modifications to a monitoring plan and/or discontinuation? Again, that careful balance between safety and not losing efficacy.

And what values should be used? Are we talking about increases in baseline, from nadir values, upper limit of normal? Are there particular patients that are at more risk and that need enhanced monitoring or should avoid certain drugs and classes? I know that was part of the talk about the biomarkers as well. And then, could other factors such as race or host or viral factors contribute as well?
All right. Thank you.