HCV Council 2014 Revisited at AASLD - Critical Appraisal of Data: Recommendations for Clinical Practice in a Rapidly Evolving Therapeutic Landscape

Michael W. Fried, MD, Course Chair; Nancy Reau, MD; David R. Nelson, MD

Hello, and thank you for joining us for this "HCV Council Revisited" at AASLD 2014. This activity is provided by Duke University School of Medicine, an educational partnership with Vindico Medical Education, and supported by educational grants from AbbVie, Gilead Sciences, and Janssen Therapeutics.

I'm Michael Fried, Professor of Medicine and Director of the UNC Liver Center at the University of North Carolina at Chapel Hill. I'm very pleased to be joined today by two expert colleagues, Dr. Nancy Reau from the University of Chicago, and Dr. David Nelson from the University of Florida.

Today, we are going to revisit the findings of the HCV Council that was first convened in July 2014 and discuss how the field has changed over the last 4 months, with particular emphasis on new data from this meeting. As a recap, the Council convened 11 national key opinion leaders in hepatology and gastroenterology in hepatitis C management to understand a comprehensive evaluation of current data regarding the best practices for integrating new regimens into existing treatment paradigms and to provide recommendations for key areas of controversy in clinical practice.

We'll cover those practice statements that still are debated in the management of hepatitis C. We'll begin with Dr. Reau and a discussion on issues related to clinical management and treatment strategies. Dr. Reau will first focus on patients with cirrhosis and if efficacy remains suboptimal for this population. Dr. Reau?

Thank you so much, Dr. Fried. I'd first like to address patients with cirrhosis with the concept that traditionally they have a lower rate of SVR compared to patients who are non-cirrhotic, and thus treatment efficacy remains suboptimal for this population. Why did we make this statement? Well, historical data certainly would suggest that cirrhosis is the strongest baseline factor that predicts treatment failure. Cirrhotics are felt to have higher adverse events, require more dose modifications, and certainly are at increased risk for treatment disruption.

On top of that, this can be compounded by prior treatment failure, and that trend seemed to be blunted but not eliminated by the addition of sofosbuvir with pegylated interferon and simeprevir with pegylated interferon and ribavirin.

So, Mike, if you remember, COSMOS really excited the treaters about the concept that we could use combination all-oral therapy in traditionally difficult-to-treat populations -- null responders, patients who had cirrhosis and null response. And at this meeting the top-line results of TARGET,

which was our observational cohort of individuals which contained a large group with cirrhosis -- nearly 50% -- confirmed the COSMO results. I think that we were all really excited about that. However, we do still recognize that cirrhosis has an impact on efficacy, especially in those that are genotype 1a.

And, as a reminder, the recently approved ledipasvir/sofosbuvir combination, ION-1, which was treatment-naïve individuals, showed minimal impact of cirrhosis. However, ION-2, which included cirrhotics who had failed prior response, where the additional of ribavirin really didn't help nearly as much as extending duration to 24 weeks in that cirrhotic/null responder or cirrhotic previously treatment experience population.

So, we're anticipating the 3D regimen with ribavirin in the near future, and again, that one in the TURQUOISE-II trial did demonstrate that although cirrhosis was not nearly as impactful, that those genotype 1a prior treatment experienced ─ especially the null responders ─ really benefitted for an increased duration of therapy from 12 weeks to 24 weeks.

So, in summary, we recognize that cirrhosis is still a baseline factor that really affects efficacy. However, that's increasingly blunted by other factors such as what we can recognize about subtype and treatment manipulation.

Well, thanks very much, Nancy. I agree that we have seen, but you know, it's amazing that even though we're talking about somewhat diminished results, there's still ... we've never seen rates of response in cirrhotic patients prior to where we are now, but I guess we still have a little bit of a ways to go.

Are there any particular subgroups that you would choose to select to intensify the treatment regimen?

I think that pretty much every study has shown that genotype 1a is more problematic than 1b, and that treatment experience matters. The TARGET data would also suggest that maybe individuals with prior decompensation might be a special interest group. So, I think that not all patients with cirrhosis are the same, and we're going to have to increasingly start to recognize the subgroups within that subgroup that will need to have special attention.

For example, you mentioned about the decompensated cirrhotics, and there was some data presented about that population here at this meeting. Dave, do you have any comments about that?

Yeah. So, some very exciting data. Typically, the clinical trials will get Child's A-category cirrhosis, and clearly we see that those patients had very high cure rates with a chance to actually improve their overall quality of life, and often liver function.

What we saw presented at this meeting was some really exciting information about treating patients with Child B and C cirrhosis ─ very high cure rates in B's, not as much in C's. I think one lesson is, as you get more advanced, we're going to need better regimens or more combinations of drugs. And I think what you also saw is that some real good hard data that Child's B and C cirrhosis can actually improve ... improvements in albumin, improvements in bilirubin, and improvements in MELD score.

So, giving a lot of hope to patients awaiting transplant, and even those with some other evidence of decompensation.

So, what do you think those improvements in synthetic function, MELD score, will ultimately mean to that decompensated group? Nancy, do you think that ... are we going to see the same picture that we see with hepatitis B?

I think we would love to see that picture. We would hope that this would diminish the need for transplantation. Just like hepatitis B, though, it's important to recognize that cure is not a cure-all, and so these individuals continue to have residual risk for liver cancers, which will drive transplantation. Liver cancer is the third-most lethal malignancy in the United States over time. And so, we ... we might eliminate the hepatitis C, and we might delay transplant. But this is still in need of observation.

So, they still need follow-up.

They still need follow-up.

What about the safety of these regimens that we've seen? So, generally in the past, when we're dealing with interferon-based regimens, of course we rarely were able to treat them. But tell us a little bit about the safety profiles of all these all-oral regimens that we're seeing.

So certainly, anyone who's used pegylated interferon and ribavirin, or telaprevir and boceprevir in a cirrhotic population ─ even non-cirrhotic population ─ is hypersensitive to safety signals. And when these presentations list the safety, there are certainly things that do pop up ─ headaches, asthenia, anything with ribavirin ─ anemia. But the discontinuation rates really speak for themselves. And when consistently cirrhotic patients discontinue therapy for side effects less than 2% of the time, I think it's hard to say that these regimens are not going to turn out to be safe.

Yeah. I think Nancy highlighted the HCV-TARGET database, which had over 2,200 patients ─ half cirrhotic, half of those with prior decompensation; discontinuation rates 2-3%; really low adverse events; minimal anemia. So, it's a new era clearly for treating patients with advanced disease.

So, even though that these treatments do seem to be safe and very effective, do you have any words of caution for those who are looking at decompensated patients? Should they still go through the transplant evaluation process? Would that be the most beneficial program for them?

So, I think that the data that has been presented looking at that decompensated group through therapy ─ we're very encouraged by the improvements in albumin, decreases in hepatic encephalopathy. But if you read the fine print, these patients still experience severe complications as you would anticipate in a decompensated group.

So, I think compensated cirrhotic patients can really be treated very differently than a person with decompensation, and they should still be considered for transplantation.

I've actually changed my practice. I used to take patients with a MELD between 10 and 15 who I was going to treat with interferon-based regimen ... refer them for transplant because of a risk of decompensation on treatment. Now, I would take all those patients, not refer them, and try to cure their hep C and try to prevent the need for transplant.

But higher MELD scores still probably benefit first for transplant evaluation, then treatment, then see what happens. Great.

Well, that's excellent that we have some new options that we'll be able to treat and cure, and hopefully improve long-term outcomes for patients with cirrhosis, both well-compensated and decompensated.

Well, the next statement that the Council evaluated related to patients with easier-to-treat characteristics. Can they be defined and treated for a shorter duration than what has previously been considered, and that's usually 12 or 24 weeks? So, Dr. Reau takes another look at that key data.

So, this statement was that patients with easier-to-treat characteristics can be defined and treated for a shorter duration. Why make this statement? The historical data certainly suggested that with pegylated interferon and ribavirin, populations such as those with low viral load and IL-28B CC ─ those that had pre-treatment characteristics ─ could help identify individuals that could truncate therapy.

Shorter therapy is certainly desirable, both for treatment duration as this drives cost and compliance; and then higher efficacy when treatment is extended might only be necessary in certain populations such as those with cirrhosis.

There was a really interesting presentation at EASL this year that demonstrated that what we would normally conceive of as difficult-to-treat baseline characteristics stack up ─ that means in people who had 3 or less, that didn't seem to have as much impact on SVR, but certainly having multiple would compromise efficacy.

On top of that, the ION-3 addressed individuals treated with ledipasvir and sofosbuvir, and this was a treatment-naïve non-cirrhotic group, and they truncated therapy in this group to 8 weeks in some, and 12 weeks in others. The 8-week arm did include ribavirin or not ribavirin. And they showed that the efficacy was actually quite good, but slightly lower than the 12-week or anticipated SVR.

However, when they then eliminated all the individuals in the 8-week arm that had incredibly high viral load, as the label would suggest, greater than 6 million, that efficacy was exactly the same in the 8-week and 12-week. That really suggests that individuals with very favorable baseline characteristics might be able to truncate significantly.

So, in summary, I think that time will tell how short we can truncate therapy, but that we can look towards a lot of favorable characteristics to drive individuals who might be able to triage towards this. We recognize that 1a and 1b might be different. The addition of ribavirin in some regimens may be not even truncating therapy in some others, but there will certainly be subgroups that won't require the traditional 12-24 weeks.

Well, thank you. And I think that's an important question. What do you think is the upside of shortening duration of therapy? What's the upside and what's the downside? Why are we even having this discussion?

Well, I think that the elephant in the room in most conversation is often cost, and if it's cost per pill, the shorter the duration, the less expensive.

However, I think that there are other things beyond just cost. We talk about cost, but it's adherence. A lot of studies have demonstrated that patients fail to refill prescriptions, and that refill ─ or failure to fill your prescription ─ goes up each month that you're expected to go to the pharmacy.

There are other things that show in pediatric populations that adherence drops off over time, so that the less may be better.

I'm not sure there is such a drive to go shorter. Right now, we've got 12-week regimens for almost everyone other than some treatment-experience cirrhotics, and the compliance/adherence has been outstanding. We've just talked about discontinuation rates 2% or less. So, I agree with Nancy; the major issue will be price, unless we get into some difficult populations where adherence and compliance may be an issue. But for us used to treating for 48 weeks, 12 weeks seems like such an incredible change, and it sounds like we're heading maybe towards 8 for certain populations. But I'm not so convinced that we need to be pushing so hard to go shorter.

And one of the key differentiating points between a "standard therapy" if you will, and a shorter course is often whether or not a patient has cirrhosis ─ leading us back to the previous talk, what

you just discussed. How confidence can we be now in the era of not biopsying everybody that we have effectively made sure the patient doesn't have cirrhosis? Cause all the shortened treatment data is related to patients with non-cirrhotic populations.

So, I supposed you can look at that two ways, Mike. We use clinical factors such as non-evasive fibrosis markers and FibroScan to triage individuals into these studies. And so, given the SVR rates on elongated therapy and 12-week therapy, certainly these may be substandard ways of identifying a cirrhotic ... still perform okay. And it might be more portal hypertension that affects SVR rates even above and beyond cirrhosis.

But I certainly think when you're taking these things that you're going to have to look for fibrosis. It's not going to be good enough to say, "Oh, this person has a platelet count of 180, and I don't think they have cirrhosis." You're going to have to do something beyond that to make sure that you're not placing that individual at risk for ineffective therapy.

I think it's really brought back the non-invasive markers into the discussion. I think we all thought we were kind of done with fibrosis assessment other than cancer screening, but now that cirrhosis is going to be an important determination for who can go shorter or who needs to go longer ... you know, I think even I'm personally using a lot more serum fibrosis markers in combination with FibroScan. So, I think it's really going to change clinical practice a little bit.

We all have those patients who are the borderline ─ probably F3. Their platelet count is low. You do serum markers, it looks like F3. You do transient elastography, it looks like F3. But imaging suggests cirrhosis, and are you going to be obligated, if you will, to put those patients on a shorter duration, or really, should you push a longer duration, because there is that slight different in relapse, we believe, with a shorter duration of therapy.

We've always been favoring whatever's best for efficacy in the patient. I remember back in the PEG/ribavirin days, interferon, when in Europe they labeled people who responded rapidly at 4 weeks who were non-cirrhotic, you could stop at 6 months; in the U.S., that happened less than 10% of physicians and patients. So, we always put the maximum effort into the efficacy as long as safety is okay, and I think that's where we're at today.

So, how low do you think we can go? What's the shortest duration of therapy? And I think there's some very interesting data that gives a lot of insight to that question from this meeting.

So, I ... I think that we probably don't know yet, but from the tools that are being looked at, 4 weeks has not been shown to be a point we can achieve. That doesn't mean we won't get there in the future. But there were a lot of encouraging studies to suggest that 6 weeks, 8 weeks, even in patients with cirrhosis, is possible. So, I don't know how low we can go.

So, in the C-SWIFT study that Nancy was referring to, there was a really good triple regimen with a protease inhibitor, a nucleoside inhibitor, and an NS5A inhibitor. And they were able to take a cirrhotic population, treat them for 8 weeks with an extremely high SVR rate. I think it was above 90%, or in that range.

But then, what they found is that in a non-cirrhotic, 6 weeks as okay; 4 weeks really not a viable option.

Yeah. The SVR-4 rate in that study was 39% in a non-cirrhotic population treated for 4 weeks with a very optimized drug regimen ─ triple drug regimen. That was a really important study because I think it informed a lot of us about, perhaps, are there certain factors that will predict how short a duration we can achieve. So, it sounds to me like it's going to be somewhere between 6 and 8 weeks.

And I don't think we understand the weight of accumulated baseline factors, so that most of these studies that are looking at truncating therapy may not actually mimic what you have in your clinical practice, which might be high BMI; unfavorable race; men; older. I mean, I think that we still need to clarify this before we decide that everyone can get away with 6-8 weeks.

So, finally in this section, the Council looked at the preferred approach to treatment for genotype 3 -- specifically if sofosbuvir and ribavirin for 24 weeks is the ideal regimen. And Dr. Reau will now take us through the findings.

Alright. So, this statement was, "The preferred approach to treatment for all subgroups of patients with genotype 3 is sofosbuvir and ribavirin for 24 weeks." So, it's important to understand why we came up with 24 weeks. That went through pretty extensive analysis that showed that 12, 16 ... these regimens were not adequate for our genotype 3 population that their best efficacy was with the 24-week sofosbuvir/ribavirin regimen -- and that was kind of well-explained in the VALENCE study.

However, cirrhosis still was highly impactful with the non-cirrhotic individuals having nearly a 90% efficacy whereas those with cirrhosis had 62%. And the price of failure ─ there isn't a lot of other options for the genotype 3 population, so that when you looked at alternatives, the other thing that we can consider is a combination of sofosbuvir, pegylated interferon and ribavirin with our available tools. And in individuals with genotype 3, this was an effective regimen, but again, less effective in those that had cirrhosis. You know, the efficacy is still much lower than what we would desire.

When you look towards the future, I think that there's a lot of excitement with pan-genotypic agents, and ALLY-3, presented at this meeting, did show combination of daclatasvir and sofosbuvir could be a reasonable strategy. This looked at 2 populations, individuals that were naïve and those

that had failed, both contained a cirrhotic subset. And with these 2 agents for 12 weeks, efficacy was actually quite high.

However, cirrhosis still was impactful. Those that had only F0-F3 had 96% SVR rates, whereas the cirrhotic population, again, was at 63%.

So, in summary, 24 weeks of sofosbuvir and ribavirin is highly effective, but less effective in those that have cirrhosis. And although there are alternative regimens such as pegylated interferon and ribavirin with sofosbuvir, that this may not offer us the same treatment advantage that we would hope, and especially in those with cirrhosis, and still comes with interferon.

We look towards the future, and although there are a lot of exciting regimens in the pipeline, maybe that daclatasvir/sofosbuvir regimen isn't going to cure all of our cirrhotics, especially those that are treatment-experienced.

Well, thanks very much. And it's interesting that, again, 2 drugs combined which have very good profiles, we still see that in the cirrhotic population. That's kind of a recurring theme that we're dealing with.

So, Dave, with these genotype 3 patients, what else could we possibly do? We see the results of ALLY-3, which is a very important study. But you saw that the drop-off in cirrhotics is quite substantial.

Well, I think we've seen two strategies that have been shown in genotype 1 cirrhotics to potentially make an impact. You can either add a third agent, and in this case right now all we can add is ribavirin, so in this case it would be sofosbuvir, daclatasvir and ribavirin for 12 weeks, so you could think about increasing the antiviral coverage and staying with the same duration; or, what's been shown to be most successful in cirrhotics has been to increase the duration.

So, I think for genotype 3 right now, where daclatasvir is approved in Europe, I think if it was my patient I would be going daclatasvir, sofosbuvir plus ribavirin for probably even a little bit longer — 16, 18 weeks, 24. I mean, those really need to be studied.

You're covering all the bases.

And again, because I'm always going to vote for what's the highest cure rate for the patient, right, because these are really safe drugs now. And if price was an issue, I don't think we would even have this conversation. We would go 24 weeks.

Interesting. We also see some newer NS5A inhibitors that are being combined with an agent such as sofosbuvir for genotype 3. Do you have any insights into some of those?

Well, I think that in the United States, at least, the only NS5A that we have access to is ledipasvir. There has been some data presented that showed that ledipasvir, sofosbuvir and ribavirin in combination could potentially be effective in the genotype 3 population. But since the

genotype 3 population has been so refractory to some of these strategies, and the efficacy *in vitro* of ledipasvir for genotype 3 is less than daclatasvir, I think that the ALLY-3 data makes me be concerned about that strategy.

Yeah. There are some second-generation NS5A inhibitors ─ 5186 is one example. You know, the data is early, but the hope is, as we get better agents to cover genotype 3 we'll have better options for treatment. And people have to remember that it wasn't that long ago that genotype 2 and 3 were easy-to-cure patients. So, all of the efforts and development of drugs went towards genotype 1. Now we just see genotype 1 cure rates approaching 100. We're going back and realizing genotype 3 is really the greatest unmet need right now.

And also, a very important genotype in many parts of the world. We may not see it as much in the U.S., but certainly in Pakistan, India, it is a very common genotype to have to deal with.

So, trying to identify these new strategies will be really important. But it looks like we have a lot of hopeful options coming down the pike.

So, the next section on treatment challenges will be led by Dr. Nelson, who will start off the discussion on prioritizing access to care. Dr. Nelson?

Thanks, Mike. You know, this has become a huge issue right now because a lot of the conversation is focusing. This question is, "Due to the high cost of medications, only patients with advanced fibrosis should be offered treatment with all-oral regiments for hepatitis C." So, why do we make this statement?

It's been suggested that it's a huge expense for the U.S. population to treat all the hep C-infected patients, at least $250 billion. So, there's been a discussion around prioritization of care. It's based on the premise the patients with advanced fibrosis have the most at risk and thus the most to gain with therapy, while those with mild disease can really wait.

There's also recently been a lot of issues around access. Many of the payers now are starting to restrict care to only those with a disease severity that's high or a risk for high disease progression. And I've just kind of shown you advanced fibrosis is the most important factor, usually F3 or F4 is required, and also, patients with these extrahepatic manifestations, cryoglobulins typically with renal disease manifested by protein in the urine.

So, at this meeting, a very huge metaanalysis was shown, looking at the impact of curing patients in the general population as well as in a co-infected population in cirrhotics. It was really nice to see very significant reductions in overall mortality based on an SVR with antiviral therapy.

So, I think two points: One is, you can, by curing people, dramatically decrease their mortality. The other, though, is that mortality is still significant over time. So, especially cirrhotics continue to need to be screened.

Another study that was in the initial Council discussion I think is really important. A large VA study looked at patients who were cured vs. those that weren't, and was able to separate out patients with cirrhosis vs. those without. And as you'll see, patients without cirrhosis had the exact same survival benefit, almost a 40-50% reduction in mortality, as compared to cirrhotics. So, this suggests that curing people without cirrhosis is going to improve survival.

It's likely hepatitis C is a systemic inflammatory disease, causes increased risk of diabetes, heart disease, stroke, all-cause cancer. So, it's hard to really justify not treating that population, in my mind.

I also want to remind you of a recent cost effectiveness analysis that looked at the two strategies we're talking about. One, stage patients and only treat those that are F3 and F4 vs treating the whole population. And what you'll see is that by treating the whole population you actually have less cirrhosis, less decompensation, less cancer, decompensation and transplant.

Also, if you look at an adjusted quality per life year and dollars spent, it really is the most cost-effective to take an entire population that's diagnosed and treat them.

So, I think, in summary, hepatitis C has a significant effect on morbidity and mortality. It's clearly highest in those with cirrhosis, but also the impact is seen in non-cirrhotics. Hep C cure reduces morbidity and mortality, and, as I stated, really, non-cirrhotics have a similar benefit. Cirrhosis also has a negative impact on SVR. We just had a discussion that we're going to longer in cirrhotics, and if the cost issue is the real issue, we're going to pay twice as much to go 24 weeks. So, I think that's something that gets lost in the discussion.

And I think treating all hep C-infected patients without using fibrosis screening-based interventions has been shown to have the greatest impact on morbidity and mortality, and would be cost-effective.

Well, thank you for that overview on a very important and timely issue, because we're all aware of various treatment recommendations that have suggested that patients with advanced fibrosis should be prioritized for treatment. What's missing there is the part about when necessarily, and sometimes I think that often the treatment recommendations ... people only look at certain sentences in there and don't look at the totality of what's recommended.

I think all of us, as hepatologists, would agree with you that hepatitis C therapy is potentially life-saving, and all these patients should have the opportunity to be treated if possible.

So, we talked a lot about SVR; we talked a lot about cure rates and improvement in mortality. There are some more subtle things that we're starting to learn about, and at the Liver Meetings there was a very interesting abstract that looked at the patient-reported outcomes from the ION studies that looked at sofosbuvir and ledipasvir. And Dave, maybe you want to mention a little bit

about what those results, because it gives us some additional reasons why patients should be treated.

So, the simple conclusion was, patient-reported outcomes from prior to treatment to 12 weeks after being cured dramatically improved. People had less fatigue, were more productive at work, and had much-improved overall patient-reported outcomes. It was also interesting that patients who got the ribavirin-free regimen had continual improvement in most of the patient-reported outcomes. Patients with ribavirin during the treatment actually had a decrease in patient-reported outcomes in terms of not feeling as well, but actually those all came back up post-treatment.

So, ribavirin brings down quality of life a little bit during treatment, but the cure rate for either regimen dramatically improves quality of life.

You know, again, talking about what the treatment recommendations, I don't know, Nancy, if you noticed that study that looked at the CHeCS cohort, the patients who were followed over time, and where they fit into that treatment priority status. Because I think it's very instructive, and kind of replicates what we might see in the clinic.

So, it was a really interesting study, and very important, showing that those that have the highest priority for therapy, those with advanced fibrosis, life-threatening extrahepatic manifestations, and then the second tier, those at high risk to become that subset, so those that have risk factors that increase their chance of becoming cirrhotic or have extrahepatic manifestations. Then overall you know, a large cohort of individuals, only 38% would not meet guidance document recommendations, suggesting that we talk a lot about who to restrict therapy to, but the vast majority of our clinic actually falls within the guidance documents recommendations.

That leaves 40% or so who potentially would have difficulty acquiring the medication, depending on ... And you've heard a lot of anecdotal stories about the treatment recommendations, sort of, like I said, selectively choosing parts of that as opposed to being more inclusive. Have you had any experiences along those lines?

We still have trouble getting access to therapy for people who clearly fall within guidelines, but it's very difficult to identify the all-cause mortality that is increased with viral replication and decreased with SVR. This is not just as simple as fibrosis and extrahepatic manifestations that are vasculitis and nephrotic syndrome.

But then when you factor in the patient-reported outcome piece...

Absolutely.

That's where should everybody get the benefit of potentially being treated...

Yes, I think that...

It's amazing how the discussions change. We've not talked in our communities about access to care and prior authorizations, and it really dominates most of the meetings we're going to now, because it's really an issue that we've got to address, and I think we've poorly addressed in the past.

And patients want to be treated. I mean, if you have something that's curable ─ even if it isn't going to hurt you in the next year ─ they would much prefer not continuing to worry about it, and be able to cross it off their problem list.

I think what's needed ─ a lot of people are talking about, "What does that study look like to try to understand the effect of this kind of policy?" The study needed would be to take patients who are in that 40% who don't have F3-F4 fibrosis or extrahepatic manifestations, and randomize that group to get treated vs. wait, say, for five years. That study's never going to happen 'cause I've never met a patient who wants to be wait to be cured of their hep C. So, we're going to live with uncertainty for a long time.

Well, is it uncertainty, because we're seeing a continuous accumulation of evidence on multiple fronts, whether it's patient outcomes, whether it's mortality/morbidity. That suggests treating hepatitis C is a good thing. And so, at what point do we say we have enough information?

We also don't address the fact that it is a disease that can be transmitted, so that part of viral eradication is eliminating the reservoir of individuals with hepatitis C. So, there are multiple reasons to eradicate virus.

Next, Dr. Nelson will lead us through the Council findings on HIV/Hepatitis C co-infected patients, and if they should continue to be a considered a "special population."

Thanks, Mike.

So, this statement is, "Patients co-infected with HIV/Hepatitis C should no longer be considered a special population." So, why do we make this statement? Historically, HIV and hep C-infected patients have had more difficult-to-treat due to three factors: poor response to interferon-based therapies; increased risk of toxicities and adverse events; and fewer options due to multiple drug-drug interactions from the prior therapies.

However, I'm going to show you in a minute recent data suggest that interferon-free therapies may be equally effective in HIV-negative and positive subjects.

Special designation ─ actually when you have that designation, it delays access to these drugs because special trials are needed in these populations usually later in the approval process. And already, this past year, EASL -- the European Guidelines Committee, has already proclaimed co-infected patients being non-special, I think recognizing the major change in response rates in this population.

Two very important studies were presented at the AASLD this year looking at treatment of co-infected populations. The first was a study called "ERADICATE," where they took sofosbuvir and ledipasvir and treated non-cirrhotic patients for 12 weeks. Stunningly, the majority of patients, 100% who were not on antiretroviral therapy, were cured, and 97% were cured in the group that was on antiviral therapy. Drugs very well-tolerated, no discontinuations, so really impressive data.

A future regimen that we think will be approved in the next month or two is the 3D plus ribavirin regimen, and again, a very similar trial design ─ 12 weeks of therapy, and here a cure rate of 97%.

The second study that was presented was looking at a 3D regimen plus ribavirin in a same, very similar population ─ 12 vs 24 weeks ─ and really, 12 weeks was just as good as 24 weeks with SVR rates above 90%. So, what we're really starting to see now are new all-oral therapies being delivered from two regimens ─ one approved, one coming very soon ─ that are really going to offer very high rates of cure.

The only caveat I'll mention is that these were in non-cirrhotics, and obviously we've got to increase the amount of data coming from more advanced populations.

So, to summarize, the efficacy with these newer agents is really now comparable to HCV mono-infection, raising the possibility that co-infected patients should no longer be special. We really need to expand the larger, more diverse populations. The one thing about HIV co-infected patients is, they do have high viral loads, and when you combine that with cirrhosis there may be an impact, so it really needs to be studied.

I didn't highlight, but drug-drug interactions are going to require ongoing evaluation, but the new drugs under study have much less drug-drug interactions. I think this can be overcome with studies prior to approval.

And I think earlier access to these new therapies is likely coming since these populations don't appear to be as special.

Well, thanks, Dave.

I think we've all seen the data, how the differential in survival between HIV infection and hepatitis C infection has flipped, and particularly in the co-infected population that for many years had been succumbing to the hepatitis C component and cirrhosis while their HIV was under good control. So, this kind of data really provides just remarkable hope for all these patients, and I think we're all quite impressed by what was presented here today.

Do you see any difficulties in managing the patients with co-infection? You mentioned about drug-drug interactions. We don't do a lot of changing of their HIV treatment regimens personally, but I imagine that that can be accomplished fairly easily when you have to.

Yeah. I think some of the other things I didn't highlight in these studies ─ there was no change in CD4 counts, no change in HIV level. So, no real evidence of interactions with their antiretroviral therapy for their HIV that would impact their HIV disease. I mean, I personally let these patients be treated by their HIV docs because of the drug-drug interactions, and I really want to make sure they're being followed closely for their HIV as well as their hepatitis C.

Nancy, what's been your approach?

Very similar. I think that from a hepatitis standpoint, our HIV colleagues have preferred for us to treat the hepatitis C, but it does require a very open discussion as to what they're going to do with the HIV regimen, what drug-drug interactions might impact other things that they might use in these patients.

I also think that it's important to highlight that morbidity is increased in co-infected individuals, and although we kind of left them off on our prioritized patients, but co-infection independent of fibrosis is a prioritized population, and that's because independent of CD4 count, independent of ART, the fact that they're co-infected increases the risk of fibrosis ... so that we should be very aggressive with these individuals, not afraid of their drug-drug interactions, not afraid of coordinating their care with their HIV specialist.

Dave, thanks very much. That was really interesting data about HIV patients, and I'm sure we'll be seeing an influx of those to be treated with this kind of data that we're seeing.

So, we've seen the data from the HIV/Hep C co-infected population. Are there other so-called "special populations" whose status may be changing based upon what we've seen at this meeting?

I think traditionally our post-transplant population is considered to be special, and just like our co-infected individuals, it's because of concerns for drug-drug interactions, comorbidities that come with immune suppression and long-term transplantation. And just like our other special populations, all the drug-drug interactions need to be considered, some with certain regimens more than others. That efficacy is still nearly, if not as high, as you would expect in our mono- or our non-post-transplant individuals.

These studies are a little hard to interpret because they are very heterogeneous populations, usually multiple genotypes; but they're not so hard to interpret when you consider that the end SVR rates are still generally above 90%, just like what we would expect from all the other more clean data sets.

Yeah, I think the data from the sofosbuvir, ledipasvir plus ribavirin study that was presented post-transplant that included both patients with milder recurrence of hepatitis C post-transplant as well as cirrhotic patients gets to the exact point that you're talking about. We're seeing very high

rates of sustained response. It's only when you start getting into the Child's B, Child's C cirrhotic that you may start seeing a drop-off in sustained response.

Right ... which we saw in the non-transplant population.

Yes, exactly.

And I think the same thing goes with the 3D plus ribavirin regimen. The study that looked at the post-transplant population. That study was only non-cirrhotics, but they also achieved, if I recall correctly, 97% sustained virologic response rate with 24 weeks of therapy that included the 3D plus the ribavirin. So, we've never seen that before, and I'm sure all of us are going to start actively trying to treat our post-transplant populations more aggressively.

Well, we had a great discussion on five of the statements that were discussed during the HCV Council deliberations earlier this year, but we'd just like to touch very briefly on some of the others -- just some of the highlights that may have altered our thinking about these.

So, Dave or Nancy, tell me your thoughts about the statement, "Genotype 1a and 1b will be treated with different regimens." True or false?

Well, I think that ... can I say, "Maybe"? I think it's obvious that for 1a individuals, some regimens do require ribavirin, and in others the 1a and 1b efficacy is essential the same with or without ribavirin, with or without treatment duration, so that ... in some regimens they will be, but not in every regimen.

Yes, I would agree. I think genotype 1a and other negative predictive factors may add up to require different treatments. So, I would agree -- I'm in the middle. For most people, no, but when you add up a number of negative factors for some of the regimens, genotype 1a is going to be treated

But they're clearly different, still. They respond differently.

Yeah.

So, the next statement, "The preferred approach to treatment for all subgroups of patients with genotype 2 is sofosbuvir and ribavirin for 12 weeks." Have we seen anything to shake our confidence in that?

I don't think so. I mean, again, you've got cure rates with that regimen for non-cirrhotics well into the mid- to high 90s. It looks like by extending therapy in the HCV-TARGET database to 16 weeks you maintain very high SVR rates, approaching 90%. So, I haven't seen anything at this meeting yet that's going to lead me to another treatment.

So, the sticker on the statement is 12 weeks, and I think you already said ... I mean, there are a group of individuals with genotype 2 that might deserve another month of therapy who were cirrhotics.

Very small data set that supports that, but yes.

This is a good one. "Given the high-efficacy and low-viral breakthrough rates, on-treatment viral load monitoring is no longer required." Now, we've seen some data that might alter your thinking.

I think there's data that supports that, but my own anxiety is someone who consistently got viral loads through a year and a half.

A hard habit to break, huh?

It's a hard habit to break, yes, like sucking your thumb. But I think that for compliance reasons or adherence reasons, people want to get a 4-week viral load. However, if you're not adherent by Week 4, the cat's kind of out of the bag, especially if you're looking at an 8-week regimen. I mean, if you need to identify non-adherence very early in your treatment regimen, so that 4-week time point is probably obsolete.

I would agree. I mean, every data set presented at this meeting suggests that the Week 4 viral load determination is not helpful at trying to select out a group at higher risk where you could do something. Like, the older days, when if you were below quantification but still detectable you would go longer for therapy and decrease the relapse rates. Now, we see that both those groups have about the same response.

So, traditionally we're being asked not by payers to check a viral load to document patients' adherence, but clinically I think it's really not valid to check it to make a clinical decision.

Yeah. And the data suggested it doesn't matter really when you become below the level of quantitation -- whether it's Week 1, 2, 4, or eve Week 6; you still have a very high chance of sustained virological response almost identical across all of those time points. So, I agree that the response-guided treatment of checking HCV RNAs routinely is kind of obsolete.

This whole idea about checking it ... I like to check it not so much to see if the patient's adherent; I like to check it to encourage more adherence, because at Week 4 they like to see the fact that their virus is undetectable. Hopefully you've already selected the patient that they're going to be adherent, that you've educated them in the importance of adherence. And I think if we use the Week 4 time point as a restriction on therapy, ironically we're going to be in the position where we're creating non-adherence because they can't get their prescriptions refilled and everything, and I think that's a ... a huge mistake, and we've already all had example of that, probably.

"Patients with decompensated cirrhosis should be treated with an all-oral regimen for hepatitis C in order to improve survival." That was one of the statement that we addressed. Perhaps we have a little bit more information from this meeting. Has it changed your thoughts about it? Do we really have the definitive answer?

Well, I think that David already touched on the fact that the decompensated cirrhotics with therapy do improve their MELD scores; maybe resolve ascites a little bit, improve some of the clinical labs that we consider important ─ driving that MELD score. But I don't know that we've yet demonstrated that they survive longer. You would expect that, and we would hope for that. But that data's still pending.

And then finally, "The treatment of hepatitis C should remain within the domain of hepatologists, gastroenterologists, and ID physicians." We spent some time talking about shorter duration, great tolerability. Does that now mean that we can open up or should open up treatment to a wider range of physicians and other healthcare providers who are treating hepatitis C?

I think the answer is, that's probably the future, where we're going to have to ... if we're going to diagnose over the next few years another few million hep C-infected patients, there aren't enough gastroenterologists, hepatologists and ID docs to treat them all. But I think in the current world, where we're still debating shortening of therapy, assessment of fibrosis, long-term cancer screening, I think the current trend is, it'll still be evaluated and treated through a subspecialty, but that can't be the future long-term.

I think that there is likely a way to identify individuals at higher risk for complications. It could be as simple as cirrhosis or maybe comorbidities that we understand increases the risk of advanced fibrosis. And then that subset, that hopefully small subset, can be sent to ID, GI, and Hepatology. The majority of these individuals just need a knowledgeable provider; they don't necessarily need a hepatologist.

Thank you, Nancy and David. Well, as you've clearly seen, this has been a very informative and practical discussion of the most pressing issues in this ever-changing era of hepatitis C management. On behalf of my friends and colleagues, Dr. Nancy Reau and Dr. David Nelson, I'd like to thank you all for joining us today. Please don't forget to take the post-activity test to receive CME credit. I'm Michael Fried, and thank you for joining us.